Clinical

Laboratory

Improvement

Advisory

Committee

Summary Report

May 28-29, 1998

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Clinical Laboratory Improvement Advisory Committee

May 28 - 29, 1998

Summary

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Record of Attendance

Committee Members
Dr. David Baines
Dr. Thomas Bonfiglio
Dr. Lemuel Bowie
Dr. Ronald Cada
Dr. Patricia Charache
Dr. Susanne Gollin
Dr. Verlin Janzen
Dr. Bereneice Madison
Ms. Diana Mass
Dr. Toby Merlin
Dr. Glenda Price
Ms. Sharon Radford
Dr. Morton Schwartz
Mr. Elliott Segal
Dr. Ulder Tillman

Ex Officio Members
Dr. Carlyn Collins, CDC
Dr. Steven Gutman, FDA
Ms. Judith Yost, HCFA

Liaison Representatives
Dr. Fred Lasky (HIMA)

Executive Secretary
Dr. John Ridderhof (representing Dr. Edward Baker)

Centers for Disease Control and Prevention
Ms. Nancy Anderson
Dr. Rex Astles
Ms. Genoria Bridgeman
Ms. Carol Bigelow
Dr. Joe Boone
Ms. Diane Bosse
Ms. Cheryl Coble
Ms. Carol Cook
Ms. Sharon Granade
Dr. Ed Holmes
Dr. Adam Manasterski
Dr. John Ridderhof
Ms. Renee Ross
Dr. Shahram Shahangian
Ms. Marianne Simon
Mr. Darshan Singh
Mr. Gregory Smothers
Dr. Steven Steindel
Ms. Glennis Westbrook
Ms. Rhonda Whalen
Ms. Laurina Williams

Clinical Laboratory Improvement Advisory Committee

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

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

The Committee consists of 20 members, including the Chair. Members are selected by the Secretary from authorities knowledgeable in the fields of microbiology, immunology, chemistry, hematology, pathology, and representatives of medical technology, public health, clinical practice, and consumers. In addition, CLIAC includes three ex officio members, or designees: the Director, Centers for Disease Control and Prevention; the Commissioner, Food and Drug Administration; the Administrator, Health Care Financing Administration; and such additional officers of the U.S. Government that the Secretary deems are necessary for the Committee to effectively carry out its functions. CLIAC will also include a non-voting liaison representative who is a member of the Health Industry Manufacturers Association and such other non-voting liaison representatives that the Secretary deems are necessary for the Committee to effectively carry out its functions.

Due to the diversity of its membership, CLIAC is at times divided in the guidance and advice it offers to the Secretary. Even when all CLIAC members agree on a specific recommendation, the Secretary may not follow their advice due to other overriding concerns. Thus, while some of the actions recommended by CLIAC may eventually result in changes to the law, the reader should not infer that all of the advisory committee's recommendations will be automatically accepted and acted upon by the Secretary.

Welcome and Introductory Information

The meeting was called to order by CLIAC Chair Dr. Morton Schwartz. The Committee members made self-introductions and disclosure statements of their relevant financial interests as they relate to the topics to be discussed during the CLIAC meeting. Dr. John Ridderhof, acting as Executive Secretary for Dr. Edward Baker, welcomed the Committee, and thanked the Genetic Testing Subcommittee which met on May 27 - 28, 1998.

Presentations and Committee Discussion

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS OF 1988 (CLIA) UPDATE

Health Care Financing Administration (HCFA) **Addendum C-1**

Ms. Judy Yost, Director of Outcomes and Improvement, HCFA, presented a status report on CLIA implementation. She reviewed laboratory demographics, including laboratories that are accredited by a HCFA-approved accrediting organization, according to the CLIA statistics. She reported that HCFA has completed three cycles of inspections, and indicated that although the most frequently cited deficiencies remain the same, the percentage of laboratories receiving them is decreasing. The alternative quality assurance surveys forms have been updated, resulting in a more streamlined version which decreases the amount of documentation that must be provided by the laboratory.

Ms. Yost next reported that HCFA has a task force for fraud and abuse investigations, and emphasized that these investigations are independent of CLIA inspections. The fraud and abuse investigations performed by a medical reviewer or carrier are generally done electronically on a sample of laboratories. She also noted that Medicare/Medicaid reimbursement for laboratory tests is being denied for laboratories that are not appropriately certified under CLIA to perform the services. Approximately 80% of the Medicare money inappropriately being paid has been reduced, and 10,000 more laboratories are now registered under CLIA.

The last update presented by Ms. Yost was the status of the CLIA regulations under development. The reinventing government, or REGO regulation was published on May 14, 1998. This regulation clarified several items in the final CLIA regulations, including the educational approach to proficiency testing, the self-assessment survey and the outcome-oriented inspection process. The regulation to extend the dates for the quality control requirements is undergoing Department review for clearance. The laboratory registry for 1997 will be available in the near future and can be accessed via the HCFA website (www.hcfa.gov). Ms. Yost ended by noting that the HCFA CLIA computers have been updated for the millennium.

Food and Drug Administration (FDA)

Dr. Steven Gutman, Director, Division of Clinical Laboratory Devices, Office of Device Evaluation, Center for Devices and Radiological Health, described the regulations and processes for FDA's evaluation of clinical laboratory tests prior to marketing these products. He began with the Medical Device Amendments of 1976, which established the premarket notification [510(k)] process for review of Class I and II devices, and the premarket approval (PMA) process for the review of Class III devices. The 510(k) process is a paper review to evaluate the accuracy, bias, sensitivity, and specificity of a device and determine substantial equivalence to a similar product already on the market. The PMA process is used to prove that a device is safe and effective *de novo*, and is used for devices that are not equivalent to a previously approved device and are determined to be of high risk. It includes an evaluation of the diagnostic sensitivity and specificity of the product, and reflects the intended use of the device. The 510(k) review process is used much more frequently than the PMA process for new laboratory tests.

Dr. Gutman explained that since 1993, new laws and regulations have resulted in a number of changes to FDA's review processes. Information on these new programs may be obtained on the FDA's website (www.fda.gov/cdrh) or by calling 1-800-638-2041. The Quality Systems Regulations (QSR) and FDA Modernization Act of 1997 (FDAMA) have directly affected the way in which products are reviewed and the determination as to whether or not a premarket review is even performed. The FDAMA calls for a risk-based restructuring of FDA's workload, and a number of revisions to the 510(k) review process [510(k) paradigm]. Changes to the PMA process are smaller in scope. In step one of the 510(k) paradigm, certain Class I and II devices that are identified as being low risk are exempt from review. A list of 130 devices (measuring a wide variety of analytes) that were determined to be exempt was published in February of 1998 (along with some exemptions to the exemption). The next step in the revised process uses QSR's to replace the premarket review for some submissions. A special 510(k) review is performed when there are certain product modifications. If the product modification results in a change in performance or labeling, a review is performed. However, if the modification does not result in a change in performance or labeling, no submission is required. The third step in the 510(k) paradigm includes the use of an abbreviated 510(k) for some product reviews. In this process, the enhanced use of standards replaces part or all of the review process. The mechanics of this process are still being refined.

Centers for Disease Control and Prevention (CDC) **Addendum C-2**

Dr. Carlyn Collins, Director of the Division of Laboratory Systems (DLS), Public Health Practice Program Office, asked the CLIAC to consider whether CLIA has a responsibility to ensure that laboratory computer systems are accurate and operational in the year 2000. She introduced Ms. Daphne Walters, the CDC Year 2000 Coordinator, who briefly reported on potential scenarios relative to laboratory instrumentation that contain the date and time embedded on microchips, and what should be done to prevent any problems when the millennium occurs. Several CLIAC members suggested mechanisms by which information could be provided to laboratories regarding

this situation. These included working with proficiency testing providers, professional laboratory organizations, large reference laboratories, vendors and distributors of instruments. These groups could all be used to alert laboratories that if they use instrumentation containing date and time, they need to be aware of potential problems. It was also suggested that making information available on the Internet, and using surveyors to inform laboratories should be considered.

GENETIC TESTING

Genetic Testing Subcommittee Report — Addendum C-3

Dr. Wendell O'Neal summarized the activities of the May 27 - 28 meeting of the Genetic Testing Subcommittee. He explained that the Subcommittee formed three workgroups based on the pre-analytic, analytic, and post-analytic phases of genetic testing, and noted that a significant portion of the Subcommittee meeting was dedicated to allowing each of the workgroups to independently discuss issues pertaining to their phase of testing. Because the full Subcommittee did not have time to consider all of the topics addressed by each of the workgroups, the Subcommittee report presented by Dr. O'Neal to the CLIAC for consideration included only those issues which had been addressed by the Subcommittee. In giving this report, Dr. O'Neal identified the issues which the Subcommittee needs additional time to discuss.

CLIAC Recommendations per Subcommittee Report — Addendum C-4

The CLIAC considered each of the issues noted in the Subcommittee report, and in most cases, either agreed with the suggestions made by the Subcommittee or made slight changes to the proposals in the report. The CLIAC made the following recommendations:

Pre-analytic phase

- Appropriateness of tests - add to the CLIA regulations "Appropriate clinical information must be provided on the request form".
- Specimen handling/preparation - adequately addressed in the CLIA regulations.
- Confidentiality - although adequately addressed for the pre-analytic phase of testing, decision was deferred pending discussion of confidentiality for other phases of testing.
- Communication with provider community - adequately addressed in the CLIA regulations.
- Ordering additional tests - for clarification, changed "Ordering additional tests" to "Followup tests", to indicate sequential ordering of a panel of tests or confirmatory tests. Although it was felt that this is adequately addressed in the CLIA regulations, an additional item was added to the list for further discussion - that being "Nonwritten requests for new tests".
- Ownership of specimen - not under the purview of CLIA, unless subsequent discussion suggests reconsideration of this position.
- The following pre-analytic issues remain for Subcommittee consideration:
  -- Informed consent
  -- Consent to re-use specimens

-- Genetic counseling
-- Nonwritten requests for new tests

Analytic phase

- Personnel qualifications
  Laboratory Director:
  -- Be an M.D., or D.O. with certification in clinical and/or anatomic pathology, or
  -- Be an M.D., D.O. or Ph.D. and be certified in medical genetics, or
  -- Be an M.D. or D.O. and have two years directing or supervising high complexity testing, or
  -- Hold a doctorate degree in chemistry, physical, biological, or clinical laboratory sciences, be certified, and have two years of supervisory experience in high complexity testing, or
  -- Be grandfathered.
  Technical Supervisor - for genetic testing:
  -- Be an M.D., or D.O. with certification in clinical and/or anatomic pathology and 2 years sub-specialty training in genetics plus 2 years supervisory experience in high complexity genetic testing, or 4 years supervisory experience in high complexity genetic testing in the relevant subspecialty, or
  -- Be an M.D., D.O. or Ph.D. and be certified in the appropriate medical genetics specialty and have 2 years experience directing or supervising high complexity genetic testing in the relevant subspecialty, or
  -- Hold a doctorate degree in chemistry, physical, biological, or clinical laboratory sciences, and have 4 years of training or supervisory experience in high complexity genetic testing in the relevant subspecialty, or
  -- Be grandfathered.
- The following analytic issues remain for Subcommittee consideration:
  -- Personnel qualifications for General Supervisor, Clinical Consultant, Genetic Counselor, and Testing Personnel
  -- Personnel responsibilities
  -- Contamination
  -- Specimen integrity
  -- General and specific QA/QC measures
  -- Proficiency testing
  -- Validation of tests
  -- Re-use of previously tested specimens
  -- Confidentiality

Post-analytic phase

- Since no issues were addressed by the complete Subcommittee due to a lack of time, all items for this phase of testing remain for Subcommittee consideration.

Committee Discussion of Additional Issues **Addendum C-4**

To provide assistance to the Genetic Testing Subcommittee as it further considers the pertinent issues, Dr. Schwartz asked the CLIAC for input on a number of items that the Subcommittee has not yet fully addressed. In addition, the CLIAC discussed and revised the working definition of a genetic test, which was drafted at the January 1998 meeting. A summary of the discussion of the additional issues and revisions to the genetic test definition are part of the CLIAC report.

Genetic test definition

In considering the working definition of a genetic test, several Committee members suggested that it was too broad and nonspecific as written. It was decided that two more specific definitions were needed instead of the general definition. After discussion, the following terms and their corresponding definitions were recommended to replace the earlier working definition of a genetic test:

- *Molecular genetic and cytogenetic test* - The analysis of human DNA, RNA, and chromosomes, in order to detect heritable or acquired disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations.
- *Biochemical genetic test* - The analysis of materials derived from the human body, including human proteins and certain metabolites, predominantly used to detect inborn errors of metabolism, heritable genotypes, or mutations for clinical purposes. [Tests that are used primarily for other purposes, but may contribute to diagnosing a genetic disease (e.g. blood smear, certain serum chemistries), would not be covered by this definition.] Such purposes include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations.

Additional issues discussed

The CLIAC made suggestions on a number of analytic and post-analytic issues for the Genetic Testing Subcommittee to consider. For some items, additions to the CLIA regulations were recommended and for other items, amendments to the guidelines for surveyors and laboratories were suggested. For some issues, the Committee discussed whether revisions might be made to the general CLIA regulations, to apply to all laboratory testing.

- General quality control (QC) - adequately addressed in the CLIA regulations
- Specific QC - suggested adding to the regulations "A specimen should be stabilized but not processed until the clinical information becomes available". For the details regarding the specific information needed to perform a genetic test, the Committee recommended additions to the surveyor guidelines, which may also be used by laboratories. The CLIAC proposed several requirements be added to the regulations for controlling contamination when performing nucleic acid amplification procedures and suggested that these issues might be relevant for the general laboratory QC requirements.
- Specimen integrity - adequately addressed in the CLIA regulations, but recommended adding specific information on specimen identification and demographics to the surveyor

guidelines.

- Proficiency testing (PT) and alternatives - adequately addressed in the CLIA regulations where PT is required, but since PT is not required for genetic testing, requested that a list of genetic tests for PT consideration be developed. Suggested that options for alternative means to evaluate performance when no PT exists be included in the guidelines.
- Special reporting requirements - recommended that language be included in the CLIA regulations to require that laboratory reports be written in a manner to ensure that a health care provider who is not a geneticist can understand the report. Recommended adding specifics to the regulations to include items that must be part of the genetics laboratory report (including the signature of the laboratory director or technical supervisor when appropriate, and a means to quickly contact either of them), with additional items mentioned for molecular genetic testing.

Public Comments

There were no public comments for the CLIAC regarding genetic testing.

ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

Introduction and CDC Update **Addendum C-5**

Dr. Carlyn Collins, DLS, and Dr. Susie Meikle, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, presented information on CDC's activities in implementation of the Fertility Clinic Success Rate and Certification Act of 1992 (FCSRCA). Dr. Collins described the CDC mandates that are in the law, and discussed the model certification program for embryo laboratories being developed by the DLS. Dr. Meikle reported on the annual pregnancy success rate reporting and publication, which is being carried out by the DRH. It was pointed out to the committee that the question of applicability of the CLIA statute to ART embryo laboratories has been raised by professional organizations, consumer groups, and members of Congress.

Presentations by Technical Experts **Addenda C-6, C-7**

Presentations on technical aspects of ART embryo laboratories were made by two directors of such laboratories. The presenters described procedures and considered whether these procedures fit within the CLIA definition. Thomas Pool, Ph.D., H.C.L.D., Fertility Center of San Antonio, San Antonio, Texas explained that diagnostic information is generated when performing ART embryo laboratory procedures, including the examination of a patient's follicular fluid, oocyte evaluation, and fertilization assessment (C-6). He stated that this type of health information may be used to diagnose infertility and affect future medical therapy, which would be covered under CLIA by definition. Jacob Mayer, Ph.D., H.C.L.D.,The Jones Institute for Reproductive Medicine, Norfolk, Virginia, described embryo laboratory procedures as part of a patient's

treatment protocol for infertility (C-7). He stated that diagnostic information is not provided at any point in the process, and therefore, CLIA would not apply.

Public Comments

The technical presentations were followed by an opportunity for public comment. Representatives from the American Association of Bioanalysts (AAB), the American Society for Reproductive Medicine (ASRM), the Society for Assisted Reproductive Technology (SART), and RESOLVE, a consumer organization providing support to infertile couples, provided additional information for CLIAC consideration. The AAB representative supported the position that ART embryo laboratory procedures fit the CLIA definition of laboratory testing, and should be subject to the mandatory CLIA standards. The ASRM and SART representatives made public comments that ART, including the procedures performed in the embryo laboratory, is part of clinical medicine, and that CLIA does not apply. The RESOLVE representative commented that the organization is in favor of uniform regulations, standards, and guidelines which do not limit access to medically appropriate treatment for infertile patients.

Committee Discussion

Dr. Schwartz asked for discussion and questions, but stressed that no recommendations would be made by CLIAC at this time. He invited the technical experts and public commentors to participate in the discussion, which included the following:

- Several CLIAC members compared the ART process to transfusion services provided to patients and noted that blood bank testing is covered by CLIA.
- CLIAC members expressed some concern that ART laboratories are not subject to regulation. The SART representative responded that although it is a voluntary program, approximately one third of the ART laboratories that are members of SART are accredited by the College of American Pathologists (CAP) program for reproductive laboratories and are subject to CAP oversight. In addition, the SART Board of Directors has voted that CAP accreditation for reproductive laboratories will be mandatory for future membership in SART.
- A CLIAC member noted that CAP is concerned specifically with laboratory testing, and stated that this organization (which has a certification program for embryo laboratories) would not be involved in oversight of reproductive laboratories unless laboratory testing is performed.
- The ASRM/SART representatives stated that they are not opposed to regulation of the ART laboratory, if the requirements are specific and appropriate. Several CLIAC members responded that CLIA includes laboratory specialty requirements, such as the standards under discussion at this meeting for genetic testing.
- One CLIAC member suggested that the model certification program for embryo laboratories being drafted as part of the implementation of the FCSRCA could be inserted into the CLIA requirements with a minimum number of changes.
- The subject of outcome studies to measure the performance of ART laboratories was

raised. The annual CDC pregnancy success rate report was briefly discussed as an outcome measure of ART practices.

Concluding Remarks

Dr. Schwartz announced that the dates for the next CLIAC meeting would be September 17 - 18, 1998, and adjourned the CLIAC meeting.

I certify that this summary report of the May 28 - 29, 1998, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.

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