Clinical

Laboratory

Improvement

Advisory

Committee

Summary Report

February 11-12, 2004

Embassy Suites Hotel
Atlanta, Georgia

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Clinical Laboratory Improvement Advisory Committee
February 11-12, 2004
Summary Report

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Record of Attendance

Committee Members Present

Dr. David Sundwall, Chair
Dr. Kimberle Chapin
Dr. Barbara Robinson-Dunn
Dr. Kathryn Foucar
Dr. Ronald Gagné
Ms. Paula Garrott
Dr. Peter John Gomatos
Dr. Cyril (Kim) Hetsko
Dr. Anthony Hui
Ms. Cynthia Johns
Mr. Kevin Kandalaft
Dr. Michael Laposata
Dr. Ronald Luff
Dr. Margaret McGovern
Dr. Valerie Ng
Dr. Jared Schwartz
Mr. Albert Stahmer
Dr. Ronald Valdes
Dr. Jean Amos Wilson

Committee Member(s) Absent

Dr. Alice Weissfeld

Executive Secretary

Dr. Robert Martin

Ex Officio Members

Dr. Toby Merlin, Centers for Disease Control and Prevention (CDC)
Ms. Judith Yost, Centers for Medicare & Medicaid Services (CMS)
Dr. Steven Gutman, Food and Drug Administration (FDA)

Liaison Representative - AdvaMed

Ms. Luann Ochs, Roche Diagnostics Corporation

Centers for Disease Control and Prevention

Ms. Nancy Anderson
Ms. Pam Ayers
Ms. Diane Bosse
Ms. Carol Bigelow
Ms. Kathy Cahill
Dr. Bin Chen
Ms. Carol Cook
Ms. Judy Delany
Ms. Joanne Eissler
Ms. MariBeth Gagnon
Ms. Sharon Granade
Dr. Tom Hearn
Ms. Stacey Holt
Ms. Heather Horton
Dr. Dale Hu
Dr. Ira Lubin
Mr. Kevin Malone
Dr. Adam Manasterski
Ms. Leslie McDonald
Ms. Anne Pollock
Ms. Andrea Pratcher
Dr. Eunice Rosner
Mr. Darshan Singh
Dr. Suzanne Smith
Dr. Julie Taylor
Mr. Howard Thompson
Ms. Pamela Thompson
Ms. Glennis Westbrook
Ms. Rhonda Whalen

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

Ms. Valerie Coppola (CMS)
Ms. Cecilia Hinkel (CMS)
Ms. Penny Mattingly (CMS)
Ms. Raelene Perfetto (CMS)
Ms. Kathy Todd (CMS)
Ms. Virginia Wanamaker (CMS)
Ms. Carol Benson (FDA)
Dr. Jean Cooper (FDA)
Dr. Elliot Cowan (FDA)
Ms. Laura Epstein (FDA)

In accordance with the provisions of Public Law 92-463, the meeting was open to the public. Approximately 35 public citizens attended one or both days of the meeting.

Clinical Laboratory Improvement Advisory Committee

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

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

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

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

CALL TO ORDER – INTRODUCTIONS/FINANCIAL DISCLOSURES

Dr. David Sundwall, CLIAC Chair, welcomed the Committee members and called the meeting to order. Dr. Suzanne Smith, Acting Director, Public Health Practice Program Office (PHPPO), Centers for Disease Control and Prevention (CDC), also welcomed the members, acknowledged the public health importance of their work, and congratulated them on the Committee's accomplishments thus far. She expressed appreciation of laboratorians' thorough understanding of quality systems and processes and noted this knowledge is invaluable and could serve as a model for assessing quality in other areas of public health. Dr. Smith commented that much of laboratorians' work in public health has been unrecognized because those outside the laboratory arena lack a complete understanding of what laboratories do. She stated the time has come for laboratorians to shine as the public health community learns what they have to offer insofar as a comprehensive approach to delivering services in a manner that serves customers, improves health, and assures quality. Dr. Sundwall briefly explained the requirements and process for public disclosure, including those for conflicts of interest. All members then made self-introductions and financial disclosure statements relevant to the topics to be discussed during the meeting.

PRESENTATIONS AND COMMITTEE DISCUSSIONS

■ Post-market Activities - Industry Perspective *Addendum A*

Ms. Luann Ochs, AdvaMed Liaison to CLIAC and Director, Regulatory Submissions, Near Patient Testing, Roche Diagnostics Corporation, presented an overview of the laboratory device industry's post-market activities. She discussed the Quality System Regulation, 21 CFR Part 820, which requires manufacturers to establish procedures for receiving and evaluating customer complaints and implementing corrective and preventive action (CAPA). She also described the Medical Device Reporting (MDR) Regulation, 21 CFR 803, which requires manufacturers to report to FDA when a device has caused or contributed to a death or serious injury. Ms. Ochs used flowcharts to demonstrate Roche Diagnostic Corporation's processes for evaluating customer complaints and product failures. She explained the principles of risk management and how they are used throughout product development, referring to the FDA's August 1999 guidance document "*Device Use Safety, Incorporating Human Factors in Risk Management.*" She concluded her presentation with a chart summarizing quality processes used by industry to identify, mitigate, and eliminate product risk.

Committee Discussion

- A member asked if post-market processes include a mechanism to evaluate non-technical complaints or to differentiate biological versus technical problems. Examples were given of out of range glucose or abnormal INR results. Ms. Ochs replied that in these instances,

consumers are lead through reflex scripts to troubleshoot the problem, such as whether or not controls have been run and if reagent strips have been stored properly and are in date. If a technical reason for the out of range or abnormal result cannot be identified, the customer is advised to consult the ordering physician. In the event a device has contributed to patient harm, the situation is reviewed by the device manufacturer's staff physician.

- Another member inquired if the manufacturer tracks "user misunderstanding." Ms. Ochs responded that all complaints are tracked and evaluated using trend analysis. If it is determined that "user misunderstanding" is due to confusing instructions, the instructions are clarified.
- Members inquired whether complaints are separated by who reports them, e.g., problems reported by physicians versus those reported by a patient. Ms. Ochs replied that calls are categorized by who places the complaint, e.g., healthcare professional, consumer, or other, and noted the telephone numbers used by professionals and consumers for reporting complaints are different. A member then asked if the process for evaluating problems differs for waived and nonwaived tests. Ms. Ochs assured the Committee that the CAPA process is the same for waived and nonwaived tests.
- Dr. Sundwall asked Ms. Ochs to identify the most commonly performed waived tests by volume, and whether this high degree of post-market monitoring of waived testing is performed industry-wide. Ms. Ochs estimated that urinalyses, glucose, pregnancy, fecal occult blood, and group A streptococcal antigen tests are performed most frequently. She acknowledged that while each company may have slightly different post-market monitoring processes, the basic principles apply to all manufacturers.

■ Post-market Activities - FDA Perspective

Addendum B

Dr. Steve Gutman, Director, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), Center for Devices and Radiological Health (CDRH), FDA, briefed the Committee on FDA's post-market activities. He began by reviewing the requirements of the Medical Device Amendments of 1976, which provide for the safety and effectiveness of medical devices intended for human use. He then shared CDRH's strategic plan to monitor devices for adverse events through their "total product life cycle" and to facilitate better knowledge management, both internally and externally. Dr. Gutman also explained the process for issuing a recall or removal of a device from the marketplace. He emphasized that recalls are viewed as learning tools and may be an indicator of the effectiveness of a manufacturer's corrective action system. Because there are no perfect devices, FDA is more concerned with manufacturers that have no recalls. Dr. Gutman then discussed manufacturers' responsibilities for voluntary and under MDR, the mandatory medical device reporting of problems and described some of the surveillance systems FDA uses to monitor device performance, e.g., MedWatch, MedSun Pilot, and LabSun Pilot. He concluded his presentation by noting the Agency's underutilization of post-market regulatory tools and the commitment of OVID to correct this oversight.

Committee Discussion

- A member noted that some companies market devices both domestically and internationally and inquired whether FDA has considered exchanging information with the European Union (EU) to increase its data set related to device performance. This member also commented on the lack of a common exchange system for data, particularly among foreign governments. Dr. Gutman acknowledged the market is indeed global and informed the Committee of FDA's current discussions with representatives from the United Kingdom (UK) regarding international collaboration. The UK has a strong post-market vigilance program and has expressed interest in setting up a special users' group to connect the UK with the United States. Dr. Gutman also noted FDA's recent participation on a global harmonization task force, as well as its preliminary interactions with Canada.
- Another member commented that most post-market data is passively collected and relies on others to proactively proceed through a rigorous reporting process. The member suggested CDC's National Nosocomial Infections Surveillance System as a good model for a post-market surveillance system.
- One member asked if FDA has expanded or is considering expanding LabSun to include "non-laboratory" sites performing waived testing. Dr. Gutman stated this has not been considered because of concerns that these sites may be less accessible and they may lack the experience to recognize device problems.
- Another member inquired whether there is a budgetary commitment to expand LabSun's post-market surveillance efforts. Dr. Gutman affirmed this commitment, but acknowledged the funding may not be sufficient. Alternative mechanisms are being examined that may be more cost-effective.
- Dr. Merlin mentioned CDC's activities related to the post-market surveillance of the OraQuick® Rapid HIV-1 Antibody Test. He acknowledged the device is robust, but the surveillance focuses on the system in which the device is being used, particularly the performance by CDC-trained individuals. He noted the expense associated with doing active surveillance and pointed out the necessity for being selective in monitoring tests that are high risk, error prone, and may require intensive oversight. He also referred to CDC's activities involving the Institute for Quality in Laboratory Medicine (IQLM), noting that one of the Institute's purposes is to bring industry and physicians together to establish voluntary surveillance networks for gathering data.

■ Certificate of Waiver - Data/Surveys *Addendum C*

Ms. Judy Yost, Director, Division of Laboratory Services, Centers for Medicare & Medicaid Services (CMS), began her presentation by providing background information related to waived testing and provider-performed microscopy procedures (PPMP). She then gave an overview of CMS's Certificate of Waiver (COW) pilot project and expanded pilot plan that assessed testing in 270 waived and 190 PPMP laboratories. Ms. Yost discussed the findings of the pilot and presented CMS's recommendations and actions. She stated that a new project, initiated April 2002, entails surveying 2 percent of all waived laboratories each year for three years and will collect more comprehensive information than the pilot. The information will be evaluated to determine the effectiveness of the educational efforts CMS has provided to laboratories and help

determine future needs and actions. Ms. Yost provided a summary of the 2002 survey findings and preliminary data from the 2003 survey, stressing although there have been measurable improvements in waived laboratories since the pilot project, quality issues still remain. In particular, she noted a high turnover of testing personnel in these laboratories and thus an on-going need for education on CLIA and training in laboratory procedures. Ms. Yost concluded her presentation by sharing some of the positive feedback CMS has received on the survey process.

Committee Discussion

- Members complimented CMS on the information gathered and on the continuing efforts to collect this critical information.
- Several members requested clarification on Medicare and Medicaid reimbursement policies for waived testing and one member asked if the COW survey findings could be tied to reimbursement. Ms. Yost explained that Medicare/Medicaid billing codes for waived tests are unique and to be reimbursed for the testing, the facility must have a CLIA certificate. She acknowledged discussions about "paying for quality" have taken place over the years, but no decisions have been made concerning changes to the current payment policies.
- Dr. Sundwall inquired whether there are any private payers that require Certificate of Waiver documentation as a condition of reimbursement for laboratory tests. A Committee member volunteered to investigate this topic as a follow-up item.
- One member expressed the opinion that the description of a waived test as one that does no harm is unrealistic; all tests have the potential to do harm. Another member, referring to CMS's COW data, commented the percentage of surveyed laboratories operating in a manner posing immediate jeopardy to human health is unacceptably high, if the number of potentially affected patients is considered.
- Several members agreed education is important and suggested manufacturers provide CD-ROMs with test kits; the CD-ROMs could include instructions for performing the test procedure as well as when and how to perform quality control (QC) procedures. One member added that providing mechanisms such as downloadable QC charts on a CD-ROM would provide assistance to physician office laboratory (POL) personnel who are unsure of how to comply with regulations or standards. This approach might also decrease instances of improper training from one employee to another. Another member suggested education without oversight would only be minimally effective.
- One member inquired whether punitive action is taken when waived laboratories are discovered to have quality problems, reasoning that without punitive action, laboratories might have no incentive to improve. Ms. Yost emphasized CMS has authority to require waived laboratories to correct problems found during the inspection process.
- Dr. Sundwall noted the importance of waived tests and the contributions they offer to patient care, but stressed there are risks. CMS data demonstrate effective surveillance is needed for these tests, particularly the post-market system approach. He suggested a component of that approach may be some level of regulatory oversight. A member pointed out that some physician laboratories would resist regulatory oversight of waived tests.
- Dr. Merlin commented that in providing training for the OraQuick® Rapid HIV-1 Antibody Test, CDC determined the degree of waived testing oversight by states is very heterogeneous. While some states have no requirements for waived testing, others require registration with the state health department. Several states have extensive regulations, and a few apply the

same requirements to both waived and moderately complex tests. As CMS data demonstrate, the laboratories in the states with more stringent standards had fewer deficiencies noted in the CMS survey data.

- Another member commented that unless the law is changed, many of the Committee's suggestions cannot be implemented. This member added that a consensus document of best laboratory practices would be a useful resource for waived laboratories.
- Dr. Sundwall suggested that public comments be heard prior to Dr. Barbara Goldsmith's presentation of the Waiver Workgroup Report.

PUBLIC COMMENT

Health Industry Distributors Association – Overview ***Addendum D***

Ms. Jennifer Alfisi, Director of Government Affairs, Health Industry Distributors Association

Committee Discussion

Dr. Sundwall inquired about HIDA's involvement in healthcare provider education. Ms. Alfisi responded that one of HIDA's roles is to educate its membership so they in turn can educate their healthcare provider customers. As an example, she cited a recent collaborative effort between the Association and CDC to assure providers were fully informed about the influenza vaccine. Ms. Alfisi assured the Committee that HIDA would welcome the opportunity to assist in efforts to educate waived testing sites on best laboratory practices.

■ Waiver Workgroup Report ***Addendum E***

At the September 2003 CLIAC meeting, a Waiver Workgroup was established following CLIAC's recommendation that federal agencies, industry, CLIAC, and other stakeholders should review pertinent waiver data and recommend to CLIAC appropriate changes to the waiver determination process and oversight of waived tests. Dr. Barbara Goldsmith, Chair of the Waiver Workgroup, reported on the Workgroup's January 16, 2004, meeting. She reviewed the charge to the Workgroup, listed the stakeholders (Workgroup members) who participated in the process, and presented the issues that were considered. The issues included studies needed to support waiver, specimen characteristics, test system characteristics, labeling, fail-safe/failure-alert mechanisms, QC, sales restrictions and post-waiver surveillance. At the Workgroup meeting to stimulate discussion, each issue was presented with proposals, taken from previous CLIAC recommendations, the FDA Waiver Guidance, the 1995 Notice of Proposed Rule-Making (NPRM), AdvaMed's Waiver Proposal, and public comments. Dr. Goldsmith gave an overview of these proposals, followed by a summary of the Workgroup's discussion and suggestions on each issue.

■ CLIAC Waiver Discussion *Addendum F*

Dr. Sundwall commended Dr. Goldsmith for an excellent overview of the Waiver Workgroup's suggestions. He reminded the Committee the authority for developing and issuing CLIA waiver rules and guidance was delegated to FDA on October 31, 2003, and emphasized the importance of providing recommendations to FDA at this time. Dr. Gutman likewise stressed the urgency of obtaining recommendations from CLIAC, explaining FDA is currently in the process of developing a Level 1 guidance document for waiver determinations. Thus, FDA will immediately consider CLIAC recommendations as it generates this preliminary guidance. As a reminder, Ms. Yost reviewed the statutory and regulatory requirements for waived testing and suggested CLIAC keep these requirements in mind when considering appropriate waiver criteria and oversight of waived testing. Dr. Merlin and Dr. Goldsmith then opened Committee discussion, presenting slides reiterating the Workgroup's suggestions. Committee members discussed each topic outlined in the report and provided their recommendations. In some cases, CLIAC agreed with the Workgroup's suggestions and adopted these as recommendations without modification. In other instances, there was significant discussion on a topic with varying viewpoints among Committee members. A summary of the relevant discussion and CLIAC recommendations for each topic follows, arranged in the order of the statutory waiver criteria of simplicity and having an insignificant risk of an erroneous result.

Demonstrating Simple

CLIAC discussed the test system and specimen characteristics that would meet the statutory criterion of requiring waived tests to be simple.

TEST SYSTEM CHARACTERISTICS

The Committee adopted the Waiver Workgroup recommendations without discussion.

CLIAC Recommendations

- Waived test systems should be fully automated, unitized, or self-contained and should provide direct read-out of results (quantitative tests) or distinct positive/negative endpoint (qualitative tests)
- Test systems with distinct color gradations should be considered for waiver only when studies demonstrate test performance by intended users is comparable to a traceable reference method
- The adequacy of any test system should be based on valid, empirical data

SPECIMEN CHARACTERISTICS

Committee members expressed varying views as to whether waived test specimens should be limited to direct, unprocessed specimens. While there was concern about expansion of specimen types to include those that would require "significant manipulation," e.g., centrifugation or evaluation of specimen quality or integrity, the Committee did not want to make a recommendation that would preclude the use of new technology. In this regard, some members recommended against exclusion of serum or plasma per se, as these and other specimen types may be considered in the future if technology that eliminates the need for specimen processing becomes available.

CLIAC Recommendations

- Waived test specimens are currently limited to direct unprocessed specimens, including capillary whole blood, urine, throat swabs, saliva/oral fluid, stool, and tissue biopsies. Although expansion of waived test specimens may be considered, CLIAC does not support specimen types that require significant pre-analytic manipulation/processing such as centrifugation and/or assessment of specimen quality and integrity
- At this time, the use of plasma and serum for waived testing are not recommended because the manipulation and centrifugation steps in processing increase the likelihood of errors. Future technology may reduce the degree of manipulation required for these specimens, warranting reconsideration

Demonstrating Insignificant Risk of an Erroneous Result

The Committee discussed the requisite studies, fail-safe/failure-alert mechanisms, quality control, and labeling to fulfill the statutory criterion that waived tests have an insignificant risk of an erroneous result.

FLEX STUDIES

- A member requested clarification of the definition of "risk" in the context of risk assessment and risk mitigation. Ms. Ochs responded the term relates to the risk of obtaining an erroneous result. Dr. Merlin further explained risk assessment and mitigation are standardized methods used by manufacturers for examining a test system to determine what could go wrong, performing an analysis of the likelihood of that occurring, and implementing mitigating steps to prevent or control such occurrences. The Waiver Workgroup recommended this approach as a standard for waived tests.
- One member suggested information related to risk assessment/mitigation should be included in test system labeling. Ms. Ochs commented that only relevant information should be included. She explained that frequently in the process of risk assessment/mitigation, corrective actions are taken by the manufacturer that eliminate potential test system problems. She stressed this information would be unnecessary and that labeling should be limited to what the user must understand to perform and interpret the test correctly.

CLIAC Recommendations

- Waived tests may need to be more robust than non-waived tests
- Potential sources of error need to be identified and studies should demonstrate that sources of error are controlled or mitigated
- As part of the waiver submission, manufacturers should include information on
  - Risk assessment (risk of erroneous results)
  - Likelihood of erroneous results
  - Measures provided or incorporated to mitigate risk

FAIL-SAFE/FAILURE ALERT MECHANISMS

The Committee agreed with the Waiver Workgroup's recommendations, but modified the language to emphasize the importance of evaluating external QC testing "over time."

CLIAC Recommendations

- Fail-safe mechanisms should ensure that a waived test system does not provide a result (lock-out) if the result exceeds the reportable range or any component malfunctions
- Lock-out features are the ideal fail-safe mechanism, but may not always be feasible
- When fail-safe mechanisms are not feasible, failure-alert mechanisms are critical and may serve as risk mitigation tools by notifying the operator of test system problems
- Manufacturers should provide built-in checks or QC materials whenever feasible
- If some components of waived test systems are not monitored internally
  - Electronic checks, when available, should be performed and evaluated at specified intervals
  - External QC should be tested at regular intervals and evaluated over time to monitor
    - Operator performance
    - Test system operation
    - Environmental conditions (e.g., temperature, humidity)

EXTERNAL QUALITY CONTROL

- CLIAC engaged in extensive discussion regarding the use of external QC testing as a failure-alert mechanism and considered a variety of ways to increase the likelihood that QC for waived testing will be performed.
- Dr. Merlin reported the Waiver Workgroup strongly encouraged manufacturers to include QC materials in test kits whenever possible. CLIAC members also felt it more likely the user would perform QC testing if these materials were provided along with the test kits.
- Ms. Ochs acknowledged the concern of the Workgroup and CLIAC members, but discussed a variety of reasons manufacturers may not be able to include QC materials in the test kits, such as differences in product storage requirements and the fact that test systems and QC materials are often purchased through medical distributors, rather than manufacturers.
- A Committee member asked if distributors might play a role in assuring end-users receive and test QC materials. In response, Dr. Sundwall suggested that the Health Industry Distributors Association (HIDA) give a presentation at the September 2004 CLIAC meeting.
- A member described this issue as "extremely vexing" and stated problems surrounding performance of external QC testing are only one aspect of the conundrum of waived tests. This member pointed out that when external controls are necessary, a test is no longer simple and opportunities for error are significant. A second member concurred and suggested manufacturers should work toward building QC into newly waived test systems.
- A Committee member inquired whether any of the waived laboratories surveyed by CMS that failed to perform QC testing per the manufacturer's instructions gave an explanation as to why QC was not performed. Ms. Yost responded this was primarily due to a general failure to follow the manufacturer's written instructions.

- One member proffered expense as part of the reason QC testing is not performed by some waived laboratories. The additional cost of purchasing QC materials or the time and resources required to test controls may not have been represented as part of the overall cost of waived testing.
- A member suggested changing test system labeling to reflect QC "must" be run, as opposed to "should" be run. Ms. Ochs responded manufacturers determine the necessary QC testing frequency through risk assessment. She suggested CLIAC not mandate external controls, but rather permit flexibility with respect to external QC to allow for technological advances.
- Several Committee members recommended integrating QC testing instructions within the test performance instructions to increase compliance.
- A member recommended, as waived tests evolve, manufacturers should focus on development of devices that employ a lockout feature and unitized test systems that have built-in QC. Ms. Ochs suggested that CLIAC should send a letter to AdvaMed specifically directing pertinent recommendations to the laboratory device industry **(*Addendum G-1*)**.

  CLIAC Recommendations

  When external QC is needed to monitor test system components
  - ♦ Regulatory guidance should address minimum frequency based on studies
  - ♦ Manufacturers should
    - Determine minimum frequency based on risk assessment and risk mitigation. As part of the risk assessment/mitigation, manufacturers should conduct stress studies evaluating
      - ◊ Lock-out features
      - ◊ Built-in QC
      - ◊ Internal process controls
      - ◊ Environmental (e.g., temperature) controls
      - ◊ Electronic QC
      - ◊ Sensitivity of built-in QC to analytical and test system errors
      - ◊ Ability to determine mishandling (e.g., dropping) of the device
      - ◊ Multiple skill levels of users
      - ◊ Stability (e.g., shelf life) of reagents/test systems
      - ◊ Lot-to-lot reproducibility
    - Specify minimum frequency in the test system instructions
    - Provide recommended levels of QC materials appropriate for medical decisions
    - Integrate QC instructions (including QC testing and evaluation) within the test system performance instructions
  - ♦ QC materials should be
    - Provided with, preferably in, test kits to facilitate the performance of QC testing
    - Ready-to-use or require only simple preparation
  - ♦ If QC materials are not provided, the manufacturer shall recommend sources for QC materials in the package insert

WAIVER STUDIES

- A Committee member inquired as to the type of training a manufacturer would provide to study participants, since variations in the amount of training and information provided could influence study outcome. Ms. Ochs explained the participants in a waiver study are limited to instructional material identical to that ordinarily provided to a customer purchasing the test.
- Considerable Committee discussion ensued regarding the Waiver Workgroup's suggestion that studies should be conducted on the intended sample type/matrix, specifically with respect to the phrase "whenever possible." Dr. Merlin commented, and CLIAC members agreed, that not including the specimen collection step may bias studies. They noted the importance of evaluating intended user performance at the site of intended use, including specimen collection.
- Ms. Ochs explained that as part of accuracy studies, manufacturers must sometimes supplement real patient specimens with contrived samples in order to challenge the cutoff of certain test systems. She further explained to evaluate precision across the sites, every site must test the same samples, which are contrived and set at medical decision levels. Thus, every site and every study participant will test these same samples over time during the study.
- The Committee also emphasized studies should demonstrate likely test performance for real specimens, from real subjects, in real time. Several members acknowledged that testing over time in a typical clinical setting could result in significantly different test performance than conducting waiver studies in an isolated setting.

  CLIAC Recommendations

  - Studies should demonstrate likely test performance in actual clinical use by including
    - Intended clinical testing sites
    - Intended users (e.g., non-laboratorians, waived testing personnel) as study participants
    - Intended sample type/matrix, whenever possible
    - Testing over time as in typical clinical testing
  - In lieu of separate studies demonstrating accuracy and precision, one two-armed study that includes split samples, similar to a clinical trial, may be used
    - One arm of the study should demonstrate precision of waived test performance by including multiple intended users in multiple intended sites, with testing performed over several days time
      - Fresh, clinical specimens should be used for the study, whenever possible. Although contrived specimens may sometimes be necessary, studies should not be based solely on contrived specimens
      - The study should demonstrate statistically valid precision within sites, between sites, and among sites
    - The second arm of the study (accuracy) should include a statistically valid comparison of waived test performance to laboratory professional performance of a well-documented, traceable method

- ♦ To facilitate waiver studies, guidance should be developed to
  - Address statistically valid sample sizes relative to prevalence. Special considerations may be needed for low prevalence diseases to ensure adequate numbers of positive and negative specimens
  - Include examples of statistical methods for evaluating study data
  - Include references for evaluating test methodology, such as NCCLS EP12-A: User Protocol for Evaluation of Qualitative Test Performance and NCCLS EP21-A: Estimation of Total Analytical Error for Clinical Laboratory Methods

Labeling Elements

- Ms. Ochs clarified for the Committee that the term "labeling" refers to what is printed on the outside packaging, the device itself, the package insert and the quick reference guide.
- Several Committee members expressed the need for a provision to ensure users understand that CLIA certification (i.e., Certificate of Waiver) is required to perform a waived test. One member stated users are often unaware of this requirement and suggested including a clarifying statement on the outside of the packaging when a test system is identified as "CLIA waived." The Committee recommended that labeling should state CLIA certification is necessary to perform the waived test. In addition, CLIAC mentioned the important educational role manufacturers and distributors could play, which would contribute to improving the quality of waived testing.

  CLIAC Recommendations

  - ♦ Test system labeling format should be standardized
  - ♦ Labeling should include a warning that failure to adhere to manufacturer's instructions, including instructions for limitations/intended use and for performing QC testing, is off-label use, resulting in the test being uncategorized, high complexity and subject to all CLIA regulations
  - ♦ Labeling for newly waived test systems should
    - Include a quick reference guide
    - Identify the test system as waived and notify users that when testing is performed, CLIA certification is required
    - Include risk assessment/mitigation information
    - Include results of waiver studies
    - For test systems waived based on home-use approval, include a cautionary statement that the test has not been evaluated for use in clinical settings, unless this evaluation has been performed
  - ♦ Limitations/intended use
    - The context of testing and clinical impact should be considered when making decisions about waived test limitations and intended use
    - Major limitations need to be prominently displayed on the outside of test packaging
    - Limitations, restrictions and special considerations should be included in test system instructions and quick reference instructions

- Labeling should include a warning when color-blindness could affect reading test results

♦ Test system instructions need to
- Be clear
- Be easy to understand
- Be in readable font
- Be written at no higher than 7th grade level
- Include specific elements concerning quality control, calibration, patient test performance, limitations, and fail-safe/failure-alert mechanisms

Waiver Sales Restrictions/Best Laboratory Practices

- A Committee member advocated the development of best laboratory practices guidelines for waived testing to promote quality testing and use for training and education of waived testing personnel. The member suggested publication of the guidelines in the *Morbidity and Mortality Weekly Report* (MMWR) as a means to make these the *de facto* standard of practice, citing the models of Universal Precautions and personal protective equipment, which were widely implemented through agency-issued guidance rather than legislation.
- Ms. Yost pointed out CMS is collaborating with NCCLS to develop a standard for best laboratory practices that is designed to be easily understandable and helpful to users of waived tests. A member stated support for the CMS/NCCLS collaboration, but stressed the mode and mechanism of publication of best practices guidelines would be key, and noted that NCCLS documents may not reach the wider, intended waived testing audience. Dr. Martin interjected that there is a role for NCCLS in developing a best laboratory practices standard for waived testing and suggested an MMWR publication could refer to a synthesized version of those guidelines.
- The Committee requested a report to CLIAC in September 2004 on the feasibility and logistics of establishing best practices guidelines for laboratories performing waived testing.

CLIAC Recommendations

♦ Sales restrictions/recommendations for appropriate use (e.g., selling only to CLIA-certified laboratories or laboratories having an adequate quality assurance program) may need to be considered for some waived tests

♦ Guidelines addressing "best laboratory practices" should be developed to promote quality testing and used for the training/education of waived testing personnel

♦ Consideration should be given to development of training and education programs for the end-user

Post-waiver Reporting/Surveillance

In support of the Workgroup's recommendation that surveillance of waived tests is preferable to passive event reporting, one member suggested encouraging voluntary participation in proficiency testing surveys.

CLIAC Recommendations

Surveillance of waived test use and performance is needed and is

- Preferable to passive event reporting to FDA by manufacturers
- Especially critical in waived laboratories that have no system of monitoring test performance
- The shared responsibility of manufacturers, laboratories and government

Waiver Discussion Summary

Dr. Sundwall concluded the Committee's discussion on the Waiver Workgroup's suggestions by recognizing this as a landmark meeting wherein agreement has been reached on some very complex issues, allowing for forward movement toward development of FDA guidance on the waiver criteria and process. He complimented AdvaMed and industry for stimulating these discussions, and invited Ms. Ochs to make closing remarks for the topic of waiver. Ms. Ochs thanked Dr. Sundwall for his comments and stated most of the major issues were addressed in a manner industry can implement.

CLIAC Waiver Recommendations

On April 8, 2004, CLIAC's Waiver Recommendations were forwarded in letters to AdvaMed ***(Addendum G-1)*** and FDA ***(Addendum G-2)***. A complete list of the CLIAC Waiver Recommendations can be viewed in ***Addendum G-3***.

AGENCY UPDATES

■ Centers for Medicare & Medicaid Services (CMS) Update *Addendum H*

Ms. Judy Yost, Director, Division of Laboratory Services, CMS, provided the Committee with an update of CLIA laboratory enrollment statistics and reviewed the most frequently cited deficiencies ***(Addendum I)***. She pointed out the most common deficiencies have been in the area of quality assurance and quality control, but survey data show laboratories improving over time. She then reviewed CMS's progress in implementing the Final Quality System Regulation, noting all surveyors have now received training on the regulation and revised Surveyor Guidelines, which provide surveyors and laboratories interpretations or clarifications of the CLIA requirements, were published in January. Both the regulation and the guidelines may be accessed on the CMS website: http://www.cms.hhs.gov/clia under "Current CLIA News."

Ms. Yost summarized the regulatory changes within CLIA Subpart K, "Quality System for Nonwaived Testing," and explained that the term "nonwaived" is being used because the requirements apply to both moderate and high complexity testing. She described the objectives of the Quality System approach as accuracy, reliability and timeliness and outlined the laboratory's responsibilities for quality assessment, which was previously called quality assurance. She added

that quality assessment measures are now interspersed throughout the regulatory text to emphasize their important role in all phases of the testing process. Ms. Yost noted that most of the changes in the regulation were in the analytic section and briefly reviewed the requirements for method performance verification and calibration. She then discussed the requirements for control procedures, including the provision pertaining to equivalent QC options. Relative to proficiency testing, Ms. Yost informed the Committee the level of consensus for PT provider grading was dropped from 90 percent to 80 percent to minimize the number of ungradable PT results.

Ms. Yost also covered CMS survey policy regarding the new CLIA QC regulation stressing an educational approach in the first survey cycle, with laboratories having problems meeting the new provisions receiving a letter in lieu of a deficiency statement. However, she emphasized the laboratory would be cited if it fails to meet any requirement it was previously subject to and the requirement is also contained in the new regulations.

Ms. Yost ended her presentation by updating the Committee on the status of the Notice of Proposed Rule Making (NPRM) for genetic testing, stating the NPRM, drafted by CDC, is currently under review by CMS. Once the review is completed, it will be added to the CMS regulation publication schedule.

No committee discussion

■ Food and Drug Administration (FDA) Update *Addendum J*

Dr. Jean Cooper, Director, Chemistry and Toxicology Devices, OIVD, CDRH, FDA, recapped the relatively short history of OIVD, its functions, initiatives, and role in CLIA. She stated that OIVD continues to focus on standardizing and implementing "least burdensome" reviews and streamlining processes. In addition, new OVID initiatives are addressing communications with manufacturers and device users. For example, OIVD's web-site provides a comprehensive overview of programs, laboratory safety tips, news items, and databases relevant to CLIA test categorization (including waived tests) and over-the-counter (OTC) approved devices. Also, in keeping with FDA's move toward transparency, OIVD posts product reviews on its website. The next step is to standardize the product review application process using a data template. This template, currently in the pilot phase, will migrate into an electronic version mid-Spring and allow electronic submissions of new devices for FDA review. OIVD also initiated a "Compliance Corner" on its web-site for posting relevant communications and to clarify positions on important FDA actions.

Dr. Cooper informed the Committee that OIVD will be working closely with CDC and CMS to develop a waiver guidance document and emphasized CLIA is a high priority program for OIVD. She briefly covered several "hot button" items facing FDA, including analyte specific reagents (ASRs), the in vitro analytical test (IVAT) proposal (proposal for review process for in vitro diagnostic tests in which analytical validity is established, but clinical utility has not yet been proven), informed consent, drugs of abuse, and pharmacogenomics. Dr. Cooper concluded by noting OIVD is still a creative work-in-progress.

Committee Discussion

- Dr. Sundwall complimented Dr. Cooper and her colleagues on the ease of working with FDA since the creation of OIVD and the introduction of a transparent process. He asked for clarification on Dr. Gutman's statement at a previous meeting that FDA does not intend to regulate ASRs developed and used in-house; rather, the agency will focus on commercially-developed tests sold to others. Dr. Cooper affirmed FDA's concern is for kits being sold commercially.
- Another member asked if FDA was aware of the new science of proteomics, a technology using mass spectrometry to look at protein signatures. This member pointed out that an important issue arises as to when an undefined protein pattern can be used as a diagnostic test, adding that some of the tests are already being proposed for cancer diagnostics. Dr. Cooper acknowledged that FDA is aware of proteomics. She explained that FDA invites speakers from universities to come to OIVD to educate and update the staff about genomics and proteomics. FDA is proactive in seeking information on new science as applications using these technologies are submitted for review.

■ Centers for Disease Control and Prevention (CDC) Update

Futures Initiative-Creating the Future for CDC in the 21st Century ***Addendum K***

Ms. Kathy Cahill, Senior Advisor for Strategy and Innovation, Office of the Director, CDC, updated the Committee on the progress of CDC's Futures Initiative. She described the transformation of CDC as a project that is outside-in, interactive, data-driven, and focused on customers. Strategic direction will be set and then followed with structure and processes. The transformation includes the four phases of input, ideas, implementation, and impact measurement. Input into the process has come from CDC's "customers," staff, and "partners." Customers (the general public) were asked to provide information about their health concerns, their primary sources of health information, and their understanding of CDC's roles and activities. Responses indicated that few were aware of CDC's role in prevention and chronic disease management, and CDC was not spontaneously mentioned as a resource for health information. However, Ms. Cahill noted CDC's website is sought whenever there is an outbreak or incident involving a potential terrorism agent, such as the recent ricin episode. Responses also showed, though there is limited knowledge of CDC, the Agency is viewed with respect and valued for work in research and infectious diseases. Partners, mostly public health organizations, generally appreciated CDC's credibility and value. They indicated CDC's key products and services are in research and epidemiology, assistance to state and local health departments, information and guidance, and providing a voice for disease prevention. Some partners criticized CDC for being organized too much into "silos" and for not opening sufficient two-way communication with its partners. They also challenged CDC to take the lead role in public health. Ms. Cahill noted while CDC's "silos" have certain advantages for accomplishing research, there is a need to manage effective cross-cutting communications. She also stressed CDC would not abandon its tradition of public health partnerships. In order to improve health system partnering activities, CDC must effect several transitions: from disease orientation to health focus; from designing and implementing sponsored programs to informing and guiding health care systems; from allocating resources to leveraging resources; and from collecting and analyzing health data to creating integrated health information

systems.
Ms. Cahill described the workgroups established to evaluate input from all sources and to develop ideas for improvement. One workgroup is reviewing the health systems overall and how CDC might work with partners to tackle many health problems through public health prevention efforts. A second workgroup is addressing global health efforts and a third workgroup is focusing on CDC's research. Ms. Cahill highlighted some of the workgroups' findings and noted CDC is in the process of assessing how best to strategize and implement recommendations.
Ms. Cahill concluded by summarizing the major themes from the input phase and reviewing supporting strategic initiatives. These include revitalizing and redefining the public health system, developing marketing and communication as an effective intervention arm, strengthening public health research, increasing global health impact, re-inventing how CDC conducts business, and redesigning CDC organizational structure and accountabilities to support its strategic direction.

Committee Discussion

- A Committee member asked if copies of the workgroups' reports are available. Ms. Cahill said they would be on CDC's web site in the near future.
- Another member asked Ms. Cahill if she had any concerns about budget cuts for CDC. Ms. Cahill acknowledged this is a time of tight budget constraints but CDC is optimistic about fiscal years 2004 and 2005. Ms. Cahill said, because priorities of the country are monumental, CDC needs to make a better case for prevention. Through the process for the Futures Initiative, CDC has learned it must be more accountable for what it does as a public health agency. She described the challenge of justifying costs for public health prevention when beneficial effects may not be realized until 20 years hence.

CDC HIV Rapid Test Training: A Collaborative Effort ***Addendum L***

Ms. Judy Delany, Chief, Laboratory Practice Training Branch, Division of Laboratory Systems (DLS), PHPPO, CDC, gave an account of a recent training effort accomplished through intra-agency cooperation between PHPPO/DLS and the National Center for HIV, STD and TB Prevention (NCHSTP) and through extramural collaboration with the Association of Public Health Laboratories (APHL), the National Laboratory Training Network (NLTN), state health departments, and CMS. This effort involved training counselors associated with CDC-funded community-based organizations to perform the OraQuick® Rapid HIV-1 Antibody Test safely in a variety of non-traditional settings, such as STD clinics, correctional facilities, drug treatment programs, community health centers, and homeless shelters. Training consisted of a 3-day session incorporating the CDC *Quality Assurance Guidelines for the OraQuick® Rapid HIV-1 Antibody Test*, biosafety concepts, hands-on instruction in fingerstick procedures and test performance, and instruction in HIV prevention counseling. Ms. Delaney described the challenges of developing course materials, scheduling courses, setting up logistics and supplies, and identifying and training CDC staff to deliver the training, all in a short time frame. She recounted that in an eleven-week period, twenty courses were taught in twenty sites around the country to a total of 364 participants. Feedback from the participants was very positive, revealing that 99 percent of participants felt confident they could perform the fingerstick procedure, safely dispose of biohazardous waste, and accurately perform the test; 98 percent were confident they could reliably interpret test results. Post-course test scores showed improvement from pre-course

test scores, particularly for the laboratory component.
Ms. Delany concluded her presentation by sharing plans for the next phase of the training effort, which consists of scheduling an additional 20 courses by September 2004. Training for this next series of courses will be through a contractor who will provide experienced laboratory trainers and manage the logistics and transport of supplies. She added DLS will continue to be involved with course scheduling, logistics, communication, evaluation, and oversight; and plans are in process to develop materials for a program manager's course.

Committee Discussion

- One member asked how the need for training was determined. Another member inquired about its funding. Dr. Merlin explained CDC has a major initiative to reduce the incidence of HIV and one of its efforts towards meeting this goal is to make HIV testing more accessible to people at risk. Hence, this training effort was initiated at the request of NCHSTP to support CDC-funded programs throughout the country which provide counseling and testing to individuals. Funding for the training came from NCHSTP's budget.
- A member asked whether this training program was designed in part to satisfy the sales restriction FDA placed on the OraQuick® Rapid HIV-1 Antibody Test as a condition of waiver and which required documentation of training. Dr. Merlin responded that since CDC was the purchaser of 200,000 test kits to be distributed to the community-based organizations it funded, it felt an obligation to ensure the users of the kits could use them properly. He explained that the burden is on the purchaser to assure that its users are properly trained.

Quality Institute ***Addendum M***

Dr. Toby Merlin, Associate Director for Laboratory Medicine, DLS, PHPPO, CDC, provided an overview of recommendations resulting from the April 2003 Quality Institute Conference, convened in Atlanta, Georgia, by CDC and 38 partner organizations. He noted the Quality Institute has recently been renamed the Institute for Quality in Laboratory Medicine (IQLM) to better reflect its mission to improve health care through quality laboratory services. In this regard, Dr. Merlin reviewed the Institute's strategic goals, which are to: (1) drive continuous quality improvement and excellence in laboratory services, (2) be a clearinghouse for laboratory practices, and (3) highlight the role of laboratory services in patient care. He added DLS has marketed IQLM to CDC internal constituencies and has begun marketing to current and potential external partners. DLS is also developing a business plan to launch the ILQM as an independent, public–private partnership and to this end, has formed three focused workgroups. The Awards Workgroup is charged with recognizing efforts that challenge and innovate, build and strengthen partnerships, enhance economic value, and improve patient and public health outcomes. The Indicators Workgroup is to identify and classify current quality indicators, select broadly applicable indicators, and increase focus on pre- and post-analytic indicators. The Networks Workgroup will be evaluating existing networks, assessing feasibility of surveillance models, and determining current use of quality measures. Dr. Merlin concluded with a summary of IQLM's evolution, timeline, and a list of the 38 current partner organizations. He added that DLS is actively seeking other organizations to become involved and noted the vision of IQLM is of an organization with broad participation by the healthcare and device manufacturing industry.

Committee Discussion

- One member questioned how IQLM will be funded and commented that because of tight budgets in the current economy it may be difficult for many organizations to participate if impacted financially. Another member countered that laboratory results are the basis for approximately 70 percent of medical decisions; thus, healthcare organizations and practitioners cannot afford to not be involved with IQLM. Dr. Merlin explained a realistic budget is planned for IQLM and pointed out the need for an organization that can provide information, particularly standards and guidelines. IQLM could fulfill that need and, similar to the Institute of Medicine (IOM), could possibly work under contract to the government. Dr. Martin added that CDC management recognizes the need for start-up money.
- A question was asked about the structure of IQLM in terms of partner organizations, expectations of partners, and how they would interface with IQLM. Dr. Merlin responded that currently the partner organizations would simply request participation with CDC in convening a conference. The future structure is not yet well defined, but may conceivably have different levels of participation and membership. He added that IQLM does not intend to duplicate the work of other organizations; rather it will focus on identifying gaps and ways to address them.
- One member commented that with any new venture, when defining what the organization will be, it is equally important to define what it will not be. The member then asked if IQLM would be similar to the IOM, in that it would serve as a think tank to identify critical issues and solicit white papers on specific issues. Dr. Merlin acknowledged the IQLM is modeled on the IOM in that members will identify needs and commission studies or white papers. Another of its functions will be to collect critically needed data. For example, data is sparse related to waived test performance, where waived testing is performed, and the level of training of waived testing personnel.

PUBLIC COMMENTS

Waiver Criteria/Process ***Addendum N***

College of American Pathologists - written comment

CMS State Operations Manual: Interpretive Guidelines for CLIA ***Addendum O***

Mr. Greg Cooper, Manager, Clinical Standards and Practices, Bio-Rad Laboratories - written comment

Health Industry Distributors Association – Overview ***Addendum D***

Ms. Jennifer Alfisi, Director of Government Affairs, Health Industry Distributors Association

FUTURE AGENDA ITEMS

The Committee suggested the following topics for future CLIAC meetings:

- Report from the workgroup, headed by Dr. Foucar, investigating the feasibility and process for publishing the CMS waived laboratory survey data in the CDC's MMWR.
- Presentation from HIDA addressing waived testing logistical and educational issues currently under discussion by CLIAC
- Progress report on IQLM
- Presentations from organizations whose membership includes significant numbers of COW laboratories, such as the American Academy of Family Physicians, the American Association of Physician Offices and Laboratories, and the American Medical Directors Association, to describe current practice and efforts to promote compliance with best laboratory practices

ADJOURN

Dr. Sundwall adjourned the Committee. The next CLIAC meeting is scheduled for September 22-23, 2004.

I certify that this summary report of the February 11-12, 2004, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.

David N. Sundwall

David Sundwall, M.D., CLIAC Chair
Date: May 12, 2004