Clinical

Laboratory

Improvement

Advisory

Committee

Summary Report

November 5-6, 2014

Atlanta, Georgia

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Clinical Laboratory Improvement Advisory Committee
November 5-6, 2014, Summary Report

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RECORD OF ATTENDANCE

Committee Members Present
Dr. Burton Wilcke, Jr., Chair
Mr. Eugene Augustine, Jr.
Dr. Robert Baldor
Edward Chan
Dr. Roger Klein
Ms. Karen Lacy
Dr. Elizabeth Marlowe
Dr. Anthony Okorodudu
Dr. Richard Press
Dr. John Sinard
Dr. Hardeep Sigh
Ms. Paula Vagnone
Dr. Linda Ward
Mr. Robert DiTullio, AdvaMed (Liaison Representative)

Committee Members Absent
none

Ex Officio Members
Dr. Barbara Zehnbauer, CDC (Acting)
Ms. Karen Dyer, CMS (Acting)
Dr. Alberto Gutierrez, FDA

Designated Federal Official
Dr. Devery Howerton, CDC

Executive Secretary
Ms. Nancy Anderson

Record of Attendance – cont'd

Centers for Disease Control and Prevention (CDC)

Dr. J. Rex Astles
Ms. Diane Bosse
Dr. Roberta Carey
Dr. Alexis B. Carter
Dr. Pollyanna R. Chavez
Dr. Bin Chen
Dr. Nancy Cornish
Mr. Steven Ethridge
Ms. Sonnet J. I. Gaertner
Ms. Maribeth Gagnon
Dr. Amy Gargis
Dr. Shaw Gargis
Ms. Stacy Howard
Dr. Michael Iademarco
Dr. Lisa Kalman
Dr. Edward Lockhart
Dr. Ira Lubin
Dr. William MacKenzie
Counselor Kevin Malone
Ms. Laura Y. Martin
Ms. Leslie McDonald
Dr. Toby Merlin
Ms. Graylin Mitchell
Dr. Michele Owen-Gray
Ms. Anne Pollock
Ms. Nakeva Redmond
Dr. John C. Ridderhof
Dr. Paramjit Sandhu
Ms. Megan Sawchuk
Dr. Shahram Shahangian
Mr. Darshan Singh
Ms. Theresia Snelling
Ms. Heather Stang
Ms. Sonya Strider
Dr. Julie Taylor
Mr. H. Eric Thompson
Ms. Monica Toles
Dr. Robin Wagner
Ms. Karlyn Wilson
Dr. Lyna Zhang
Mr. Jonathan Zhong

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

Ms. Daralyn Hassan, CMS
Ms. Penelope Meyers, CMS
Ms. Gwendolyn Williams, CMS
Dr. Sally Hojvat, FDA
Dr. Prakash Rath, FDA

In accordance with the provisions of Public Law 92-463, the meeting was open to the public. Approximately 30 public citizens attended one or both days of the meeting. The meeting was also available by webcast.

CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC) - BACKGROUND

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 pertaining to improvement in clinical laboratory quality and laboratory medicine. In addition, the Committee provides advice and guidance on specific questions related to possible revision of the CLIA standards. Examples include providing guidance on studies designed to improve safety, effectiveness, efficiency, timeliness, equity, and patient-centeredness of laboratory services; revisions to the standards under which clinical laboratories are regulated; the impact of proposed revisions to the standards on medical and laboratory practice; and the modification of the standards and provision of non-regulatory guidelines to accommodate technological advances, such as new test methods and the electronic submission of laboratory information.

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 AND COMMITTEE INTRODUCTIONS

Dr. Devery Howerton, Designated Federal Official (DFO), Clinical Laboratory Improvement Advisory Committee (CLIAC), and Associate Director for Science (Acting), Division of Laboratory Programs, Standards, and Services (DLPSS), Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Office of Public Health Scientific Services (OPHSS), CDC, welcomed the Committee and the members of the public, acknowledging the importance of public participation in the advisory process. Dr. Burton Wilcke, CLIAC Chair, welcomed the Committee, called the meeting to order, and publicly thanked Dr. Devery Howerton, Designated Federal Official (DFO), for co-chairing the last CLIAC meeting in March. All members then made self-introductions and financial disclosure statements.

Dr. Wilcke conveyed that the agenda topics included a refresher on the advisory committee process and updates from the CDC, the Food and Drug Administration (FDA), the Centers for Medicare & Medicaid Services (CMS), and the CDC Office of Infectious Diseases Board of Scientific Counselors. He explained that each agency would address the issue of waived testing, to include the historical background, the FDA CLIA waiver approval process and criteria, and an update from CMS. In addition, Dr. Wilcke said there would be presentations and discussions including a report from the workgroup charged with providing input to CLIAC regarding the acceptability and application of virtual crossmatching in lieu of serologic crossmatching for transplantation, the FDA draft guidance on laboratory developed tests, and laboratory biosafety in the United States.

Dr. Zehnbauer informed CLIAC of the retirement of Dr. Devery Howerton, CLIAC DFO, and recognized her for her contributions to CLIAC as well as her history with CDC working to improve the quality of clinical laboratory testing nationwide.

Advisory Committee Process Review ***Addendum 01***

Devery Howerton, PhD
Associate Director for Science (Acting)
Division of Laboratory Programs, Standards, and Services (DLPSS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention

Dr. Howerton presented a brief overview on the operational aspects and roles of CLIAC. She stated CLIAC is a mandated advisory committee whose purpose is to provide recommendations to the federal agencies responsible for the CLIA program (CDC, CMS, and FDA). She discussed the type of scientific and technical advice CLIAC provides to HHS and reviewed CLIAC's operational aspects. Dr. Howerton concluded the presentation with an overview of the recommendation process.

AGENCY UPDATES AND COMMITTEE DISCUSSION

Centers for Disease Control and Prevention (CDC) Update *Addendum 02*

Barbara Zehnbauer, PhD, FACMG, FACB
Director (Acting)
Division of Laboratory Programs, Standards, and Services (DLPSS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention

Dr. Zehnbauer's presentation highlighted the major activities DLPSS is currently conducting or participating in. She discussed DLPSS' role in the Ebola response noting the Division is providing advice on clinical laboratory issues as well as providing staff to support CDC's emergency operations center. She related the Division took part in CDC's laboratory safety efforts by assisting in the inventory of over 6 million specimens. Dr. Zehnbauer provided an update on the two-year contract awarded to the American Society for Cytotechnology Services, Inc. She reviewed the assessment of the survey distributed in 2014 and said time measure studies will be conducted in 2015. She briefly discussed the Laboratory Health Information Technology (LabHIT) team report, "Ensuring the Safety and Effectiveness of Laboratory Data in EHRs," developed in part due to a recommendation from CLIAC, and reviewed the aLOINC (Logical Observation Identifiers Name and Code) order code initiative accomplishments. She provided a progress report on the proposed rule for proficiency testing and an overview of ongoing cooperative agreement projects. Dr. Zehnbauer concluded with an overview of Laboratory Medicine Best Practices activities (LMBP™).

Committee Discussion

- Noting that the display of laboratory results in electronic health records (EHRs) is not standardized, a member urged that CLIAC or CDC embrace a leadership role to spearhead a standardization effort. Dr. Zehnbauer commended the idea and replied that currently CDC is attempting to standardize the codes for ordering tests. Although leadership for laboratory result data display in EHRs will need to come from a level beyond CLIAC and CDC, CLIAC could contribute to providing the laboratory perspective.
- Another member asked about any efforts CDC is making in developing a primary literature base to encourage publication of data that can be used to perform systematic reviews and help establish evidence-based recommendations. Dr. Zehnbauer replied that the LMBP™ A6 method was developed to serve that purpose and to define criteria that are rigorous enough for unpublished quality improvement data to be included in the database for evidence reviews.

Centers for Medicare & Medicaid Services (CMS) Update *Addendum 03*

Karen Dyer MT(ASCP), DLM
Deputy Director
Division of Laboratory Services
Survey and Certification Group
Centers for Medicare & Medicaid Services

Ms. Dyer's presentation focused on CLIA statistics and survey deficiencies, status of the patient access rule, other CLIA regulations, the individualized quality control plan (IQCP) approach to QC, and the CMS role in the Ebola response. As part of this, she reviewed the progress of the proposed proficiency testing (PT) rule and the rules to address PT referral. Members were reminded of the Taking Essential Steps for Testing (TEST) Act signed by the President at the end of 2012. Ms. Dyer discussed the implementation of IQCP, which will be incorporated into the CLIA interpretive guidelines for all specialties except cytology and histopathology and noted CMS is collaborating with CDC on IQCP educational materials. Information on IQCP is now posted on the CMS CLIA website. She described the efforts of CMS in providing policy memos to laboratories in reference to handling and transporting specimens possibly contaminated with the Ebola virus. Last, she provided resources on where to obtain more information and invited those with questions to contact her at the email address provided.

Committee Discussion

- A member noted that some states already allow patients access to their laboratory reports and asked if there are any data from those states that show how the laboratories and hospitals handle the requests. Ms. Dyer replied that CMS's primary focus has been on states where patients' access to laboratory reports had not been authorized or addressed prior to implementation of the patient access rule.
- Another member asked if there were any plans to perform a post-implementation evaluation on the impact of the patient access rule. Ms. Dyer replied CMS had no plans for a formal evaluation at this time.

Food and Drug Administration (FDA) Update *Addendum 04*

Alberto Gutierrez, PhD
Director
Office of In-Vitro Diagnostic Device Evaluation and Safety (OIVD)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Dr. Gutierrez began his presentation by providing a brief organizational update and recapping the Medical Device User Fee Act (MDUFA) III status. He reviewed the de novo down-classifications, pre-market approvals (PMAs), and the past year's meetings. He discussed final and draft guidances published in 2014 and described two draft guidance documents developed for over-the-counter and point-of-care glucose monitors. Dr. Gutierrez related the FDA had granted emergency use authorization to five

devices for Ebola detection and concluded his presentation with a brief discussion of CLIA waiver approvals.

Committee Discussion

- A member asked if there were any new developments with antimicrobial susceptibility testing breakpoints. Dr. Gutierrez explained the FDA continues to work with the industry in speeding up the process to allow changes to the FDA-cleared breakpoints, but there are no new developments at this time. The same member inquired if the manufacturers of HPV test kits that were approved before the Roche test kits for primary screening would need to conduct extra tests to obtain the same type of approval. Dr. Gutierrez replied no manufacturers had requested such approval at this time.
- A member requested the percentages for the number of waiver approvals and waiver rejections as compared to the total number of requests for the last fiscal year. Dr. Gutierrez replied he did not have the numbers but rejections are not uncommon. He indicated FDA continues to work to improve the waiver process.
- Another member asked for an update on the regulation for direct-to-consumer genetic testing. Dr. Gutierrez replied that guidance is forthcoming. The last manufacturer to openly sell their device directly to the consumer is working with the FDA for CLIA approval of that device. The FDA hopes to develop a guidance document on direct-to-consumer genetic testing devices.

PRESENTATIONS AND COMMITTEE DISCUSSION

CLIA Waived Testing

Historical Background ***Addendum 05***
Nancy Anderson, MMSc ***Addendum 05a***
Chief, Laboratory Practice Standards Branch (LPSB) ***Addendum 05b***
Division of Laboratory Programs, Standards, and Services (DLPSS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention

Ms. Anderson provided the background and history of waived testing, beginning with its origin and the regulatory requirements for performing waived testing. She reminded the Committee that over the last 20 years there has been a significant increase in the number of laboratories that hold a Certificate of Waiver and the number of waived tests.
Ms. Anderson reviewed the criteria and process for waiver approval, noting that CLIAC has provided eight recommendations related to this. She outlined the steps taken by HHS to clarify the waiver criteria, reviewed the transfer of waiver responsibilities from the CDC to the FDA in 2000, and recounted the FDA's development of their waiver guidance, including the role CLIAC played in its development. Addressing concerns with

waived test performance, she noted aspects of waived testing have been discussed either through formal presentations or as part of agency updates at 29 of the 49 CLIAC meetings. One of the outcomes of these discussions was CDC's development of waived testing educational products. Ms. Anderson concluded her presentation with a review of waived testing trends and current laboratory statistics.

FDA CLIA Waiver Approval Process and Criteria *Addendum 06*

Prakash Rath, PhD
Policy Analyst
Office of In-Vitro Diagnostic Device Evaluation and Safety (OIVD)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Dr. Rath began his presentation by noting that CMS, CDC, and FDA work together to assure quality laboratory testing and then discussed the FDA's specific role in CLIA categorization and waiver approvals. He described the pathways for determining waived status under CLIA and explained how a test system could meet the CLIA waiver criteria. Dr. Rath presented two case studies involving blood glucose meters and hematology analyzers that illustrated what he described as the "clearance-categorization-conundrum" and that highlighted issues with the CLIA waiver application process. He concluded with a summary of the issues and four discussion points for CLIAC to consider.

CMS Waived Testing Update

Daralyn Hassan MS, MT(ASCP) *Addendum 07*
Division of Laboratory Services
Survey and Certification Group
Centers for Medicare & Medicaid Services

Ms. Hassan began her presentation with an overview of waived testing, highlighting the exponential growth of available waived tests and Certificate of Waiver (CoW) laboratories. She discussed the CoW project, begun as a pilot in 1999, and delineated CMS' short-term and long-term plans for the project. She reviewed the CDC educational materials containing recommended practices for waived testing and the Government Performance Review Act (GPRA) "Ready? Set? Test!" Project. Ms. Hassan discussed the CLIA requirements for waived blood glucose meters and the impact of using the meters other than as described in the manufacturer's instructions. In summary, she said facilities performing only waived testing must enroll in the CLIA program and follow the manufacturer's instructions; they may be visited as part of the CMS CoW/GPRA Project; and they have improved due to the education provided by CMS and CDC.

Committee Discussion

- Referring to the CoW project finding that some CoW sites are performing non-waived testing, a member asked if there was any commonality in the non-waived tests being performed. Ms. Hassan replied there was no commonality.

- A member asked if the agencies' efforts were having any positive impact on sites that perform only waived testing. Another member requested confirmation that only 50% of the CoW sites that received the "Ready? Set? Test!" booklet changed their practices. Ms. Hassan replied education of the CoW sites during CMS visits and via distribution of the "Ready? Set? Test!" booklet is having a positive impact. She added that surveyors have seen improvements in sites that received the booklet prior to an educational survey. Dr. Gutierrez stated that access to waived testing with appropriate training and education was shown to improve the public's health, as seen with the first waived HIV tests.
- A member suggested designing an annual or bi-annual self-assessment or risk assessment tool based on information in the "Ready? Set? Test!" booklet and asked if survey visits to CoW sites could be unannounced. Ms. Hassan noted there was, at one time, a self-assessment tool used for non-waived laboratories and she said CMS can only visit CoW sites under certain circumstances to verify their testing menu and assure that they are not causing harm to the public.
- A member asked if waived testing sites are cited for improper testing. Ms. Hassan stated serious deficiencies are cited and CMS follows up to make sure that the deficiencies have been addressed and corrected.
- A member asked if the FDA had a point-of-care CLIA testing category. Another member commented that waived testing has become a one size fits all category, particularly for over-the-counter (OTC) devices. A third member requested clarification of the difference between OTC and waived test status. Dr. Gutierrez replied the designation 'point-of-care' is considered intended use by the FDA. Under CLIA, tests are categorized as moderate or high complexity, or are approved as waived. He noted that by law any device approved for OTC use is automatically CLIA waived when used as described in the manufacturer's instructions. For glucose meters, the FDA guidance has alleviated that issue somewhat by clarifying the difference between single and multiple patient use of the meters.
- A member suggested that the Secretary of HHS re-visit the rules and redefine the CLIA waiver process for OTC. A second member asked for clarification regarding changes to the CLIA law for waived testing. Ms. Hassan stated that CMS had submitted form A19 requesting the CLIA law be opened. This would have allowed the Secretary of HHS the discretion to make changes to the CLIA law, including the possibility of increasing oversight of waived testing laboratories. The request was denied at the time it was submitted.
- One member expressed concern about the strict interpretation of information in the manufacturer's instructions, which generally includes indications of the populations and settings in which the test can be performed. He asked if a process was in place that allowed the extrapolation of the data gathered in pre-market studies of a test so that it could be used in populations or settings for which it was not specifically tested before it was FDA-approved or cleared. Dr. Gutierrez replied that CLIA-waived settings often do not have a laboratory director with the expertise to understand a test's technical issues including whether its use could be expanded or what additional controls may be needed in those circumstances. The member then asked if there was a process for the FDA to approach the test manufacturer with the suggestion of expanding a test's use. Dr. Gutierrez stated that waived tests seem to be moving

toward narrower intended use. However, narrowing the intended use of a test to make it safer may actually make it more difficult for the waived testing sites to understand how to use this as a control.

- A member asked if a manufacturer could have an application expedited based on an acute public health need for a test. Dr. Gutierrez replied there is now a mechanism that could result in obtaining FDA clearance and waiver approval at the same time. However, communication between the manufacturer and the FDA during this process is crucial. A member asked what the process is for reclassifying a device from moderate complexity to waived status. Dr. Gutierrez replied the manufacturers must go through the waiver approval process to reclassify the device.
- A member asserted it is important that the FDA's test approval process be as efficient as possible.
- Another member asked if there is post-market surveillance of CLIA-waived tests. Dr. Gutierrez replied manufacturers are required to report adverse events, including erroneous results that cause harm, but that there is no specific surveillance of CLIA-waived tests. The AdvaMed liaison stated that manufacturers are required to vigilantly perform post-market surveillance through the complaint handling process for all tests, including those that are waived. When a customer files a complaint, the company is required to investigate and if needed, perform stability studies. The FDA inspects manufacturers for the veracity of their post-market surveillance programs.
- Dr. Wilcke, the CLIAC chair, called for formal recommendations. The Committee made the following recommendations:
    - HHS should facilitate the development of a non-punitive and non-regulatory self-assessment checklist-type tool and recommend it for biennial use by all Certificate of Waiver testing sites. It could also be used prior to or at the time a site first applies for a CLIA Certificate.
        - Items on the checklist should include recommended practices based on the "Ready? Set? Test!" booklet and should address known problem areas of importance (e.g., off-label use of waived tests).
        - The checklist could also assess whether the Certificate of Waiver site reports test system performance problems to the FDA.
        - Certificate of Waiver testing sites should be encouraged to keep copies of their completed assessments on file to be validated during CMS site visits and/or the assessments could be reported to CMS through an online portal.

    - CMS should revisit the A19 request to open up the CLIA law to allow changes to the waived testing requirements and provide a description of the details of the A19 request at the next CLIAC meeting.

Virtual Crossmatching for Transplantation

Introduction – Virtual Crossmatch

Penelope Meyers, MA, MT(ASCP)SBB
Technical Director
Division of Laboratory Services
Survey and Certification Group
Centers for Medicare & Medicaid Services

Ms. Meyers introduced the topic of virtual crossmatching, a process to assess donor-recipient compatibility prior to organ transplantation. She explained that CMS was contacted by a representative from the American Society for Histocompatibility and Immunogenetics (ASHI) about CMS's position on virtual crossmatching. This organization, one of seven CMS-approved laboratory accreditation organizations, is interested in writing virtual crossmatching standards for their accredited laboratories. The CLIA regulations do not address virtual crossmatching nor is it addressed in CMS' Interpretive Guidelines for Laboratories. Ms. Meyers explained that CMS was seeking a recommendation from CLIAC regarding if or how virtual crossmatching should be incorporated into the CLIA regulations.

Ms. Meyers noted that the CLIA histocompatibility regulations were written to apply to physical crossmatching, the only process in use when the regulations were published in 1992. She provided a brief explanation of the process of physical crossmatching, elaborated on the laboratory tests performed on donors and recipients prior to transplantation (typing for human leukocyte antigens - HLA, and in the case of recipients, screening for HLA antibodies), and discussed how the test results are used. Ms. Meyers said once a potential recipient has been identified for a donated organ based on antigen and antibody test results that have been accumulated over time, the last step is for a physical crossmatch to be performed. In virtual crossmatching, the usual HLA typing and antibody testing is performed on donor and recipient specimens. However, instead of performing a physical crossmatch immediately prior to the transplant, a histocompatibility expert assesses the compatibility between the donor and recipient based on the previous immunologic results comparing the recipient's alloantibody profile to the donor's HLA antigens.

Finally, Ms. Meyers presented the Committee with the two questions for deliberation.
1) What criteria do you recommend for virtual crossmatching?
2) What guidance for performing virtual crossmatching should be provided to laboratories?

Virtual Crossmatch Workgroup Report

Addendum 08
Addendum 08a
Addendum 08b

Robert Bray, PHD, D(ABHI), HCLD/CC(ABB)
Professor, HLA and Transplantation
Emory University, Atlanta, GA

Dr. Bray began by presenting the transplant community's issues and concerns regarding organ and tissue transplantation and the need to obtain the results of the crossmatch prior to transplantation, specifically in kidney transplants. He explained that the present transplantation standards are not reflective of the current and evolving clinical practice. He said the Workgroup was charged with providing input to CLIAC regarding the acceptability and application of virtual crossmatching in lieu of serological crossmatching for transplantation by providing suggestions for criteria for determining when a virtual crossmatch is appropriate and guidelines for laboratories performing virtual crossmatching. Dr. Bray detailed the purpose for performing a physical crossmatch and the scope and purpose for performing a virtual crossmatch.

In presenting the Workgroup report, Dr. Bray provided the historical background of pre-transplant crossmatch and discussed the improvements made in histocompatibility testing with the development of molecular and solid-phase technology. He then explained how this new testing technology can be used for HLA testing and reviewed the mandates or policies dictated by the United Network for Organ Sharing Policies (UNOS) for using molecular and solid-phase assays in histocompatibility testing. Sharing input from the Workgroup, he provided a definition for the virtual crossmatch and criteria for determining recipient and donor eligibility. He explained the virtual crossmatch processes, anticipated technological changes, and circumstances that require a serological crossmatch to confirm a virtual crossmatch. He related the Workgroup's suggestions for when crossmatch screenings should be performed and the requirements for performing them; the time limits for performing testing and assessing virtual crossmatch compatibility; and requirements for personnel. Dr. Bray concluded with a brief discussion on documenting and reporting donor and recipient test results, results that are required to perform and interpret a virtual crossmatch, decision algorithms for virtual crossmatching, and potential benefits and disadvantages of the virtual crossmatch.

Committee Discussion

- Several Committee members asked for clarification on the charge to CLIAC. Ms. Meyers responded the issue of a virtual crossmatch versus serological crossmatch was being brought to CLIAC to obtain a recommendation based on the information provided by the Workgroup. If CLIAC recommends a change, CMS will determine how it could be fit into the regulatory framework whether via a regulatory change or changes to the CLIA guidelines. A second Committee member asked whether the Virtual Crossmatch Workgroup report could be included in the recommendation. Dr. Howerton affirmed that the Workgroup report could be referred to in the recommendation.
- A Committee member asked if virtual crossmatching presupposes knowledge of all the genes and expressed alleles to which the recipient could be sensitized. Dr. Bray replied that was correct. The member further inquired about the confidence level of the virtual crossmatch versus the physical crossmatch in the detection of additional incompatibilities that could lead to graft failure. Dr. Bray responded in practice this issue rarely occurs.
- Another member inquired if there was adequate evidence to support performing the virtual crossmatch for all organ types. Dr. Bray replied that virtual crossmatching has

been used in many different types of organ transplants and has proven very beneficial in heart transplant recipients where using virtual crossmatching allows a transplant center to accept an organ without regard to how far away the donor organ is located.

- A member inquired about the extent to which virtual crossmatching is used to save time in selecting the organ earlier in the transplant process than occurs when performing a physical crossmatch between donor and recipient. Dr. Bray explained that the virtual crossmatch was a multi-layered process and that in some cases when people have no HLA antibodies, the transplant decision can be made more quickly. However, recipients with complex antibody patterns have to be evaluated manually at the time of organ offer. Based on all the information available, including the recipient alloantibody profile and the donor HLA type, a histocompatibility expert renders an opinion as to whether a physical crossmatch is needed prior to transplantation. He added a physical crossmatch may still be performed after the transplant takes place. The member further inquired whether certain antigen/antibody pairings would automatically eliminate a donor and recipient pairing, to which Dr. Bray responded that this could occur.
- Another member asked if there were any retrospective analyses of virtual versus physical crossmatching that would raise concerns. Dr. Bray answered there were many publications on the retrospective analyses of virtual versus serological crossmatching. He was not aware of any concerns raised by those studies. He restated the concerns with the detection of recipient antibodies that are not a part of the HLA testing algorithm and stated when physicians are aware of these antibodies, a virtual and physical crossmatch are performed.
- Several members, noting the resemblance of virtual crossmatching to very high-risk laboratory developed tests (LDTs) or other multiple algorithmic assays, wondered why virtual crossmatching was being addressed separately. Ms. Meyers responded that CLIA regulations specifically address crossmatching for transplantation and a regulatory change might be needed to allow for a virtual crossmatch in lieu of a physical crossmatch. Dr. Howerton added this is a unique situation in which the specific use of a crossmatch is codified. However, a member noted the current regulations do not include the wording “physical crossmatch,” but rather just indicate “crossmatch.”
- One member asked whether the algorithm for performing virtual crossmatching was standardized within ASHI-accredited laboratories, and if not, whether there are attempts being made to standardize the algorithm. Dr. Bray responded that the algorithm was not standardized. He explained establishing the criteria for histocompatibility testing and result reporting can be standardized, but the clinician’s interpretation and clinical use of histocompatibility test results is specific to each transplant program and cannot be standardized. A second member concurred indicating the Committee should focus on what antigens, antibodies, and test methods need to be included in virtual crossmatching. The final transplant decision was not something CLIAC should consider as it supersedes the role of a laboratory.
- Another member asked for clarification of why decision algorithms were included in the Workgroup’s recommendations. Dr. Bray clarified that the decision algorithms included in the Workgroup report were examples of what could be done with the

testing results and not what should be done. He reemphasized that decision algorithms need to be transplant program and center specific.

- Two members questioned the makeup of the Workgroup that developed the report provided to CLIAC. One of the members suggested recommendations provided by an external expert panel would add to the strength of the evidence used in developing formal CLIAC recommendations. The second member stated CLIAC did not have enough expertise in the area of virtual crossmatching to make specific criteria recommendations and suggested CMS convene another larger workgroup for that purpose. Dr. Howerton responded that the Workgroup was made up of histocompatibility experts. However, the Workgroup report was not vetted by additional subject matter experts. Ms. Anderson added the Workgroup included Dr. Klein and Dr. Zhang representing CLIAC. Dr. Bray responded the majority of the Workgroup members were histocompatibility laboratory directors and clinicians involved in organ transplant on a daily basis. ASHI and the College of American Pathologists (CAP) were also represented. Dr. Bray noted there are only 220 histocompatibility laboratories in the country. Ms. Meyers affirmed the histocompatibility community is small. An effort was made to include representatives nominated by all of the CMS-approved accreditation organizations and the two CLIA-exempt states in the Workgroup.
- Another member inquired whether there was anyone within the small group of histocompatibility laboratories and transplant professionals in the U.S who do not support the use of virtual crossmatching. Dr. Bray informed the Committee that professionals worldwide have adopted virtual crossmatching.
- Members commented that it might be helpful to vet the Workgroup's suggestions with national and international experts or through a process that allowed for public comment. The CLIAC members concurred that external validation would increase their confidence in any recommendations made by the Committee.
- The Committee passed the following recommendation:

Recommend that CMS explore:

a. Regulatory changes or guidance(s) that would allow virtual crossmatching to replace physical crossmatching as a pre-requisite for organ transplant.
b. Appropriate criteria and decision algorithms, based on the Virtual Crossmatch Workgroup input provided to CLIAC, under which virtual crossmatching would be an appropriate substitute for physical crossmatching. The determination of appropriate criteria and decision algorithms should involve a process that includes an open comment period.

Board of Scientific Counselors (BSC) Update ***Addendum 09***

Robert Sautter, PhD
Committee Liaison to CDC Board of Scientific Counselors (BSC)
Office of Infectious Diseases (OID)
Director of Microbiology
Carolinas Pathology Group

Dr. Sautter provided a summary of the August 2014 CDC OID BSC meeting. The meeting included reports from the OID and the three infectious disease National Centers; updates focused on the Ebola outbreak in West Africa, the spread of chikungunya fever in the Americas, the humanitarian crisis involving thousands of unaccompanied children entering the United States from Central America, and CDC's intensified efforts to improve laboratory safety. The meeting also included reports from the Antimicrobial Resistance Working Group, BSC Food Safety Modernization Act Surveillance Working Group, and the Infectious Disease Laboratory Working Group. He briefly related several topics important to public health and private health laboratories including the West Africa Ebola outbreak and the response activities by CDC OID and gave an update on CDC laboratory safety improvement activities.

Food Draft Guidance on Laboratory Developed Tests ***Addendum 10***

Alberto Gutierrez, PhD
Director
Office of In-Vitro Diagnostic Device Evaluation and Safety (OIVD)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Dr. Gutierrez provided an update on the proposed regulatory framework for laboratory developed tests (LDTs). He explained the evolution of LDT technology created a public health need for greater oversight of these tests. He described the benefits of FDA oversight of LDTs, which includes independent premarket reviews, clinical validation, post market surveillance and controls, and oversight of investigational stage devices. Dr. Gutierrez next discussed the FDA's LDT draft guidance (http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf) which includes the collection of information on all LDTs through a new notification process, use of advisory panels to obtain input on risk and priority for regulation, a phased-in regulatory framework over approximately nine years beginning with the highest-risk LDTs, and continued enforcement discretion for specific categories determined by the FDA to be in the best interest of public health. He provided a timeline emphasizing that premarket review of new highest-risk LDTs will occur immediately after the final LDT guidance is published. The FDA will publish a priority list for the timeframe for premarket submissions for the remaining high-risk LDTs in year two and a priority list for moderate-risk LDTs in year four. The next steps include the publication of the draft guidance, a Federal Register Notice announcing the 90-day public comment period, and a public meeting in early January 2015 to collect additional input during the comment period.

Committee Discussion

- A member asked if the majority of LDTs are either molecular diagnostic tests or biochemical assays. Dr. Gutierrez responded that the majority of LDTs are molecular diagnostics but there are many other LDTs as well.
- A member requested clarification on the distinction between low, moderate, and high risk LTDs. Dr. Gutierrez explained that since 1976, the FDA has been performing a

similar classification of in vitro diagnostic (IVD) products according to the level of regulatory control necessary to assure safety and effectiveness. To explain the classification scheme being proposed for LDTs, he used cancer biomarkers as an example of the same analyte having different risks depending on usage. Biomarker-based tools used in screening for the early detection of cancer in asymptomatic people are classified as high risk because false negatives may result in missed diagnoses and false positives may result in unnecessary therapies. In contrast, use of the same biomarker-based tools for a patient diagnosed with cancer is classified as moderate risk because the clinician will use the test in combination with other tests to monitor the patient, and a false test result is of lower risk to the patient.

- The AdvaMed liaison commented that industry advocates a risk based approach in regulating all diagnostic tests. The proposed LDT guidance should take into account the possible effects on review and clearance times for these devices, given the recent trend by FDA in reducing these timeframes. He stated that industry hopes that the increased load caused by the addition of LDT regulation does not adversely affect the current clearance times.
- One member asked if the FDA would use discretion and not regulate LDTs that are not marketed but used internally within an academic center or CLIA-certified laboratory. Dr. Gutierrez explained that traditionally, LDTs are defined as those tests that are developed and performed in laboratories associated with hospitals or clinical systems where there is a clinician-patient-pathologist relationship. He indicated he hoped FDA would be able to move to enforcement discretion with these tests.
- Another member asked about the process and timeline for premarket reviews and approvals. Dr. Gutierrez explained that premarket review for Class III (high-risk) devices must show the device is safe and effective. There is a twelve-month review time, which can be longer depending on whether the submitter provides all the required data and if the quality systems are in place. Dr. Gutierrez stated that low-risk LDTs would be exempt from premarket review.
- The same member inquired about the LDT notification process. Dr. Gutierrez commented that there will be an online process for notification. The FDA is collaborating with the National Institutes of Health (NIH) to link the NIH genetic registry site to the FDA notification process. When a test is registered with NIH, the user will be able to transfer the data to the FDA, input missing data, and submit the test notification.
- The member asked if traditional LDTs will require notification. Dr. Gutierrez responded that the draft guidance does require notification. However, the topic is open for public comment on whether to allow laboratories to only notify the FDA of their LDTs that will be regulated or require notification of all LDTs to assist FDA in determining the current catalog of available LDTs.
- Regarding notifying the FDA about LDTs for biosecurity agents, Dr. Zehnbauer asked how detailed the provided information would need to be and how the FDA would determine what information to share with the public. Dr. Gutierrez responded that it has not been determined if the database will be publically available. Based on public safety and security, not all information may be available to the public.
- Another member expressed concern that the LDT review timeline might result in a delay of patient access to lifesaving methodologies. Dr. Gutierrez responded there is

always a risk-benefit issue in determining whether a test is safe and effective versus the immediate benefits it presents to the patient population. In terms of the immediate public health effect, LDTs available on the market when the guidance is published will be allowed to remain on the market until the review to determine clinical validity is complete.

- One member provided a scenario of a laboratory selling their LDT for detection of multiple pathogens on asymptomatic patients' vaginal swabs and asked how the FDA would regulate this. Dr. Gutierrez responded the LDT would need to be entered into the FDA notification system and regulation would be determined based on risk. He commented that regulation will be able to limit laboratory manufacturers from making claims that are risky and not credible.
- A member asked how the CMS reimbursement program plans to assess the clinical utility of LDTs. Dr. Gutierrez responded that the FDA does not address the payers' part since they assess clinical validity rather than utility. The payers will need to determine the evidence needed for reimbursement. The same member further inquired about communication between CMS and FDA on regulation and payment since they both impact the laboratory. Dr. Gutierrez responded that recently the FDA and Medicare worked together to pilot a parallel review program.
- A member urged exemption from notification for traditional LDTs that are used within the developing institution and not marketed, stating a precedent exists with the current notification exemption of software that is developed for use within the institution. The member added it is often difficult to determine the point during test development when notification should occur since many tests are never fully developed and by adding a notification requirement, academic creativity and innovation may be hindered. Dr. Gutierrez responded that there is a point during test development when the laboratory decides to offer the test and CLIA requires establishing performance specifications prior to its use with patient specimens. At this point, the laboratory has passed the test development stage.
- Another member asked if the manufacturing component that is required as part of the premarket approval process will be required for high-risk LDTs. Dr. Gutierrez responded that it is currently required in the proposal but open for comments.
- A member asked where research use only (RUO) instrumentation fits into the LDT guidance. Dr. Gutierrez responded that RUO becomes irrelevant if an instrument is sold as a medical device; the manufacturer has the responsibility to ensure all FDA requirements are met such as good manufacturing practices, agency reporting, and regulatory control. For instruments used for LDTs, the laboratory has the responsibility to determine if the instrument is safe to be used for clinical diagnostics under the quality system regulations, and many laboratories do not have the controls required for quality systems in place.
- Another member asked where manufacturer's assays, sold as kits, fit into the LDT guidance. Dr. Gutierrez commented that LDTs span many different assays and many resemble commercial products where the only difference may be that the LDT is not distributed to other laboratories.
- In summary, the Chair noted the FDA may need to refine the definition and clarify the types of tests considered LDTs and include additional clarification on traditional LDTs. The process for risk categorization may need additional explanation to help

laboratories determine if their LDT requires notification. The AdvaMed liaison presented a statement of industry support of a risk-based approach, but wanted to ensure that premarket review timelines would not be affected by the new LDT guidance. The Chair noted discussion around LDTs with biosecurity implications and the need to not publicize data that may affect the security and health of the public. He also noted comments regarding how the LDT review process could be aligned with reimbursement.

Laboratory Biosafety in the United States

CDC Laboratory Safety Improvement Workgroup and the Impact on Clinical Laboratories

Mike Bell, MD
Deputy Director
Division of Healthcare Quality Promotion (DHQP)
National Center for Emerging & Zoonotic Infectious Diseases (NCEZID)
Office of Infectious Diseases (OID)
Centers for Disease Control and Prevention

Dr. Bell began by describing the 30-year growth in the numbers of CDC laboratories and personnel. CDC now has over 1,600 laboratory staff and about 1,000 laboratories. The shift from a relatively small group of laboratories with limited activities in CDC's early years to today's large scale operation has resulted in the need to transition the agency's approach to safety and quality to a system that includes the tools and framework to ensure and support safety in today's environment. From his vantage point over the past several months focused on CDC laboratory safety, Dr. Bell emphasized the need to address all elements associated with safety, including tracking and assuring appropriate training, competency certifications, recordkeeping, and document management. He also mentioned the importance of having a communication structure in place that encouraged identifying and reporting issues that need to be fixed, and conducting systematic reviews of processes to determine critical control steps. He discussed the work of the internal CDC Laboratory Safety Improvement Working Group that had reviewed protocols for transferring materials out of Biosafety Level three and four laboratories and suggested an expanded CDC Institutional Biosafety Committee (IBC) would be helpful for reviewing future protocols and projects. He added the formation of the IBC may provide career development opportunities for junior staff to learn from historical precedents and solutions developed to address past problems. Dr. Bell stated that CDC laboratories providing clinical testing under CLIA and those that are producing reagents under good laboratory practices currently have a quality management system (QMS) in place and are acting as guides or mentors assisting others in the implementation of the elements necessary for a QMS or to obtain CLIA or ISO certification. Last, Dr. Bell discussed the re-establishment of in-house laboratory biosafety training for employees to increase the awareness of safety practices, resulting in easier error detection. He outlined the need for collaboration with CDC's Epidemic Intelligence Service Program to create a three-track

program for laboratory professionals. One track would be designated for public health service laboratory work. A second track would allow doctoral level scientists to spend two years focused on biosafety, investigating questions about safety practices. This track would also provide doctoral level scientists for on-demand consultative work to give guidance and assistance in developing protocols to avoid safety risks in the testing environment. The final track would allow masters level scientists the opportunity to achieve a doctorate in public health through a university partnership program.

Ebola Outbreak Response – CDC Testing and Guidance for Clinical Laboratories

Toby Merlin, MD
Director
Division of Preparedness and Emerging Infections (DPEI)
National Center for Emerging & Zoonotic Infectious Diseases (NCEZID)
Office of Infectious Diseases (OID)
Centers for Disease Control and Prevention

Addendum 12
Addendum 13

Dr. Merlin presented the Committee with an overview of the Ebola virus characteristics, data from the West Africa outbreak, and an overview of the recent U.S. disease cases. He described the Ebola viral disease diagnosis involving real time polymerase chain reaction (PCR) and interpretation of negative Ebola real time PCR results and provided an overview of the FDA emergency-use authorized Ebola diagnostic tests. He gave an overview of CDC's Ebola emergency response efforts including activities of the 153 Laboratory Response Network (LRN) laboratories. Dr. Merlin furnished information on the CDC interim guidance for U.S. laboratory workers and other healthcare personnel who collect or handle specimens. This guidance includes information on the appropriate steps for collecting, transporting, and testing specimens from patients suspected to be infected with Ebola and emphasizes that specimens are not to be shipped to the LRN or CDC without consultation with local or state health departments and CDC. He related problems identified with routine testing of persons under investigation in clinical laboratories, including the lack of data on decontamination of laboratory instruments used for Ebola testing. Dr. Merlin concluded with the current approach to care in the U.S. of persons under investigation for Ebola and those diagnosed with Ebola noting long-term issues for clinical laboratories.

Committee Discussion

- The Chair introduced the discussion questions related to laboratory biosafety in the United States for the Committee to consider.
    1. Should clinical laboratories conduct periodic systematic reviews of their inventories of infectious agents?
    2. If so, are there agents of special concern and how should laboratories manage inventory control?
    3. How prepared are clinical laboratories in the US to handle novel pathogens like Ebola?
    4. Do clinical laboratories need more training in laboratory safety?

5. Are there technologic advances that are or will be available in the near future to better assure the safety of personnel who perform diagnostic testing?
6. Who should assure that automated laboratory instruments can process human blood and body fluids safely and that the instruments do not create an infectious disease risk to their users? Options include manufacturers, an independent organization, a government agency, or others?
7. How can laboratories better assess and ensure adherence to safety standards? Is there a need for an enhanced role for laboratory inspectors to help assure that laboratories establish and observe safety procedures to ensure protection from hazards and biohazardous materials?

- The Chair asked if CDC requires yearly renewal of safety training. Dr. Bell explained that CDC has a broad range of online training. The Biosafety Level two laboratory training is generic and there is a need to make it more applicable to work performed in CDC laboratories.
- A member asked if any data exist on the aerosolization of the Ebola pathogen. Dr. Merlin commented that very strong epidemiological data indicates that the spread of Ebola is through person-to-person contact and not by aerosolization. There is limited data available on the infectivity of the organism when it is aerosolized. There is no data on whether laboratory instruments aerosolize Ebola.
- Another member asked where the laboratory testing for the Dallas Ebola cases was performed. Dr. Merlin stated that Texas Health Presbyterian Hospital in Dallas performed the testing in their central laboratory. Testing would be performed at a set time during the day only on the Ebola patient's sample and all non-essential personnel would leave the laboratory. Emory University Healthcare and the University of Nebraska Medical Center were funded to develop high containment facilities and had performed preparedness exercises whereas the Dallas hospital did not have time to prepare.
- A member commented it has been difficult to determine the best process to handle potential Ebola specimens in the laboratory. The member provided an example of the type of issues laboratories are struggling to address, including the use of a biosafety cabinet and appropriate personal protective equipment. Dr. Merlin commented it is difficult to provide guidance in the absence of evidence so every laboratory must analyze the risks to minimize the element of fear associated with Ebola. He stated if a facility has a person under investigation for suspected Ebola, the current protocol requires patient isolation followed by notification of the public health department who will assist with the next steps.
- The same member commented on packaging and shipping of Ebola specimens noting that their state performs the packaging, which has helped. Several members added that once a specimen is packaged it has been difficult to find a courier. Dr. Merlin commented that laboratories should contact their local health department who will arrange for proper labeling and shipping to assure that the specimens will not be rejected by couriers.
- The Chair suggested using data from laboratory personnel in West Africa to determine the risk of laboratory acquired Ebola infection. Dr. Merlin explained that

the CDC laboratory uses a continuous staff rotation and many other agencies are also operating laboratories, so identifying a single laboratory process for risk assessment would be difficult.

- Another member addressed the issue of the proper decontamination procedures for instrumentation used to perform Ebola testing suggesting CDC, FDA, and industry representatives investigate. Dr. Merlin agreed that there is a need to address gaps with proper decontamination procedures of laboratory instruments and suggested that instrument manufacturers, government agencies, and other laboratory safety experts come together to discuss these issues. The AdvaMed liaison commented that manufacturers already have instrument decontamination procedures for HIV and hepatitis that are used when field service is performed on-site or when instrumentation is returned for resale. He indicated that industry would be willing to participate in such a discussion.
- The same member commented that in many clinical and public health laboratories, the safety officer is a volunteer position and that person may not have the appropriate knowledge. The member agreed with Dr. Bell that fellowships with an emphasis on biosafety would be beneficial in building an infrastructure of safety experts in laboratories.
- In summary, the Chair noted the questions and issues related to possible Ebola aerosolization and that there is strong epidemiological data discounting the question. He noted the shipping challenges associated with proper packaging and transportation of Ebola specimens, and added there is a need for the agencies and industry to determine the proper decontamination procedures for instrumentation used during Ebola testing.

The Chair summarized the meeting discussion highlights and recommendations:

- Recommend that: HHS should facilitate the development of a non-punitive and non-regulatory self-assessment checklist-type tool and recommend it for biennial use by all Certificate of Waiver testing sites. It could also be used prior to or at the time a site first applies for a CLIA Certificate.
  - Items on the checklist should include recommended practices based on the "Ready? Set? Test!" booklet and should address known problem areas of importance (e.g., off-label use of waived tests).
  - The checklist could also assess whether the Certificate of Waiver site reports test system performance problems to the FDA.
  - Certificate of Waiver testing sites should be encouraged to keep copies of their completed assessments on file to be validated during CMS site visits and/or the assessments could be reported to CMS through an online portal.
- Recommend that: CMS should revisit the A19 request to open up the CLIA law to allow changes to the waived testing requirements and provide a description of the details of the A19 request at the next CLIAC meeting.

- Recommend that: CMS should explore:
  a. Regulatory changes or guidance(s) that would allow virtual crossmatching to replace physical crossmatching as a pre-requisite for organ transplant;

b. Appropriate criteria and decision algorithms, based on the Virtual Crossmatch Workgroup input provided to CLIAC, under which virtual crossmatching would be an appropriate substitute for physical crossmatching. The determination of appropriate criteria and decision algorithms should involve a process that includes an open comment period.

- Discussion around the FDA guidance for laboratory developed tests topic included support for a risk-based approach to regulation of LDTs.
- Discussion around the laboratory biosafety in the United States topic included potential changes in safety that might result from the Ebola outbreak.

Useful Links for CLIAC ***Addendum* 14**
***Addendum* 15**

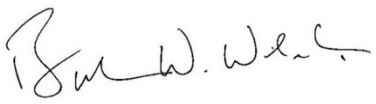
ACRONYMS ***Addendum* 16**

PUBLIC COMMENTS ***Addendum* 17**
***Addendum* 18**
***Addendum* 19**
***Addendum* 20**

ADJOURN

Dr. Wilcke acknowledged the staff that assembled the meeting program and thanked the CLIAC members and partner agencies for their support and participation. He announced the Spring 2015 CLIAC meeting dates as April 15-16, 2015, and adjourned the Committee meeting.

I certify this summary report of the *November 5-6, 2014*, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.



_____ Dated: 1/ 26 /2015

Burton Wilcke, Jr., Ph.D., CLIAC Chair