Clinical Laboratory Improvement Advisory Committee (CLIAC)
September 27-28, 2000

Summary Report

Table of Contents

Record of Attendance

Committee Members
Dr. Toby Merlin, Chair
Dr. George Birdsong
Dr. Joseph Campos
Dr. Patricia Charache
Dr. Brenta Davis
Dr. Andrea Ferreira-Gonzalez
Dr. Jaime Frias
Dr. Ronald Gagne
Dr. Barbara Goldsmith
Dr. Edward Hook
Ms. Cynthia Johns
Dr. Ronald Luff
Dr. Valerie Ng
Dr. Timothy O'Leary
Mr. Stewart Richardson
Dr. Lawrence Silverman
Dr. Lawrence Sturman
Dr. Roland Valdes
Dr. Alice Weissfeld

Ex Officio Members
Dr. Steven Gutman, FDA
Dr. Robert Martin, CDC
Ms. Judith Yost, HCFA

Liaison Representative
Ms. Kay Setzer, AdvaMed

Executive Secretary
Dr. Edward L. Baker, CDC

Centers for Disease Control and Prevention
Ms. Nancy Anderson
Dr. Rex Astles
Ms. Carol Bigelow
Dr. Joe Boone
Ms. Gail Bosley
Ms. Diane Bosse
Dr. Bin Chen
Ms. Judy Delany
Ms. Sharon Granade
Dr. Thomas Hearn
Dr. Adam Manasterski
Ms. Priscilla Patin
Mr. Darshan Singh
Dr. Barbara Slade
Dr. Steven Steindel
Mr. Eric 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; 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 regulations, 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 INTRODUCTORY/ORIENTATION INFORMATION FOR NEW MEMBERS

Dr. Toby Merlin, CLIAC Chair, began the orientation session for new CLIAC members by introducing Dr. Robert Martin, Director, Division of Laboratory Systems (DLS), Public Health Practice Program Office (PHPPO). Dr. Martin welcomed the CLIAC, and stressed the value of the Committee's input to the Department of Health and Human Services (HHS) and the agencies responsible for implementation of the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Dr. Martin also thanked DLS staff who support the CLIAC meetings, after which the CLIAC members and CDC staff attending the meeting made self-introductions.

As part of the orientation, Dr. Martin presented the organizational structures of CDC, PHPPO, and DLS. He then described the major CDC initiatives for the year 2000, the DLS priorities, and summarized the projects and activities conducted in DLS.

Dr. Merlin outlined the framework for CLIAC operations, emphasizing that CLIAC is an HHS advisory committee, and is not responsible for writing regulations. He added that the meetings provide an opportunity for open discussion by Committee members and input from the public.

ORIENTATION FOR NEW MEMBERS

Travel Guidelines – Addendum A

Ms. Priscilla Patin, Committee Management Specialist, DLS, reviewed the travel rules and guidelines that apply to CLIAC members. She briefly outlined policies and procedures for making airline reservations, and reimbursement of allowable expenses, including hotel, meals, ground transportation, and other miscellaneous expenditures.

Federal Advisory Committees

Mr. Kevin Malone, Senior Attorney, Office of General Counsel, Office of the Director, CDC, described the Federal Advisory Committee Act (FACA) passed on October 6, 1972, explaining the role and purpose of federal advisory committees. He said that more than 1000 federal advisory committees exist, and serve as a means of public participation in the government decision-making process. Members of the committees are appointed by relevant government agencies, with committee membership balanced to represent varying points of view, expertise, geographic distribution, gender, ethnic and minority groups. Committee members are special government employees when they serve on advisory committees, and are subject to the same rules as other government employees when serving in this capacity. Most federal advisory committee meetings are open to the public, except where there are issues of national security, industry trade secrets, or other proprietary information being discussed. However, even closed meetings are announced to the public by publishing the notice of the meeting in the Federal Register.

Administrative Procedure Act / Conflict of Interest
Mr. Kevin Malone briefly explained how federal laws are enacted and regulations developed, with input from the public at several points in the process. He noted that CLIAC was established in 1992 to provide a means for public input on the CLIA regulations, which will continue to evolve as laboratory testing and technology change over time. He then introduced a videotape on FACA and ethical issues that pertain to special government employees.

Following the videotape, Mr. Malone gave a brief overview of conflict of interest rules that apply to CLIAC members. He stated when serving on the Committee as federal employees, members should not have financial interests that would compromise their participation. However, he explained, in as much as financial conflicts of interest are inherent in certain instances of advisory committee membership, waivers are granted if the need for service outweighs the conflict.

CLIA History and Overview – Addendum B
Ms. Rhonda Whalen, Chief, Laboratory Practice Standards Branch (LPSB), DLS, PHPPO, presented a chronological overview of the CLIA law and its implementation, emphasizing key features of the law, and revisions to the regulations since publication of the final regulation in 1992. She explained that the regulations are based on the complexity of laboratory testing, and reviewed the CLIA technical standards, including proficiency testing (PT), patient test management, quality control (QC), personnel, and quality assurance. Ms. Whalen also outlined the roles and responsibilities of the Health Care Financing Administration (HCFA), Food and Drug Administration (FDA), and CDC in CLIA implementation, and showed the relationship of CLIAC to the organizational structure of HHS.

CLIAC Process
Dr. Merlin concluded the orientation session by describing the process usually followed at CLIAC meetings. He read section 493.2001 of the CLIA regulations describing the establishment and function of the CLIAC, and explained that, in general, presentations are made to the CLIAC by HHS representatives or technical experts on a specific topic, followed by group discussions by the Committee. Since the meetings are public, there is also opportunity for public comment. Although there may be consensus at the end of a discussion, CLIAC may not vote on every issue. Dr. Martin clarified that although the CLIAC is an advisory committee, some meetings are primarily informative and not intended to solicit specific advice. Dr. Merlin also explained that there may be instances where there is a need for CLIAC Subcommittees or Workgroups to be formed to address certain issues relevant to clinical laboratory testing.

CALL TO ORDER – FULL COMMITTEE INTRODUCTIONS
Dr. Toby Merlin called the CLIAC meeting to order, and reviewed the role of this Advisory Committee. Dr. Robert Martin welcomed CLIAC members, who had not attended the

orientation session, and summarized the materials covered. He introduced three new DLS branch chiefs:
Dr. Barbara Slade, Chief of the Laboratory Practice Assessment Branch (LPAB); Ms. Judy Delany, Chief of the Laboratory Practice Training Branch; and Ms. Rhonda Whalen, Chief, LPSB. All CLIAC 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.

PRESENTATIONS AND COMMITTEE DISCUSSION

CLIA Update

Centers for Disease Control and Prevention (CDC)

Laboratory Medicine Sentinel Monitoring Network – Addendum C

Dr. Steven Steindel, Supervisory Health Scientist, LPAB, DLS, PHPPO, presented a brief history of the Laboratory Medicine Sentinel Monitoring Network (LMSMN) and an update on current network activities. He envisions this network as developing into a data source for information on laboratories, that could be used to assess the impact of CLIA. He pointed out that many anecdotal statements are made about the health system; the network is designed to pose questions and collect data to prove or disprove these anecdotal statements. The network serves as a mechanism to monitor the performance of emerging tests and factors that impact the performance of these tests.

The original LMSMN cooperative agreements to gather data on laboratory operations were awarded to the State of Washington, New York City and the University of Alabama, Birmingham. New York City and the University of Alabama no longer participate in the program, however the University of Alabama data is now being used for outcomes research. Washington has remained in the program and monitors approximately 600 laboratories in four states in the Pacific northwest. Half of the laboratories monitored in this program are laboratories that perform moderate and/or high complexity testing, with the remaining half comprised of waived laboratories. There are currently 15 Washington reports available via the DLS intranet site (www.phppo.cdc.gov/dls).

Examples of areas examined by Washington State are the following:

1. Corrected patient reports. This has been the only prospective report conducted. Dr. Steindel said that laboratory response to prospective reports is poor, however there were no unique problems identified in this study.
2. Training sources. This study gathered data on the various sources of training used by laboratories in the network and reported the preferred method of training by laboratory type.
3. Proficiency Testing (PT). This study found that most laboratories would continue to participate in PT if it was not required, although many would prefer fewer PT challenges per year.

In 1998, CDC re-solicited proposals to expand the LMSMN project. Washington continues to participate in the program, with the addition of Arkansas and New York. Arkansas is monitoring more than100 laboratories, most of which perform only waived testing. New York is primarily looking at the laboratory practices of limited service laboratories and assessing the accuracy of waived testing performed in these settings versus traditional laboratories.

Health Care Financing Administration (HCFA)

HCFA Update and Discussion of Pilot Project – Addendum D

Ms. Judy Yost, Director, Division of Laboratories and Acute Care Services, Center for Medicaid and State Operations, HCFA, presented an overview of the number of laboratories registered, accrediting organizations approved and deficiencies cited in inspections of certificate of compliance laboratories. According to the data presented, the top four deficiencies over the past three survey cycles were: 1) failure to follow the manufacturer's instructions; 2) no quality assurance (QA) program; 3) no QC testing; and 4) personnel deficiencies. She said HCFA is taking an educational approach to address these problems. She noted that laboratories are constantly changing and laboratory registration provides a means to monitor trends. The laboratories self-select their application type, with the majority registering as physician office laboratories (POLs) and applying for a certificate of waiver. She pointed out that laboratories issued a certificate of waiver have minimal regulatory requirements, and 74% of the laboratories are in the waiver/provider-performed microscopy (PPM) category with no oversight under CLIA.

Due to complaints about waiver and PPM laboratories, HCFA initiated a pilot study of a sample of those laboratories in Ohio and Colorado. The study demonstrated that over 50% of the laboratories had problems, and the three most common deficiencies were: 1) failure to follow the manufacturer's instructions; 2) absence of QC testing; and 3) testing beyond the scope of the certificate. The pilot study is being expanded to include laboratories in eight additional states, with 2.5% of the laboratories in those states evaluated through an announced survey. The surveyors will gather information on waived and PPM testing and assist the laboratories in correcting any problems identified during the survey. In addition, surveyors from Ohio and Colorado will revisit laboratories that were previously evaluated to determine whether identified problems have been corrected.

In discussing the criteria FDA should use in determining waived status, Ms. Yost provided the following HCFA recommendations:

- Develop level of accuracy of test system appropriate for untrained users.
- Include previous performance (e.g., proficiency testing) data in review.
- Consider use of device (e.g., monitoring, screening) when developing threshold for waiver decision.
- Develop criteria for re-evaluation if device fails in field.

Committee Discussion
Members pointed out the perception that waived tests don't have a negative impact on patient care. They asked whether there is any data on the improper use of waived devices or any data associating testing errors with patient harm. Ms. Yost said no and noted that surveyors only cited deficiencies that could have an impact on patient care and suggested further studies may be possible after the expanded pilot study is completed. Dr. Steindel pointed out that outcome studies are difficult to obtain because of the limited amount of laboratory data on patient care.

One member asked about the type of deficiencies cited in the pilot studies. Ms. Yost said the most frequent problem was obsolete instructions or the lack of the appropriate instructions for the specific test kit being used by the laboratory. She said there is no training requirement for personnel performing waived tests. She emphasized that in many cases, personnel performing waived testing are non-laboratory personnel.

Members expressed the following concerns:
- Correlation between patient outcomes and test results is needed.
- There is a wide range of off-label use of test systems. Concerns were expressed about preventing off-label use and regulatory authority for oversight.
- Although the instructions for some rapid tests for group A streptococcus indicate that a negative test should be confirmed by culture, cultures are not performed.
- Physicians do not have laboratory training. A mechanism is needed to disseminate information on laboratory practices.

Ms. Yost said the solution will need to be multifaceted. Education is important, however there are costs associated with conducting the surveys, and waived and PPM laboratories are not charged an inspection fee.

Dr. Baker commented that anecdotes plus data leads to policy and requested that the Committee members relate stories based on fact.

Food and Drug Administration (FDA)

CLIA Waiver, Genetic Testing, FDA Reorganization - Addendum E

Dr. Joseph Hackett, Division of Clinical Laboratory Devices (DCLD), Centers for Devices and Radiological Health (CDRH), FDA, briefly discussed waived tests, genetic testing and structural re-organization plans for the DCLD. Dr. Hackett began with a discussion of waived tests. He referenced the proposed regulation, published in September 1995, clarifying the statutory criteria for a waived test. He reminded the Committee the FDA Modernization Act of 1997 (FDAMA) changed the definition of a waived test. He said industry believes the FDA processes for clearance (510(k) or premarket approval (PMA)) should be used to establish the effectiveness of a waived test and the waiver accuracy criterion should be defined as untrained users obtaining the same result as trained professionals. Dr. Hackett mentioned the FDA public workshop held in

August on the criteria and process for waiver, and noted that Ms. Clara Sliva would report on that meeting. After the public meeting, FDA determined the next steps with regard to waiver are:

- Review the workshop comments.
- Evaluate industry concerns.
- Draft an interim guidance document.
- Continue to follow the September 1995 proposed criteria.
- Share information with CDC and HCFA.

On the topic of genetics, Dr. Hackett said the FDA does not currently regulate "home brew" tests, although the Secretary's Advisory Committee on Genetic Testing (SACGT) feels the FDA should have oversight of all genetic tests, including "home brew" tests. He stated that FDA genetics activities now include the FDA Genetics Advisory Panel, the CDC Genetic Laboratory Forum, and SACGT.

Finally, Dr. Hackett discussed the DCLD proposed organizational changes. He said currently DCLD consists of three branches and the proposal would create six branches. He then listed the DCLD goals and five policy development categories.

Committee Discussion - Genetic Testing

A member asked about the proposal for classifying the 400 genetics tests currently in use. Dr. Hackett replied the FDA will look at some of them, but is primarily focusing on new tests. Another member expressed concern that current genetic testing might be stopped while tests are under review by the FDA. Dr. Hackett replied that there would be no interruption in testing. One member asked where, in the new structure of the FDA, genetic tests will be evaluated. Dr. Hackett stated that the evaluations will take place throughout all of the branches, but primarily in the Immunology Branch.

CLIA Waiver Criteria Public Workshop – Addendum F

Ms. Clara Sliva, CLIA Coordinator (Acting), DCLD, Office of Device Evaluation, CDRH, FDA, presented a report on the August 14 - 15, 2000, FDA CLIA Waiver Criteria Public Workshop. She briefly reviewed the history of the FDA's involvement in complexity categorization from the initial implementation of CLIA to the present. She reviewed the role of CDRH and the Center for Biologics Evaluation and Research in product review and categorization and listed the benefits to manufacturers and laboratories of test categorization performed by the FDA.

Ms. Sliva then reviewed the three paths to waiver: nine tests listed in the CLIA regulations; waiver based on criteria in the proposed rule published September 13, 1995; or automatic waiver when a product is cleared by the FDA for over-the-counter (OTC) or prescription home use. She said an increasing number of tests have been cleared by the FDA for OTC or prescription use (e.g. prothrombin time) and briefly reviewed the FDA's criteria for granting this status.

Last, Ms. Sliva discussed the FDA Waiver Workshop meeting. She reviewed the comments made by individuals representing professional organizations, industry, medical associations, inspection agencies and clinicians. She said the FDA is currently drafting a Level 1 Guidance Document on criteria for waiver and may ask CLIAC for advice.

Committee Discussion - Waiver

The CLIAC raised a number of issues regarding the criteria and process for waiver currently being developed and used by the FDA. Their concerns centered around: the interpretation of the CLIA and FDAMA statutes regarding waiver; definitions for accuracy, precision, and risk of harm; intended use of waived tests; studies required for waiver determinations versus requirements for FDA 510(k) or PMA clearance/approval; the off-label use of waived tests; waiver based on OTC or prescription home use; post-analytic concerns; post-market surveillance; the absence of required standards for laboratories performing waived testing; and potential waiver of new technology, including genetic tests. A summary of the pertinent comments and the CLIAC plans for addressing waiver issues follows.

Definition of Accuracy vs. Precision (trained versus untrained users)

- A member inquired whether accuracy is being considered for waiver determinations. Another member pointed out that making waiver determinations based on comparing the performance of untrained users to laboratory professionals (as recommended by industry) is defined as precision, not accuracy. Using this approach, manufacturers only need to show that the same test result can be obtained by trained and untrained users.
- Many members emphasized the need to define accuracy, with one member suggesting accuracy be defined for medical decision making. Ms. Sliva said there are two interpretations of the definition of accuracy, the laboratory definition (scientific) and the legal interpretation of the law (FDAMA). For waiver determinations, she said the FDA is considering using the definition of accuracy that is based on legal interpretation (i.e. data demonstrating that untrained users obtain the same result as trained professionals) rather than comparing waived test performance to the reference method.
- One member stressed that accuracy should be defined the same by everyone. Another CLIAC member recommended accuracy be documented using clinical and analytical sensitivity and precision.
- One member asked if the term accuracy should be removed from the law.
- A member suggested the FDA evaluate studies comparing trained versus untrained users.
- Ms. Sliva said the FDA is considering this approach.

Risk of Harm/Erroneous Result

- A member asked who should define risk of harm, and another member responded that perhaps CLIAC should define this.
- One member suggested that the terms "risk of harm" and "erroneous result" need to be better defined and explored further. Another member agreed this is important and an explicit explanation of "harm" is needed.
- A member noted that accuracy and risk of harm are all context specific. Another member said laboratory tests only provide information and harm only occurs when action is taken.

- A member noted that risk is a subjective term.
- Dr. Martin agreed that risk of harm is a subjective term, and for this reason, the CDC evaluated accuracy as part of their waiver determinations to minimize risk of harm.
- A CLIAC member said that the 'OR' in the statute - "employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or (emphasis added) the Secretary has determined pose no reasonable risk of harm to the patient if performed incorrectly." - should be changed to an 'AND'.

FDA 510(k) / Premarket Approval Clearance Processes

- Dr. Steindel commented that the FDA uses substantial equivalence to clear instruments/tests under the 510(k) process, and accuracy may not be evaluated in this process.
- Ms. Kay Setzer, Manufacturer Liaision, stated the process for 510(k) or PMA clearance, as defined under the Federal Food, Drug, and Cosmetic Act, assesses accuracy through comparison with a reference method, calibration, linearity and reportable range. She added if the product has no value to the public, then it doesn't get cleared. She said CLIA was meant to focus on the user of the products, and the laws (FDA and CLIA) should not be redundant.
- A member asked if studies are included in the FDA 510(k) or PMA process to show that a lay user can perform the test as well as a laboratory worker. Ms. Sliva responded that these studies are included if this is part of the manufacturer's claims for the product.
- Dr. Martin said the FDA product reviews focus on the manufacturer's claims. Dr. Hackett clarified that, under the premarket clearance/approval process, the FDA looks at accuracy, precision, and positive and negative predictive values.
- A member said the FDA evaluation clears or approves a test for market use. The waiver process should be a separate determination using parameters such as user competency and how well a user can perform and interpret the test.

Intended Use of Waived Tests

- A member suggested intended use be used for waiver evaluations.
- Another member said intended use studies are more optimistic than in real practice because the user always performs better when observed.
- One member asked whether tests could be waived on the basis of how they are used, rather than the accuracy of the test. Dr. Thomas Hearn, Deputy Director, DLS, replied that the CLIA construct does not address test use and that is the reason CDC tried to limit risk associated with waived tests by requiring these tests be highly accurate.

Off-label Use of Waived Tests

- One member asked if the FDA could cite off-label use of waived tests. Dr. Hackett said that the FDA could do so if the manufacturer promoted that off-label use.
- Ms. Setzer said the manufacturer tries to provide accurate labeling for use of a test, but users don't always read the labeling. She added that the manufacturers also provide education.
- Dr. Steindel pointed out that off-label use of a waived test would result in the laboratory performing a high-complexity procedure, because performing off-label testing would not

be categorized, and as such, would be considered high complexity. However, a member pointed out that if it was a waived laboratory, probably no one would know that the laboratory was performing a high complexity procedure.

- One member asked whether the FDA considers the consequences of off-label use when it clears a product for home use. Dr. Hackett said no, the FDA must assume the user is following the manufacturer's labeling.

Waiver Based on OTC or Prescription Home Use

- One member commented on the difficulty of reconciling the different philosophies of the FDA and CDC for determining waiver status. For example, FDA's criteria for clearing a prothrombin time test for OTC prescription use differs from the CDC process for waiver approval. Ms. Sliva responded that a different set of criteria (as opposed to waiver criteria) were used for the determination of OTC prescription use for the ITC prothrombin time test. By law, any test system approved for home use or cleared for OTC use by the FDA is also approved for waiver. Ms. Whalen said that since the prothrombin test was cleared through the home use process, and automatically approved for waiver, the comparability between the test system instructions for the professional product versus home use product was evaluated to determine waiver status of the professional product. The accuracy of the ITC prothrombin test was not evaluated by CDC. Another member commented on the difficulty in dosage regulation if the home use prothrombin time result differs from the result obtained in a laboratory.
- A member said it seemed unreasonable to be able to market a test for OTC use and not be able to use it in a POL as a waived test. It was noted that FDAMA clarified the waiver provisions by requiring that any test approved for home use is approved for waiver under CLIA.
- It was suggested that since FDAMA changed the CLIA law to waive any test system approved/cleared for home use, changes to the home use process might need to be considered.
- Ms. Setzer commented that industry develops test systems users want, and users want simple tests that will provide faster results, allowing the physician to treat the patient more rapidly. A CLIAC member said a home test may get people into the physician's office sooner, however, the patient expects the physician to perform tests that are higher quality than those that could be performed at home.

Post-analytic Concerns

- A member stated the post-analytic phase of testing needs to be considered in evaluating test systems for waiver.

Post-market Surveillance

- A member inquired about post-market surveillance of waived tests. Ms. Sliva said that if the product doesn't work in laboratory settings, it is an FDA issue.
- One member suggested there are some areas that could be monitored by the FDA after waiver approval, such as comparing performance of waived tests in different test settings. Ms. Sliva said the FDA is studying this issue.

Waived Tests Exempt from Standards

- Several members requested a clarification of waived status. Ms. Whalen said waived

tests are exempt from the CLIA regulations. A Committee member pointed out that waived tests are not subject to quality assurance, proficiency testing or personnel regulations, so moving more tests to waived status may have the effect of circumventing the intent of CLIA (quality testing). The member expressed concern that the waiver category may be a mechanism to undermine CLIA.

Waiver of Genetic Testing

- Another member asked whether genetic testing is included in the waiver process. A Committee member responded that most genetic tests are high complexity tests.

New Technology

- Ms. Carolyn Jones, representing the Advanced Medical Technology Association, expressed the opinion that CLIA is stagnant and does not fit all situations; it does not address new technology.

Summary

- Dr. Baker suggested that the Committee focus on the criteria that should be used to determine waiver status. He said the principles need to be clarified and the issues that drive policy practices need to be defined. To summarize the CLIAC concerns, Dr. Merlin suggested that the Committee try to frame a statement such as "the committee urges the FDA to exercise caution in determining the waiver criteria."
- A CLIAC member summed up the discussion by saying waived tests must be simple to perform and pose no risk of harm; the FDA needs to define accuracy more substantively; guidance on the definition of accuracy should be addressed with the FDA evaluating accuracy and the positive and negative predictive values; the place where testing is to be performed and the type of users performing testing needs to be evaluated; the implementation of the CLIA regulations is the responsibility of the laboratory director and includes a determination of which methodologies are appropriate for patient testing.
- The Committee agreed the waiver criteria of simple and accurate should be maintained. It was pointed out that since CLIAC last addressed the waiver issue, there have been changes in both testing technologies and in the statute. Dr. Baker suggested the formation of a CLIAC workgroup to evaluate the waiver criteria and noted the definition of accuracy is central to the discussion. Dr. Merlin asked the Committee to: 1) frame the question; 2) appoint members to the Waiver Workgroup; 3) clarify points for the Workgroup and; 4) identify issues of concern. He said the charge to CLIAC was to provide consultation to HHS concerning the recommended criteria to be used for determining waiver status.

The Committee identified 23 areas of concern for the Waiver Workgroup to consider:

1. Reports of lack of compliance with manufacturers directions.
2. Off-label use of waived tests.
3. Technology developing faster than policy. Waiver reviews need to consider the way a test will be used.
4. Clarification of "accuracy"; technical and clinical aspects.
5. Concept of waived does not reflect discipline specific need. (e.g. simple genetic testing.)
6. Address "Or" as used in the law.

7. Lack of data relating to adverse outcomes to waived status.
8. Home testing and internet-based testing.
9. For waived testing that is not cleared/approved by the FDA for over-the-counter use, testing personnel should have some sort of competency.
10. Assess responsibility of manufacturer/vendor to assure that the purchaser knows how to use a waived test.
11. Issue of post-analytic phase of testing. Where are post testing resources?
12. Reasonable risk of harm? Psychological?
13. Trained versus untrained person.
14. FDA-approved test versus CLIA-user venue.
15. FDA advisory panel members should participate in the Waiver Workgroup.
16. Package insert presentation.
17. Lack of personnel standards for waived laboratories.
18. Advising FDA on criteria for "home use" approval.
19. Review previous CLIAC waiver recommendations.
20. Provision for withdrawal of waiver.
21. Appeal process.
22. How to resolve interagency differences.
23. Practice venue for waived test used off-label. Multiple venues.

CLIAC nominated the following members to serve on the Waiver Workgroup: Dr. Joseph Campos, Dr. Barbara Goldsmith, Dr. Roland Valdes, Dr. Ronald Gagne, Ms. Cynthia Johns, Dr. Patricia Charache, Ms. Kay Setzer, and HHS representatives (ex officio members).

Finally, Dr. Hearn asked if CLIAC had a recommendation concerning the waiver process FDA should use while it is determining the criteria and process for waiver reviews. The Committee recommended maintaining the current guidelines published in the September 1995 Federal Register notice, and using these guidelines in evaluating waiver applications. The Committee unanimously agreed to send a letter to Donna Shalala, Secretary of HHS, expressing concerns about the waiver process, and requesting an opportunity to comment and provide advice on the criteria for waiver determinations. The letter was drafted and approved by CLIAC (see Addendum G).

PRESENTATIONS

Test Systems Not Currently Regulated Under CLIA – Addendum H

Dr. Edward Hook, Division of Infectious Diseases, University of Alabama at Birmingham, presented a summary of the CLIAC Workgroup meeting on test systems not currently regulated by CLIA. He said the Workgroup agreed that the phrase "materials derived from the human body" should be interpreted broadly and concurred that exhaled gas meets the CLIA definition of a specimen under certain conditions. The Workgroup concluded there are possible criteria that could be used to determine CLIA applicability (i.e. testing site and use of test results) to breath

tests and other tests not currently regulated, and agreed there are unique testing contexts for which CLIA would not be appropriate. They said most testing should be regulated with personnel, QC, and test reliability standards being applicable. They also said CLIA is broad enough that specimen type or manner of collection did not have to be limited. Finally, the Workgroup agreed some testing should possibly be excluded from CLIA regulation, and further discussion is needed on the topic of unregulated testing.

Committee Discussion

One member commented that there will be a broad expansion of breath testing technology and asked about future Workgroup deliberations. Dr. Hook answered that future deliberations had not been planned, and a decision must be made as to whether the Workgroup would continue. Another member said CLIA should regulate these tests and also consider new technologies. However, certain concepts should be followed: 1) identify a concrete problem; 2) define the problem, including the magnitude and consequences; 3) propose a remedy; 4) ensure the resources are available to solve the problem; 5) implement the remedy and; 6) monitor the effectiveness of the remedy. Dr. Hook said he agreed with all of the steps, except the need to identify a concrete problem. He said potential problems should be anticipated, as they are easier to deal with before they become concrete. The member explained that experience is needed to develop standards to address problems that are well defined.

Dr. Merlin summarized Committee consensus that the Workgroup on unregulated testing should continue its activities and asked what else was needed from CLIAC. Dr. Martin responded that although the primary issue was breath testing, what other tests would CLIAC suggest be considered for CLIA regulation and what other issues did CLIAC believe necessitate the continuation of Workgroup activity? Ms. Whalen commented that data is needed. She said the Workgroup discussed the data needs and suggested that broader representation was needed on the Workgroup. She also said that issues need to be prioritized. Ms. Setzer commented that the NCCLS has standards for point-of-care testing devices based on risk analysis of the devices and the unique aspect of QC testing. Dr. Merlin asked about the Workgroup recommendation that HHS proceed with rule-making for unregulated testing devices but cautiously. One member responded that a problem must first be identified before regulations could be developed. The member said that only specific test systems should be considered for regulation because the technologies available to monitor patients are different from those used in the laboratory. Dr. Martin said that CDC and HCFA would not proceed with rule-making at this time, additional consultation is needed.

Public Comment

Dr. Frazier representing the American Association for Anesthesiologists emphasized the contrast in testing equipment used at the bedside versus instruments used in the laboratory. He said in the operating room, the only requirement is to show that the devices don't shock the patient, and calibration of most devices is not performed even yearly. He emphasized resources are needed to

assure that the devices are working correctly.

CLIAC Update: Laboratory Workforce Shortages – Addendum I
Ms. Nancy Anderson, Senior Health Scientist, LPSB, DLS, PHPPO, reviewed the past CLIAC discussions on clinical laboratory workforce shortages, during which it had been suggested that more data and current data are needed to accurately assess the scope of the problem. She said the Health Resources Services Administration (HRSA) was contacted to determine whether additional data were available. HRSA has taken steps to address clinical laboratory workforce shortages, including awarding allied health training grants to academic institutions. HRSA also has two projects underway to provide additional data; development of state health workforce profiles and development of a comprehensive analysis of national trends and issues affecting approximately 16 health care professions. Ms. Anderson informed CLIAC that the letter to the Secretary of HHS alerting her of the workforce shortage was sent on May 16, 2000. Also, in response to the CLIAC concerns about the laboratory workforce, two DLS staff members attended the Summit on the Shortage of Clinical Laboratory Personnel (SSCLP) hosted by the American Society for Clinical Laboratory Science (ASCLS) in June 2000. She said that based on the progress made at the ASCLS Summit and ongoing activities of this working group, it is believed that the Summit participants will complete the development of a strategic plan, which will address both long- and short- term CLIAC concerns relative to laboratory workforce shortages.

Proceedings: Summit on the Shortage of Clinical Laboratory Personnel – Addendum J
Dr. James Griffith, president, ASCLS, summarized the SSCLP held on June 16, 2000. He said the Summit was seeking to identify the components of the workforce shortage problem, categorize these components and identify solutions through development of a strategic plan. Nineteen professional organizations were represented at the Summit. Some components considered by Summit attendees included test settings, growth rate of the field, vacancy rates by geographic location, and fiscal impact of these shortages on the laboratory profession. He pointed out that the laboratory workforce is decreasing as a result of both losing people to industry and the retirement of long-term laboratory employees. He said the current training programs are not getting adequate numbers of qualified applicants and are producing only half of the personnel needed in this field. In addition, over the last 25 years, approximately half of the medical technology training programs have been discontinued. He reviewed the factors influencing people not to enter this profession. He said there is a playing field shift and, in the future, the healthcare arena may be characterized by quality-oriented issues rather than fiscally-oriented issues. He said there are five components affecting the workforce: education; transition (combined) healthcare; financial resources; human resources; and technology. He reviewed the draft of the Summit strategic plan consisting of data collection, marketing, recruitment, financing of education, profession in transition, and co-operation. He said the next phase will occur after the strategic plan is fully developed and announced that ASCLS will be sponsoring another Summit meeting in the near future to continue the work begun at the June 2000, Summit.

Committee Discussion
One member said that the methods of data collection are partially obscuring the problem. If the individual laboratory disciplines are examined, it will be apparent that some areas have greater shortages. Different points of time need to be examined, and competitors for the new workforce must be considered. Further, pay scales are dismal and financial data must be examined carefully, excluding supervisors and managers. The member also pointed out that the academic institutions have lost teachers. Another member commented that opening new training programs won't solve the problem; students must be attracted to the programs. One member asked whether the pool of trained people, who have left the profession, has been examined to determine their reasons for leaving. Dr. Griffith answered that this will be addressed at the next Summit. Another member said that the largest drain on the workforce is coming from the professions outside of medicine. Money is really the issue, employee pay and training in these non-clinical professions are more attractive. Healthcare is competing with a free market economy; therefore, the healthcare economy must be restructured. Another member agreed and said that workforce projections to 2020 indicate a low healthcare workforce overall. In general, money attracts people, but the quality of the workplace retains them. The member said that attrition is a huge factor in the shortages and retirement trends are important; older people may be retained with job sharing. Another factor is the impact of future technologies in which technical oversight may not be necessary. There will be different demands on the workforce, formulas will be altered. The Committee nominated Dr. Brenta Davis to represent CLIAC at the next ASCLS Summit meeting.

Biochemical Genetic Test Survey – Addendum K
Dr. Margaret McGovern, Mount Sinai Medical Center, spoke about the results of the survey she conducted on biochemical genetic testing and reporting practices. She said that biochemical genetic testing has some unique concerns, such as very few reference methods or reference materials for biochemical tests. She said the survey respondents consisted of greater than 1000 laboratory directors, 61% certified by the American Board of Medical Genetics (ABMG), with the majority of these clinical biochemical geneticists. The majority of the responses were from hospital laboratories. Some laboratories had two directors, each responding to a portion of the survey.

The survey showed that 92% of the laboratory supervisors had at least a Bachelor of Science degree, while 95% of the on-site supervision and 40% of the clinical consultation was provided by the laboratory director. However, the survey also showed that clinical consultation was unavailable in 32% of the laboratories.

The survey respondents indicated that their laboratories offered four types of tests: amino acids; substrates; enzymes; and organic acids. The majority of the laboratories offered both screening and diagnostic testing.

Dr. McGovern said the survey showed that 97% of the laboratories had CLIA certification, 95% participated in proficiency testing, and 98% provided interpretation for the non-geneticist

physician. The interpretation was generally provided by the laboratory director. According to the survey, only 19% of the laboratories required informed consent and only 12% had a confidentiality policy.

Dr. McGovern said the overall QA score of the participating laboratories was 77% based on the American College of Medical Genetics(ACMG)/College of American Pathologists(CAP) standards. Laboratories with a New York state permit had higher QA scores. The survey showed there were four factors associated with the QA score: 1) laboratory setting; 2) enrollment in a PT program; 3) director's academic degree; and 4) whether the director was ABMG certified.

She summarized by saying the following:

- an MD degree and ABMG certification were associated with higher QA scores
- a substantial number of laboratories did not have a clinical consultant
- participation in PT was associated with higher scores
- testing for many different analytes may make the development of additional PT programs challenging
- the use of in-house methods and reagents was common
- hospital and research laboratories had higher QA scores and were more likely to employ ABMG professionals
- few laboratories required informed consent

She identified two areas for further study: 1) The impact of substandard QA practices on mis-diagnoses; 2) The effect of deficiencies in reporting practices on the clinical use of testing results.

Committee Discussion

One member asked whether there was any correlation between the CAP PT scores and the study scores. Dr. McGovern replied that the survey did not collect information to answer this question. Another member asked about the distribution curve. Dr. McGovern replied that it was bell shaped. One member asked which individual provided test interpretation in the majority of the laboratories. Dr. McGovern said that the laboratories were not providing test interpretation and, in many cases, laboratories did not provide the test method. Another member asked if there was a relationship between the volume of testing and the QA scores. Dr. McGovern answered that data was not gathered to answer that question. One member commented on the fact that many laboratories have more than one individual who qualifies as laboratory director. Dr. McGovern replied that this was a complicated issue, and many laboratories provided information indicating there were different directors for different testing areas. Another member asked if there are reference materials for molecular genetic tests. Dr. McGovern responded for most molecular genetic tests, there are no reference materials. Another member asked whether research laboratories are CAP-approved. Dr. McGovern responded most research laboratories conducting diagnostic tests had CLIA certification. One member asked if the survey results of laboratories

performing biochemical testing differed from those of laboratories performing molecular testing. Dr. McGovern said in molecular testing, the QA is methodology driven and that independent and hospital laboratories had better QA scores in this study. One member asked if Dr. McGovern could identify the non-respondents in the survey. Dr. McGovern said that information was yet to be captured. Another member asked about the high percentage of laboratories that did not have a clinical consultant. Another member responded it could be due to a misunderstanding concerning the functions of a clinical consultant. Another member said the need for clinical consultation differs with respect to laboratory setting (independent laboratory, hospital laboratory or reference laboratory). Dr. McGovern responded by stating there is a need for clinical consultants in all laboratories because requests come from all types of physicians who have different levels of knowledge about genetic testing.

Report to CLIA on the SACGT– Addendum L

Dr. Patricia Charache, Johns Hopkins Medical Institutions, reviewed the history behind the creation of the SACGT. She emphasized there is a growing public concern about genetic testing and its social, as well as medical risks. She summarized the recommendations made by the SACGT at its last meeting on August 4, 2000. The SACGT identified four levels of genetic testing and correlated those levels to the amount of oversight necessary through Institutional Review Board (IRB), CLIA or FDA. The Committee identified a triage plan for the FDA review of genetic tests. Teams were established and working groups created to report on specific topics, and SACGT identified additional areas of concern to be discussed at future meetings. Finally, she discussed how CLIA and the SACGT interface, pointing out that CLIA has special expertise in laboratories, while SACGT has special expertise in the medical/social area of genetic testing.

Committee Discussion

One member commented that a major concern in genetic testing is patents. At present, there is no information available when a patent application is being developed. If another company or laboratory begins testing, it is possible that it will be precluded from testing, if there is a patent on the method. The member said there will be a shift to well-funded laboratories due to the effects of patents. Another member proposed FDA oversight, and Dr. Charache noted the concern associated with the FDA oversight burden. She said the IRBs need appropriate oversight and institutions can provide guidance and documentation. Dr. Charache said if the IRB is set up with institutional support, oversight could be provided. One member said that accessability is also an important issue. Another member commented that small laboratories have difficulty providing training because of the overlay of bureaucracy. A member said there is also the matter of research in practice sites, solely to obtain specimens for controls. In these cases reports should not be provided to the patients or to the clinicians. Anonymity is necessary to exempt these studies from CLIA and IRB oversight. Dr. Charache noted the CLIA regulations specify the laboratory director is responsible for tests being conducted, and this includes the appropriateness of the test methodology.

CDC Genetics Laboratory Forum – Addendum M

Dr. Michael Watson, Washington School of Medicine, reported on the CDC Genetics Laboratory Forum meeting in Atlanta on September 8, 2000. The Forum had representatives from 12 professional groups. Dr. Watson commented there are many technologies with many uses in healthcare, and most of these don't raise the concerns expressed by the SACGT. He pointed out the goal to include or integrate testing into the practice of medicine. He emphasized genetic testing and associated technology is evolving and changing rapidly and used the discovery of the cystic fibrosis gene as an example, pointing out it took only 15 years from the discovery of the gene to develop testing which currently is available for 60 mutations. In addition some 500 mutations are known. He said at the beginning of this discovery, testing was family-based but, as the test evolved, the target population changed to individuals at risk, although the initial use was diagnostic and to identify carriers. Now, as testing for known mutations increases, the significance of each mutation becomes important. He said we now evaluate populations to determine the incidence of mutations, and the sensitivity changes based on the population.

Dr. Watson discussed the proposed SACGT genetic test oversight algorithm and reported that when the participants at the Forum evaluated the model using six genetic tests, the model was unable to address the concerns identified in the algorithm. He discussed the Notice of Intent (NOI) and commented that, under CLIA, all genetic tests would have the same requirements. He said the laboratory director's responsibility of documenting clinical validity is important. Dr. Watson said tests should be ordered by qualified personnel, and all medical procedures should require informal consent, but neither consent requirements nor the need for clinical information should compromise specimen integrity. Laboratories should not be required to provide counseling to patients but should work with providers to ensure appropriate use of test services. Finally, pre-analytical and post-analytical concerns should be focused on constitutional testing and PT should be required.

Genetic Testing Notice of Intent (NOI) Comments – Addendum N

Dr. Joe Boone, Assistant Director for Science, DLS, PHPPO, CDC, presented an overview of the comments received concerning the NOI. He noted that 818 total comments were received, with specific comments addressing 152 issues. In general, the comments were somewhat negative, with commenters expressing concern that genetic testing was singled out for regulation. The following seven issues received the most comments:

- laboratory documentation of informed consent
- laboratory providing counseling/consultation
- personnel qualifications/responsibilities
- definition/categories of genetic testing specialty
- authorized person ordering a genetic test
- clinical validity
- confidentiality

Dr. Boone reviewed the time-line for implementing the CLIAC genetic testing recommendations and suggested that CLIAC form a Genetic Testing Workgroup to evaluate the NOI comments.

CLIAC appointed the following members to the Genetic Testing Workgroup: Dr. Timothy O'Leary, Dr. Patricia Charache, Dr. Lawrence Silverman, Dr. Ronald Luff, Dr. Andrea Ferreira-Gonzalez, Mr. Stewart Richardson, and Dr. Jaime Frias. The Committee also suggested that Dr. Margaret McGovern participate, as well as others with experience and expertise in genetic testing.

Public Comment – Addendum O

Dr. Deborah Leonard, representing the Association of Molecular Pathology (AMP), spoke on the impact of implementing the proposed revisions to the CLIA requirements published in the NOI. She said the AMP's concerns focus on three issues: the definition of genetic testing; regulations that are important for all laboratory testing, without singling out genetic testing; and requirements that will increase the cost of testing and delay the time required to report results. She urged that some of the proposed regulations be reconsidered, and suggested that the proposed regulations be confined to testing for inherited conditions.

Date for the next CLIAC meeting: February 7-8, 2001.

I certify that this summary report of the September 27-28, 2000, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.

/S/ Toby L. Merlin, M.D.
Chairman