Clinical Laboratory Improvement Advisory Committee

Summary Report

March 6-7, 2013

Atlanta, Georgia

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

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RECORD OF ATTENDANCE

Committee Members Present
Dr. Paula Santrach, Chair
Mr. Eugene Augustine, Jr.
Dr. Robert Baldor
Dr. Edward Chan
Dr. Martha Crenshaw
Dr. Judy Daly
Dr. Anand Dighe
Dr. John Fontanesi
Ms. Lezlee Koch (remote)
Ms. Karen Lacy
Dr. Anthony Okorodudu
Dr. Robert Sautter
Ms. Paula Vagnone
Dr. Linda Ward
Dr. Burton Wilcke, Jr.
Dr. David Wilkinson
Dr. Qian-Yun Zhang
Mr. Robert DiTullio, AdvaMed (Liaison Representative)

Committee Members Absent
Dr. Keith Kaplan
Dr. Gail Vance

Ex Officio Members
Dr. Devery Howerton, CDC
Ms. Judith Yost, CMS (remote)
Dr. Alberto Gutierrez, FDA

Designated Federal Official
Dr. May Chu

Record of Attendance—continued

Centers for Disease Control and Prevention (CDC)

Dr. Simon Adebola
Mr. Todd Alspach
Dr. J. Rex Astles
Mr. Michael Astwood
Ms. Yashieka Blount
Ms. Diane Bosse
Dr. Denise M Cardo
Dr. Roberta Carey
Dr. Bin Chen
Dr. Nancy Cornish
Dr. Tracy Dalton
Dr. Maryam Daneshvar
Mr. Swapnil Deshpande
Dr. Jan Drobeniuc
Ms. Evelyn Dunn
Ms. Joanne Eissler
Ms. Maribeth Gagnon
Ms. Mary Garcia
Dr. Amy Gargis
Dr. Christopher Greene
Mr. Jeffrey Hageman
Ms. Patricia Haskell
Dr. Lisa Kalman
Ms. Susan Kikkert
Dr. John Krolak
Ms. Melanie Lawson
Mr. Ken Long
Ms. Rachel Lovett
Dr. Ira Lubin
Dr. Feda Masseoud
Ms. Alana McCoy
Ms. Leslie McDonald
Ms. Graylin Mitchell
Dr. Janet Nicholson
Mr. Urmil Parekh
Dr. Joe Perz
Ms. Terri Phan
Ms. Anne Pollock
Dr. John C Ridderhof
Mr. Adeeba Saboor
Dr. John Saindon Jr.
Ms. Megan Sawchuk
Dr. Melissa Schaefer
Dr. Shahram Shahangian
Mr. Darshan Singh
Dr. Elizabeth Skillen
Ms. Theresia Snelling
Ms. Jessica Soper
Mr. Patrick Sprinkle
Ms. Heather Stang
Ms. Sonya Strider
Dr. Shambavi Subbarao
Ms. Vickie Sullivan
Dr. Julie Taylor
Ms. Angela Thompson
Mr. H. Eric Thompson
Ms. Monica Toles
Dr. Hubert Vesper
Ms. Elizabeth Weirich
Ms. Glennis Westbrook
Ms. Irene Williams
Dr. Laurina Williams
Ms. Yasmine Zavahir
Dr. Barbara Zehnbauer
Mr. Jonathan Zhong

Record of Attendance—continued

Department of Health and Human Services (Agencies other than CDC)
Dr. Steve Gitterman (FDA) (remote)
Ms. Daralyn Hassan (CMS)
Ms. Leslie Landree (FDA) (remote)
Dr. Clem McDonald (NIH)
Dr. Sheila Murphey (FDA) (remote)

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 to all CDC and FDA staff on intranet protocol television (IPTV).

CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC) BACKGROUND

The Secretary of Health and Human Services (HHS) 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 (US). The Secretary is authorized under Section 222 to establish advisory Committees.

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 Clinical Laboratory Improvement Amendments (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, CDC; the Commissioner, FDA; the Administrator, CMS; and such additional officers of the US 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. May Chu, Designated Federal Official (DFO), Clinical Laboratory Improvement Advisory Committee (CLIAC), and Director, Laboratory Science, Policy and Practice Program Office (LSPPPO), Office of Surveillance, Epidemiology and Laboratory Services (OSELS), CDC, welcomed the Committee and the members of the public, acknowledging the importance of public participation in the advisory process. She said the agenda was forward-looking and that she was anxious to hear what CLIAC would discuss, given that HHS benefits from the Committee's advice.

Dr. Chu recognized the four outgoing CLIAC members who were to receive plaques and letters of appreciation for their service on the Committee. They were Dr. Judy Daly, Dr. John Fontanesi, Dr. Paula Santrach, and Dr. Gail Vance. Dr. Santrach also recognized Dr. Jeffrey Kant, who was a member of CLIAC but was never able to attend the meetings. Dr. Kant passed away on September 29, 2012.

Dr. Paula Santrach, Chair, CLIAC, welcomed the Committee and called the meeting to order. All members then made self-introductions and financial disclosure statements relevant to the meeting topics.

AGENCY UPDATES AND COMMITTEE DISCUSSION

Centers for Disease Control and Prevention (CDC) Update ***Addendum 01***

Devery Howerton, Ph.D.
Division of Laboratory Science and Standards (DLSS)
Laboratory Science, Policy and Practice Program Office (LSPPPO)
Office of Surveillance, Epidemiology and Laboratory Services (OSELS)
Centers for Disease Control and Prevention

Dr. Howerton's presentation highlighted the plans for a gynecologic cytology workload study, several proficiency testing (PT) projects, *Healthcare News*, genetic testing guidance, on-line training products recently made available by CDC, and the DLSS quality improvement research program. She reminded everyone that CLIAC has discussed the workload in image-assisted gynecologic screening on several occasions, and that problems with Pap smear testing were one impetus behind passage of CLIA. Cytology and workload continue to be topics of major interest, and Dr. Howerton reviewed some of the issues that have previously been presented to CLIAC regarding these topics before describing the upcoming study. Regarding PT, the regulatory revision is still in progress and the survey to be conducted in conjunction with the Association of Public Health Laboratories (APHL) in 2013 is currently undergoing the Office of Management and Budget clearance process. Information promoting the survey is expected to be published soon. DLSS' weekly compilation of clinical laboratory and related news, *Healthcare News*, is now available through the LSPPPO website. Those interested may access and subscribe to the newsletter at: http://www.cdc.gov/osels/lspppo/healthcare_news.html.

Regarding genetic testing guidance and on-line training products, Dr. Howerton discussed the training for good laboratory practices for molecular genetic testing which was based on a previous CDC *Morbidity and Mortality Weekly Report: Recommendations and Reports (MMWR R&R)* publication. This free training can be accessed through the APHL website. Another on-line training now available is "Strategies for Improving Rapid Influenza Testing in Ambulatory Settings (SIRAS)." This training was developed by CDC in collaboration with the Joint Commission. Dr. Howerton shared data regarding the number of continuing education credits awarded for the two courses and reported that feedback has been positive for both. She also mentioned that CDC has been assessing issues regarding quality standards for next-generation sequencing (NGS), which would be discussed in more detail later in the meeting. She concluded by updating the Committee on the Clinical Laboratory Integration into Healthcare Collaborative (CLIHC™) and Laboratory Medicine Best Practices (LMBP™) initiatives, future DLSS plans to evaluate the impact of laboratory practice recommendations and guidelines, and expanded efforts and partnerships in the Genetic Testing Reference Material (GeT-RM) Program.

Committee Discussion

- Responding to inquiries from a Committee member regarding whether the articles in *Healthcare News* are solely from the lay press and if they are international or US only, Dr. Howerton indicated that for the most part, the publication includes excerpts from the lay press and links to the articles are included in the newsletters. While the sources of the articles are primarily from the US, some may discuss cutting edge tests developed in other countries.
- In response to a member's question regarding whether CDC or the CLIHC™ group is engaged in any efforts related to laboratory- or pathologist-driven algorithms for test ordering, Dr. Howerton reported that the CLIHC™ group is considering developing algorithms and CDC hopes to be able to develop more apps. Potential opportunities are being explored, in collaboration with CDC informatics specialists, for integration of algorithms into electronic health records (EHRs) and computerized provider order entry systems in ways that would allow point-of-care access to the algorithms. There have also been discussions with CDC's HIV program about developing algorithms for HIV tests. Dr. Howerton acknowledged that development of algorithms is complicated since a number of stakeholders need to be involved.
- A member commended the Joint Commission and CDC for the influenza website that had been developed and asked about the need for annual updates to the information regarding rapid testing, noting the fact that influenza variants change from year to year. The member expressed concern that there is misinformation in the physician office community about the reliability of the rapid tests. Dr. Howerton acknowledged the member's comment and indicated that CDC hopes to update the training if new information is made available.

Food and Drug Administration (FDA) Update *Addendum 02*

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

Dr. Gutierrez reported that the FDA completed its major reorganization process and reviewed and explained the new organizational chart. Two positive aspects of the reorganization were a refocus of OVID on total product life cycle regulation and an increase in the number of first line managers. The Medical Device User Fee and Modernization Act III (MDUFA III) was implemented in October 2012, and Dr. Gutierrez described some of the changes and additions to the Act. He reviewed premarket application approvals, de novo down-classifications, and guidances that FDA has developed over the past year. He said the guidance "Factors to Consider When Making Benefit-Risk Determinations in Medical Devices" is of particular interest because it marks the first time FDA has developed guidance focusing on how the agency balances risks and benefits and reaches determinations regarding whether devices are safe and effective. He also described two notable panel meetings convened in the last year and reminded the Committee of the three ways in which tests can become waived under CLIA. He related this information to waiver of test devices such as glucose meters and concerns about infection control and their accuracy when being used with critically ill patients. The FDA convened a public meeting in March 2010 that resulted in the development of warning labels for meters stating, "Not to be used for patients who are critically ill." Due to the subsequent outcry from hospitals regarding what constitutes "critically ill" and implications pertaining to contraindications, the language in the manufacturer instructions was changed to "the performance of this system has not been evaluated in the critically ill." Incorporation of this language in manufacturer instructions has raised concerns since use of glucose meters for critically ill patients in hospital settings would thus constitute off-label use of the devices.

Committee Discussion

- Regarding a member's question about whether a point-of-care system is defined as a screening or definitive device, Dr. Gutierrez indicated that the FDA clears devices based on what the manufacturer claims is the intended use. The data FDA requires from manufacturers differs depending upon whether the manufacturer claims that the intended use would be screening or definitive. While devices are cleared one way, physicians may sometimes use them differently (e.g., off-label). However, in doing so they are responsible for assuring that the off-label use is safe and effective. There is no guarantee that a device used off-label will work the same way as intended or that the manufacturer has the necessary controls for such use.
- A member asked what kind of liability a laboratory would have if they use a laboratory-developed assay that is comparable to, but differs from, an assay submitted as the companion test for a certain drug. Dr. Gutierrez responded that liability is difficult to address and laboratories may use tests they develop if they validate (establish performance specifications) for those tests. He added there are a number of

issues pertaining to companion diagnostics and use of other than the approved companion diagnostic may not be a sustainable model for public health.

- A member asked whether differences between FDA and Clinical and Laboratory Standards Institute (CLSI) breakpoints for antimicrobial susceptibility testing had been reconciled. Dr. Gutierrez replied the issue pertains to whether OIVD can clear a test for use with breakpoints not in the drug label. By law, FDA is not permitted to do so and the labels cannot contradict each other. He stated FDA is working on this issue.
- Several members commented on the FDA's approach to clearing assays for use with critically ill patients and, specifically referring to glucose tests, the expected accuracy and precision of meters, especially at very elevated glucose levels. The Chair added the issue is really performance of the tests when glucose levels are outside of the normal range. It can be difficult to define what is considered critically ill. Also, because hospitalized patients' glucose levels tend to be higher than levels observed in outpatients, performance characteristics of the tests being used are important.
  Dr. Gutierrez indicated that the FDA is particularly concerned about the use of CLIA-waived tests, especially in non-laboratory sites. Testing in these settings needs to be performed by individuals who understand clinical laboratory testing, as well as how to validate a test.
- Mr. DiTullio said the FDA's input on requirements for test system performance with very elevated glucose levels would be useful. He acknowledged the need for devices to be accurate, but noted this may sometimes be overlooked because of FDA's requirements for precision throughout the range. A member noted that protocols for tight glycemic control are often made without regard to uncertainty and suggested that the laboratory has to come to consensus with medical practice because the algorithm for change should also incorporate the degree of uncertainty. Another member emphasized that point-of-care testing makes it easier to take care of patients, and faster turnaround times may actually improve care. Slight variability in accuracy or precision may not matter clinically. Dr. Gutierrez responded that accuracy for over the counter (OTC) glucose meters was set at plus or minus 20% across the range by the 2003 International Organization for Standardization (ISO) standard; however, a new ISO standard of plus or minus 15% has just been set, which is an improvement. He noted that at a recent FDA meeting there was consensus from the community that plus or minus 10% would be preferable for hospitals. The FDA is developing guidance to set standards that they believe are appropriate in the hospital setting.
- A member expressed concern that the burden of proof for glucose meter accuracy is being placed on laboratories when it should be placed on manufacturers. If the FDA believes that plus or minus 10% is suitable, the agency should address this with the laboratory device manufacturers. If the burden rests with laboratories, it could result in issues with regulatory agencies that inspect laboratories. Dr. Gutierrez agreed the FDA needs to set an appropriate standard for meters cleared for use in hospital settings and stated they are working through this process. If a laboratory and hospital decide to use a glucose meter off-label, the responsibility to establish performance for that device lies with them.

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

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

Ms. Hassan's presentation focused on CLIA statistics; the status of the Patient Access Rule and the recently passed Taking Essential Steps for Testing Act of 2012 (TEST Act); and the CMS plan to institute the Individualized Quality Control Plan (IQCP) approach. Data through January 2013 show that CLIA enrollment has increased, predominantly among laboratories with a CLIA Certificate of Waiver. The final Patient Access Rule is currently undergoing CMS clearance with a tentative publication date of late summer 2013. Once published, CMS will review the CLIA Interpretive Guidelines to ensure that laboratories and stakeholders have clear guidance on best practices/resources to implement health information technology. The TEST Act was an amendment to the CLIA statute signed by the President in December 2012. Ms. Hassan explained the purpose and benefits of the TEST Act, indicated that the next step is rulemaking to define when the discretion will be applied and when the revocation and sanctions will be imposed, and emphasized that PT samples should not be sent to another laboratory in the meantime. The CMS PT brochure located on the CLIA website offers clear guidance on PT referral. Last, Ms. Hassan provided a brief history of CLIA quality control, discussed the new IQCP and how it differs from Equivalent Quality Control (EQC), and stressed that EQC is still being implemented until IQCP is operational. There will be an education and transition period for laboratories before IQCP is fully effective. Information and guidance will be provided at http://www.cms.hhs.gov/clia/ and questions may be emailed to IQCP@cms.hhs.gov. Ms. Hassan emphasized that CMS will not issue regulatory citations pertaining to control procedures prior to the end of the education and transition period for IQCP unless they identify serious test quality problems.

Committee Discussion

- Responding to a member's question regarding how CMS would monitor the laboratories that adopt IQCP, Ms. Hassan indicated that CMS is developing surveyor training and will publish the guidelines. The guidelines will address what documentation the laboratory must have to demonstrate they are truly controlling their test systems.
- A member inquired as to whether the dates and been determined for IQCP education and transition period. Ms. Hassan replied that the dates could not be set until the guidelines are published.
- One member expressed excitement about having possible QC templates that could be used for every test and analyzer.
- Another member asked if accrediting organizations have an option as to whether to adopt the new QC approach. Ms. Hassan responded that accreditation organizations will have the option regarding adoption of IQCP.

Board of Scientific Counselors (BSC) Update ***Addendum 04***

Robert Sautter, Ph.D.
Committee Liaison to CDC Board of Scientific Counselors, Office of Infectious Diseases (OID)
Director of Microbiology
Carolinas Pathology Group
Charlotte, NC

Dr. Sautter provided a summary of the December 2012 CDC BSC meeting. He indicated that a primary theme of the meeting was strengthening the clinical and public health interface with a focus on two areas: addressing pertussis and implementing new recommendations for reducing morbidity and mortality due to infection with hepatitis C virus (HCV). The meeting also included reports from the BSC Food Safety Modernization Act Surveillance Working Group and the Antimicrobial Resistance Working Group; updates on CDC's infectious disease activities, including a presentation on the multistate outbreak of fungal meningitis; a presentation by Dr. Khabbaz that provided updates from the Office of Infectious Diseases and the three infectious disease national centers; updates focused on CDC leadership changes, budget, and cross-cutting issues; and a lengthy discussion with CDC Director Thomas Frieden regarding a variety of topics.

Committee Discussion

- A member inquired about the need to monitor antibiotic resistant organisms in animals with regard to transmission to humans, particularly from companion animals and livestock. Dr. Sautter replied this was discussed and agreed with the importance of this type of monitoring, adding animal feed should also be monitored.
- Another member requested input about the ability to acquire antibiotics through the internet and other countries and the idea that stewardship should be an international effort. While Dr. Sautter agreed that this should be a worldwide effort, he was unsure it would occur.
- One member pointed out antibiotic overuse is often patient-driven because patients expect to receive medication when they are ill. CMS contributes to that problem in terms of the quality parameters that are related to patient satisfaction. A national public health education campaign is needed to address this issue. Dr. Sautter agreed.
- Responding to a member who inquired as to whether the BSC discussed the current influenza season and to a member who reported that in their state numerous smaller hospitals were at pandemic levels, Dr. Sautter replied there was discussion pertaining to the H3N2 variant and the relief that it was not widely transmitted. At the time of the meeting, the influenza season was ramping up early and the numbers and types observed were substantial compared to the previous season when influenza was virtually non-existent. Influenza variants, including H3N2, that tests could not detect had been identified in three instances, which was of special concern.

- A member inquired whether CLIA includes quality control standards that would have prevented the 2012 multi-state outbreak that resulted from contaminated medication. Dr. Sautter replied there are many regulations for pharmacy, but the pharmacy house in which this occurred failed to make changes that would have prevented this severe event. He noted that many times pharmacies and compounding facilities use specialized laboratories for preparing their materials and solutions and may not rely on clinical laboratories that are subject to CLIA. However, he added he was concerned because of his dependence on the pharmacy in his hospital for certain products used by his laboratory.
- Dr. Gutierrez added it was the FDA's understanding that this situation was not within their purview. However, he noted some similarities to FDA's ability to exercise regulatory enforcement over laboratory-developed tests. A drug manufacturer is responsible for those who are conducting their testing and is supposed to hold them to meeting quality system requirements. Laboratories do not tend to have the same type of quality systems that the FDA requires manufacturers to have. They may not audit raw material providers as device manufacturers do. He indicated that someone from the FDA could possibly give a presentation to CLIAC regarding the quality system requirements for drug manufacturing.
- The Chair indicated she did not believe this issue falls under CLIAC's purview. Dr. Chu agreed that CLIA oversees human diagnostic testing.

Update: CDC Clinical Informatics Team Activities ***Addendum 05***

Ms. Megan E. Sawchuk, MT (ASCP)
Division of Laboratory Science and Standards (DLSS)
Laboratory Science, Policy and Practice Program Office (LSPPPO)
Office of Surveillance, Epidemiology and Laboratory Services (OSELS)
Centers for Disease Control and Prevention

Ms. Sawchuk began her presentation by noting that she attended the Department of Health and Human Services (HHS), Office of the National Coordinator for Health Information Technology (ONC) meeting in September, during which Dr. Farzad Mostashari issued the Acceleration Challenge. His message, delivered primarily to EHR vendors, was that the patient is the focus and needs the EHR to function well and be secure and private. She then presented an update on CDC's Laboratory Healthcare Information Technology (LabHIT) Team activities, indicating the LabHIT Team has been operational for about a year and a half. She described the LabHIT Team's primary role, initial work, and recent activities. She called particular attention to a white paper under development titled *A Call to Action: Ensuring the Safety and Effectiveness of Laboratory Data in EHR Systems*. The target audience for this paper is laboratory professional organizations and individual laboratory professionals. The paper includes three main recommendations with actionable strategies under each. Ms. Sawchuk reported that following the August 2012 CLIAC meeting, the Committee sent a letter to the Secretary of HHS with a four-part recommendation and that HHS has indicated a written response to that letter is forthcoming. She also described the goals/objectives of the ONC Laboratory Report Workgroup Tiger Team. CDC and CMS are involved with this team and there has been a recent increase in pathologist informaticist involvement.

The Tiger Team will soon submit their formal recommendations to ONC. Ms. Sawchuk reviewed external partner engagement activities, discussed internal CDC engagement, highlighted team activities since the August 2012 CLIAC meeting, and offered information regarding future activities. In conclusion, she emphasized that a tremendous amount of prograss has been made toward the original LabHIT vision and offered several examples.

Committee Discussion

- With respect to the CLIAC letter sent to HHS, the Chair indicated that she engaged in a conversation with Dr. Jacob Reider, the Chief Medical Officer for ONC. She thought he understood laboratory reporting and ordering issues related to usability, particularly with respect to how reporting and ordering fit into a physician's workflow. However, he did not seem to fully appreciate the laboratory workflow that is often supported by specific laboratory information systems and middleware needed to get tests done. They discussed workflow and quality measures and agreed to maintain communication and make an effort to involve CLIAC, either through the LabHIT team or by inviting him to a CLIAC meeting. There may be additional opportunities identified when CLIAC receives the HHS response to their 2012 letter.
- Ms. Sawchuk acknowledged the team's efforts and the impact they are making in this area. She also thanked the Committee for their recommendations supporting the work the LabHIT team is doing.

PRESENTATIONS AND COMMITTEE DISCUSSION

Infection Control and Point-of-Care Testing

Introduction ***Addendum 06***

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

Dr. Gutierrez pointed out that while the presentations for this session would be glucose meter-based, it was important to remember that the issues are much broader, as alluded to in the morning discussion, and must be addressed for other point-of-care test systems as well. The FDA believes that regulatory and policy decisions have been drivers of some issues, however, the ability to acquire CLIA waived status through FDA's OTC submission mechanism has resulted in the waiver approval of a number of products being used in point-of-care settings. Although the FDA does not condone this practice, it has been difficult to prevent it from occurring. In terms of quality systems, manufacturers should design devices for their actual use in order to understand and mitigate risks. Consideration must be given to how to better address point-of-care testing issues.

CDC Healthcare Acquired Infections and MMWR *Addendum 07*

Melissa Schaefer, MD *Addendum 07A*
Division of Healthcare Quality Promotion (DHQP) *Addendum 07B*
Natl Ctr For Emerging & Zoonotic Infectious Diseases (NCEZID)
Office of Infectious Diseases (OID)
Centers for Disease Control and Prevention

Dr. Schaefer's presentation focused on defining assisted monitoring of blood glucose (AMBG), bloodborne pathogen transmission during blood glucose monitoring through indirect contact transmission, the US experience with hepatitis B virus (HBV) outbreaks during AMBG, and CDC evidence-based infection prevention recommendations focused on point-of-care testing or blood glucose monitoring. She pointed out that while risks apply to any similar point-of-care testing devices, blood glucose monitoring has the longest history of outbreak experience and recommendations. She said a significant amount of work has been done by the CMS Survey and Certification Group to educate surveyors on what to look for in facilities and to ensure that they issue citations if recommendations are not being followed. Dr. Schaefer described the evidence-based recommendation targeting point-of-care testing in more detail, and shared data substantiating that meters serve as a source of transmission. She emphasized this has been the most difficult source of transmission for people to comprehend. In conclusion, Dr. Schaefer shared some CDC infection prevention resources and invited input regarding how to disseminate the recommendations to end users to reduce the problems still being observed with glucose meter use.

Committee Discussion

- A member pointed out that the FDA specifies the decontamination method to be used with multi-use devices and inquired whether the use of methods other than those specified would be considered off-label use. Dr. Gutierrez responded that the issue pertains to whether facilities validate alternative methods to ensure that they correctly disinfect and do not corrode the meter. It should also be confirmed with the manufacturer that other methods of decontamination will not invalidate their guarantee.
- One member asked who surveys assisted living facilities. Dr. Schaefer replied that while other healthcare settings are subject to routine inspections, assisted living facilities represent a gap as they are largely unregulated and the personnel working in them may not be as well-trained as in other facilities.
- A member asked whether CDC was aware of any infections caused by handheld devices, which are not easily cleanable and are being used increasingly to scan wristbands, print labels, and do phlebotomy. Dr. Schaefer responded that, while she did not have as much knowledge about those particular devices, any point-of-care device that is exposed to blood and is used from patient to patient carries the same theoretical risks.

- Thinking about the previous discussions pertaining to the use of an OTC submission mechanism as an alternative route to CLIA waiver approval, a member asked whether prescription home use approval was a similar issue. Dr. Gutierrez answered that the issues are the same, particularly if those devices are used in point-of-care settings.
- A member asked whether infection prevention and control concerns regarding point-of-care testing devices might also apply to other items related to testing that are transported from patient to patient and could be contaminated with blood. The Chair noted that sometimes a cart with a device on it may not be taken directly to patients' bedsides, but does move from one patient's room to the next. Dr. Schaefer replied that while there is less concern with cleaning and disinfecting stationary devices that remain in the laboratory and do not serve as potential vectors of disease, any devices that are taken to a patient's bedside are of concern if infection prevention is overlooked (e.g., hand hygiene, changing gloves, not using the same finger stick device).
- A member pointed out that individuals working in settings who conduct assisted glucose monitoring might be low paid, encouraged to save money, encouraged to work faster than necessary, and probably have little knowledge of infectious disease transmission. The member suggested there be a way to provide education for these individuals so they can better understand the issues and make behavioral changes, if needed. Dr. Schaefer agreed that education is critical, but suggested that improving equipment design is also important.

FDA OIVD Testing Perspective-Single vs. Multi-patient Device Usage ***Addendum 08***

Leslie Landree, Ph.D.
Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Chemistry and Toxicology Devices
Center for Devices and Radiological Health
Food and Drug Administration

Dr. Landree presented an overview of the FDA, CDC, and CMS response in 2010 to outbreaks of viral hepatitis among patients from the shared use of lancing devices and point-of-care glucose meters. Given that these outbreaks resulted in a change in the FDA regulatory review requirements related to cleaning and disinfection processes, FDA, CDC, and CMS worked closely with manufacturers to develop acceptable infection control protocols for these devices and incorporate those protocols into the glucose meter labeling. With regard to the change in requirements, FDA specified four areas that needed to be addressed by manufacturers, those being: intended use (home use by a single individual versus those intended to be used on multiple patients in a healthcare setting); separate naming schemes that tie the components (lancets, meter, and test strips) together and differentiate the systems (single- versus multiple-patient use); cleaning and disinfection validation testing protocols; and safe labeling. Dr. Landree concluded that these new infection control requirements have become standard practice for blood glucose meter reviews. FDA continues to encourage manufacturers to keep in mind the importance of designing meters for different uses, and to design them so that they can withstand repeated cleaning and disinfection.

Committee Discussion

- A member questioned whether the FDA plans to revisit the robustness of the requirement to perform 10,000 wipes to validate a glucose meter as being usable for three to five years. Some companies offered to replace meters after one year free of charge to obviate the need to meet that requirement, but they have been turned down by the FDA. Dr. Landree answered that in the beginning some manufacturers did want a shorter life cycle. The FDA's thinking at the time was that since with typical use, the life of meters is three to five years, it would be burdensome for users to replace their meters every year. They invited recommendations regarding how one-year replacement would be executed, but received no suggestions. The FDA was concerned that people would continue to use deteriorated meters, would not contact the company, and that companies may not proactively contact users to replace their meters. Dr. Gutierrez agreed that the FDA is always happy to entertain a different approach, but it is incumbent upon the manufacturer to demonstrate to the FDA that what they are proposing is reasonable and a valid way to proceed.
- A member noted that if a manufacturer recommends one type of disinfectant and someone wants to use another disinfectant, the manufacturer should indicate that alternative disinfectant(s) need to be validated. In addition, the member pointed out that a device must be cleaned with a detergent to remove protein and the detergent must remain in contact for a specified period in order for it to work. Dr. Landree responded the pre-clean step is recommended prior to the disinfecting step in order to align with EPA-registered labeling. The FDA decided to simplify this by having the user employ the same disinfectant product wipe for cleaning and disinfecting. The user would pre-clean with the wipe to remove dirt or blood from the surface and would use a second wipe to disinfect for the appropriate contact time.

FDA Guidance: Lancets ***Addendum 09***

Sheila Murphey, M.D.
Branch Chief for the Infection Control Devices Branch (INCB)
Division of Anesthesiology, General Hospital, Infection Control and Dental Devices
Office of In-Vitro Diagnostic Device Evaluation and Safety (OIVD)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Dr. Murphey emphasized that lancet safety issues have been long-term. Lancets are pre-amendment devices dating back to the 1920s, classified under the regulations for manual surgical instruments. She traced their regulatory history at the FDA and safety issues related to their improper use. She said FDA and CDC issued a joint safety communication in 2010 warning that the use of lancet devices on more than one patient had transmitted HBV and HCV, the frequency of this was increasing, and lancets should never be used for more than a single patient. Also in 2010, CMS issued a Survey Memorandum on point-of-care testing for nursing homes listing the use of lancet devices on more than one patient as a major infection control deficiency, and the FDA issued an emergency labeling guidance for blood lancet labeling. The FDA guidance recommended that all lancet devices be labeled for use only on a single patient and healthcare personnel should not use them for assisted blood draws. In August 2010, FDA indicated that the

Agency would review the classification of blood lancets. Given that regulatory entities may need more than labeling guidance to support action, FDA continues to review the regulatory status of blood lancet devices. Dr. Murphey next briefly described the three classes of medical devices and their levels of risk, explained FDA's general controls for all devices, briefly described the general guidance documents the FDA publishes for device classes, and specified the FDA options to improve device safety including labeling guidance. Consideration must be given to whether blood lancets should continue to be Class I devices or if they should be Class II or III devices. The FDA continues to work on appropriate regulatory requirements for lancets.

Committee Discussion

The Chair inquired as to whether multi-use lancets are dangerous enough to ban, given that it is extremely difficult to control who acquires them or how they are used. Dr. Murphey responded that the criteria for banning a device are very strict. The only device FDA has ever banned was plastic hair implants, although they have received petitions to ban other devices, some of which are still being reviewed and others that have been denied. Reclassification to Class III requires absolute proof of safety during use, as demonstrated through a clinical trial. She added that some people like the multi-use devices because they are easier to regulate in terms of depth and control, but someone could design a better single use only device.

CMS Survey Guidance ***Addendum 10***

Karen Hoffman, RN, MS, CIC, FSHEA
Division of Laboratory Services
Survey and Certification Group
Centers for Medicare & Medicaid Services

Ms. Hoffman discussed the CMS standards for infection control, particularly with regard to finger stick and point-of-care devices and how these standards are applied in the survey process. CMS recognizes the risk of point-of-care devices for transmission of infectious diseases, has offered trainings to surveyors to increase awareness of the risks, and has worked with CDC to develop infection control surveyor tools that include point-of-care devices. The CMS infection control tools can be used as an assessment tool for healthcare facilities. They can be downloaded from the CMS or CDC website. In 2010, CMS and CDC also began the Hospital Patient Safety Initiative for hospitals to address outbreaks and patient safety issues. As part of this initiative, a different pilot survey tool was created and this tool is also accessible online. It is important to note that surveyors are not citing facilities during the pilot study. Hospitals are aware of this, and the tools are being promoted on websites focused on infection control and prevention.

Regardless of the facility type, Ms. Hoffman explained that healthcare personnel must clean and disinfect their point-of-care meters after every use and must follow the manufacturer's instructions for the meter and use the Environmental Protection Agency (EPA) registered disinfectant product. Surveyors may ask for a copy of the manufacturer's instructions. When no manufacturer's instructions exist for cleaning and disinfection, surveyors will investigate whether the methods for cleaning and disinfection

of meters follow standards of practice by authoritative references and whether cleaning agents and disinfectants are shown by the device manufacturer to be compatible with their device.

Committee Discussion

- A member thought there was a slight difference in what Dr. Hoffman stated versus Dr. Gutierrez's earlier response regarding use of a different decontamination procedure than the one in the manufacturer's instructions. Clarity was requested regarding whether use of an alternative decontamination product would be acceptable if the hospital demonstrates the alternative meets all criteria and has a written statement from the manufacturer saying that use of the alternative product will not damage the meter. Ms. Hoffman responded that the disinfection product must be validated by the manufacturer as an alternative product that will not damage the meter or affect its operation. The disinfection product also has to be on the EPA list as being effective for killing bloodborne pathogens. Dr. Gutierrez indicated the FDA looks for the manufacturer to validate a method and to give detailed information on how the validation is to be performed. If the user is not going to follow the manufacturer's instructions, it is an off-label use and does not fit into a CLIA-waived setting. Use of the alternative product would result in the test being considered high complexity under CLIA. If certified to perform high complexity testing, the laboratory could then validate use of an alternative decontamination product.
- Dr. Howerton clarified that the only requirements needed to perform waived testing are to have a Certificate of Waiver and to follow manufacturer's instructions for a test. Ms. Hoffman agreed.

CLIAC Discussion
Paula Santrach, M.D.
CLIAC Chair

At this time, Dr. Santrach posed two questions for members to consider and discuss. Committee suggestions follow each question:

1) How can HHS better assure that laboratories and healthcare facilities are aware of the guidances and infection control efforts made by CDC, CMS, and FDA pertaining to the risk of disease transmission when sharing handheld point-of-care testing devices?

    - ❑ Solicit support from laboratory accreditation organizations to disseminate information and make recommendations regarding infection control.
    - ❑ Clearly label meters and other devices to indicate that they must be cleaned between patients, and possibly incorporate a question as a means to lock out use if cleaning is not done.
    - ❑ Maintain separate labeling for single patient use versus multiple patient use.
    - ❑ Ensure that infection control is part of the initial training delivered by manufacturers.
    - ❑ Consider including a statement in labeling that only people with infection control training should be permitted to use meters or other similar devices.

- ❑ Recognize there are many point-of-care settings that are not typical healthcare facilities (e.g., assisted living centers, long-term care facilities, health fairs, medical clinics in homeless shelters, schools) and these settings may not be regularly inspected.
- ❑ Find the best mechanism to increase the visibility of infectious disease risks, such as through professional societies and educational bodies so that individuals hear the messaging from multiple directions.
- ❑ Target information to specific types of facilities where there are known risks.

2) What additional training, guidance, or educational materials would be helpful?

- ❑ Develop and post pictorial job aids or Quick Reference Guides for glucose meters that clearly show how to disinfect meters, and explain infection prevention measures.
- ❑ Post YouTube videos showing how to clean meters.
- ❑ Incorporate information about this mode of transmission into annual blood-borne pathogen training.

Next Generation Sequencing

Assuring the Quality of New DNA Sequencing Technologies in the Clinical Laboratory ***Addendum 11***

Ira Lubin, Ph.D.
Division of Laboratory Science and Standards (DLSS)
Laboratory Science, Policy and Practice Program Office (LSPPPO)
Office of Surveillance, Epidemiology and Laboratory Services (OSELS)
Centers for Disease Control and Prevention

During this session, Dr. Lubin discussed next generation sequencing (NGS) in clinical settings and the challenges and approaches to assuring NGS quality. He indicated it is now possible to sequence almost the entire 3 billion bases of the human genome, which has opened up new and unique diagnostic opportunities that have led to the documented saving of lives. The technologies are rapidly coming to a price point that is making them attractive to laboratories to replace existing molecular technologies and provide new capabilities. Dr. Lubin cited specific situations in which NGS has been used successfully in the diagnosis of rare diseases and has had applications in directing cancer therapies. Other clinical applications are in development. Dr. Lubin next explained Sanger Sequencing, the gold standard, and discussed how NGS technologies work in a fundamentally different way. The major challenge for assuring the quality of NGS in clinical practice is to meet existing regulatory requirements and professional standards. Recognizing that the new sequencing technologies are likely to have a major influence on laboratory medicine, CDC established the Next Generation Sequencing—Standardization of Clinical Testing (Nex-StoCT) Workgroup in 2011 to develop guidance for implementing NGS into clinical settings. The Nex-StoCT Workgroup addressed the topics of test validation, quality control procedures, independent assessment of test

performance, and reference materials. One of the major contributions from this work was the clarification of CLIA performance characteristics as they pertain to NGS. The guidelines that resulted from the Workgroup deliberations were published in Nature Biotechnology in November 2012 and are available at: http://www.nature.com/nbt/journal/v30/n11/full/nbt.2403.html

Dr. Lubin described several other efforts by professional and standard setting organizations, the validation framework for the implementation of clinical NGS testing, quality control procedures, PT and alternate assessment, the availability of reference materials and the challenges they pose for NGS, and two projects that are underway to address issues related to informatics. A second Nex-StoCT Workgroup meeting was convened in October 2012, the focus of which was optimization of the bioinformatics pipeline in preparation for test validation. He concluded that clinical NGS testing can be analytically and clinically valid for a number of medical scenarios, but there are scenarios for which it is probably not valid. He emphasized that there is a high level of collaboration, which should result in guidance being largely consistent and readily available. He then requested that members consider the following question:

In addition to what was presented, what additional challenges and possible approaches do you envision for assuring the quality of NGS in the clinical laboratory setting?

Committee Discussion

- A member asked about access and support for NGS in rural settings, payment for testing, and how long the process would take in these settings. Dr. Lubin replied that all of those questions are not yet answered. He suggested there would be a need to work closely with a major medical center, laboratory, and physicians. Although there is currently no CPT code or mechanism for formal payment for this testing, third-party payers have paid for these tests on a case-by-case basis, when justified.
- Mr. DiTullio requested further comments on the challenge of ensuring quality, given that the technology is changing rapidly. Dr. Lubin replied it is fair to expect that technology is going to become more robust and there will be a better understanding of the parameters for why it sometimes fails for certain regions of the genome. The best laboratories offering NGS recognize the limitations, know the regions that are questionable, and use alternate methods to confirm their results.
- A member pointed out that the marketplace seems unregulated based on internet advertising for $79 DNA testing and requested input on how the discussion of clinical laboratories applies to consumer marketing for these types of tests. Dr. Lubin indicated that the CLIAC discussion at this meeting was intended to focus on how to integrate NGS into a CLIA-compliant clinical laboratory that has appropriate expertise to perform the testing. He stressed that there are many complex issues related to direct-to-consumer marketing of genetic testing. Test results can mean different things for different patients and in different populations, so it is important for individuals to understand the context of the test and the relevance of their results. Dr. Gutierrez added that many direct-to-consumer tests are laboratory-developed tests for which clinical validation is not being assessed. Tests being offered directly to the consumer should come through FDA for clearance before they are offered.

- A member pointed out the challenges of incidental findings when performing NGS and data storage challenges for variants that cannot be interpreted immediately but may be determined later. Dr. Lubin replied the issue of incidental findings has been a major point of discussion among many groups; the American College of Medical Genetics is developing guidance to address this. Several laboratories that offer NGS provide counseling for their patients and discuss incidental findings as part of the counseling. Some have suggested there are serious sequence variations that should be reported if detected because they are clinically actionable. This is somewhat controversial because it puts laboratories in the precarious position of having to validate the incidental findings before reporting them. Data storage has also been widely discussed. It is generally agreeable that data should be kept for reanalysis as more is learned that can perhaps inform reinterpretation of a test result. However, there is currently no practical mechanism for doing this.
- A member inquired as to whether there are defined skill sets for NGS testing personnel and whether Dr. Lubin foresees including these in curricula for medical technology programs. Dr. Lubin responded that he did foresee this as eventually being part of medical laboratory training curricula.
- A member noted the indication for testing is central to the NGS analysis and suggested that traditional order entry may not be feasible. The member stated it was sometimes necessary to consult with a geneticist to determine which genes to test for prior to ordering NGS.
- A member pointed out that when applying NGS to microbiology there would be lot of background noise since 70% or more of microorganisms identified are endogenous. Since there are thousands of organisms present in the body, it is unclear how this technology will be used as a direct detection mechanism. In addition, microbial resistance mechanisms develop quickly and it is unclear whether detection of resistance can be incorporated into sequencing. Dr. Lubin responded that the technology permits sequencing of each DNA fragment independently and the development of signature profiles of microorganisms. Direct sequence information will be rapidly available without having to isolate, grow, or otherwise prepare each of the organisms in a sample. The challenge is knowing whether the organism for which a signature is detected is the pathogen responsible for disease.
- A member pointed out that standardization of gene panels will be important. Dr. Lubin agreed this is a particularly challenging issue. There needs to be an effort by an appropriate professional organization to address variation that can cause errors in diagnostic laboratory testing and create a recommended panel.
- The Chair questioned whether there is a role for building a test formulary that meets guidelines to allow someone to judge whether they want to order certain tests for their patients. Dr. Gutierrez responded that this raises the issue of laboratory-developed tests (LDTs). The FDA has determined that its role is to define standards for instruments used in NGS so that laboratories can understand their performance. Comparing performance is particularly difficult because reference materials are not available. The FDA has contracted with the National Institute of Standards and Technology to develop reference materials for the genome and microbiome. With those reference materials, FDA can require that manufacturers conduct testing, define error rates, and define areas that are difficult to sequence so that laboratories can

decide which instrument manufacturer to select. The FDA has to decide how they will regulate the broad areas of instruments and reagents.

- Regarding the concern about tests marketed directly to consumers, Dr. Gutierrez indicated that FDA has recognized this as the agency's responsibility and has been working on the related issues for more than a year. They convened a panel of experts to address these issues. Questions about what type of information should be shared directly with patients have also been raised, since that could result in patients misdiagnosing or mistreating a medical condition.
- A member pointed out that since reimbursement is sporadic, it would be beneficial to link indications with reimbursement. Another member noted that science tends to be a few steps ahead of practice, and practice is always somewhat ahead of reimbursement. Over the last couple of years, over 300 analyte-specific related codes have been created in the CPT code system, but when that process began, people typically were testing for one to three genes at a time. Now many more genes can be sequenced and there is a tendency for those with the ability to perform NGS to sequence everything possible regardless of its relevance to the disease. It is necessary to develop a coding strategy for NGS. Dr. Lubin expressed his hope that members would discuss the issue of reimbursement. He related that he knew of one medical center that was approached by a third-party payer to explore the possibility of formalizing reimbursement for cancer related testing. Specifically, their interest was in determining whether there was a way to use the technologies to better target cancer treatments thereby reducing their expense. The Chair added that while CLIAC could discuss this, reimbursement may be changing and could render some of this much more challenging in terms of how it impacts the total cost of patient care.
- In summarizing the responses to Dr. Lubin's initial question about challenges of NGS, challenges identified during this session included the following:

  - ❑ Handling incidental findings from NGS
  - ❑ Storing data for future interpretation of findings that cannot yet be readily interpreted
  - ❑ Understanding the context for ordering tests and interpreting test results
  - ❑ Addressing personnel skill sets
  - ❑ Addressing standardization between laboratories in terms of instruments and gene panels
  - ❑ Ensuring the quality of tests that are marketed directly to consumers
  - ❑ Determining appropriate reimbursement for NGS

Harmonization of Clinical Laboratory Results

Introduction ***Addendum 12***

Ms. Megan E. Sawchuk, MT (ASCP)
Division of Laboratory Science and Standards (DLSS)
Laboratory Science, Policy and Practice Program Office (LSPPPO)
Office of Surveillance, Epidemiology and Laboratory Services (OSELS)
Centers for Disease Control and Prevention

Ms. Sawchuk indicated that the speakers for this session would discuss harmonization throughout the laboratory process, including harmonization and interoperability of terminology along with harmonization of data or numerical values. This is really the cradle-to-grave process of assessing all aspects of the testing process to ensure comparability in the electronic records of the future. With respect to the EHR, harmonization includes the process of standardizing the terminology and the format used to transmit electronic messaging. At present, format usually refers to Health Level 7 (HL7) standards. Ms. Sawchuk explained that this session would focus on the content of the message, including the terminology/nomenclature used to communicate. She referred everyone to LOINC.org for a free mapping tool that laboratories can use called Regenstrief LOINC Mapping Assistant (RELMA®). Ms. Sawchuk also called attention to the fact that a number of stakeholders, including large EHR vendors, are interested in interoperability of systems to enable them to communicate with each other. Manufacturers of in vitro diagnostics (IVD) have interoperability initiatives, and the American Medical Informatics Association has referred to a new Center for Interoperability as part of their business plan.

EHR Interoperability: Semantic Harmonization for Clinical Laboratory Results

Clem McDonald, MD, FACMI, FACP ***Addendum 13***
Lister Hill Center for Biomedical Communications (LHCBC) ***Addendum 13A***
U.S. National Library of Medicine (NLM) ***Addendum 13B***
National Institutes of Health (NIH)

During this session, Dr. McDonald focused primarily on LOINC® and laboratory issues. He first reviewed the NLM's 27-year interest in standard vocabularies, support of the electronic medical record, and support of medical research. NLM directly supports three clinical vocabulary systems, each of which Dr. McDonald defined. LOINC® is the question or the name of the variable and Systematized Nomenclature of Medicine Clinical Terms® (SNOMED CT®) is the answer for questions with coded or multiple choice answers. LOINC® and SNOMED CT® are close to a tight collaboration agreement. He further explained that IVD manufacturers are mapping the LOINC® codes to their reported test measures, and will report the LOINC® code(s) for each result in their product labeling. All of the eight largest international IVD companies and many smaller ones claim they have mapped their instrument test codes to LOINC®. In terms of challenges receiving requests for LOINC® codes, variation in conceptualization of a given test and its result reporting can cause problems. Dr. McDonald explained some of these problems and shared some examples. He also discussed challenges with LDTs, because the analytes being identified or measured with these tests are not always clear. Last, he described the challenges associated with major variation in the units of measure and indicated that this is where the Unified Code for Units of Measure (UCUM) is useful. In conclusion, he shared several resources for information pertaining to HL7 and UCUM.

Committee Discussion

- Dr. Gutierrez explained that some of the differences in terminology and rationales behind result reporting may have come about as a result of standards set by FDA. For example, he described why FDA considers some tests semi-quantitative rather than

quantitative. He offered to provide Dr. McDonald with information to help clarify some of the coding issues. However, he acknowledged that would not address the issues seen with LDTs.

- Dr. McDonald expressed his hope that CLIA might have some influence over requirements for LDTs with respect to their intended use and what analyte is being measured.
- Several members commented on various aspects of unit standardization, including the concept of standard international units, the creation of units by industry over time, and enzyme units. Dr. McDonald acknowledged that standard international units are somewhat confusing and stated that in some cases their creation has decreased standardization rather than improving it.

FDA Semantic Interoperability Pilot Project ***Addendum 14***

Steve Gitterman, M.D., Ph.D.
Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health (OIVD)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration (FDA)

Dr. Gitterman emphasized that interoperability of electronic systems is essential, particularly given that much of the information in an EHR is laboratory data. Individual decision support, public health epidemiology, and decision support mandate semantic interoperability at the individual, community, and national levels. In terms of a solution, tools are already available. Dr. Gitterman briefly described each of these tools in the context of a model solution: LOINC® (question), SNOMED® (answer), HL7 (transmitting information), UDI (unique device identifier), GMDN (global medical device nomenclature - what the test does), SPL (structured product labeling - wrapper). He emphasized that to some extent, UDI can be "the glue" that makes the model work because it will provide a way to uniquely identify the production model of each device. He also explained how SPL could be a wrapper for UDI/LOINC®/SNOMED®/GMDN information, noting that the FDA currently uses SPL to transmit labeling information. The FDA Division of Microbiology Devices will use this model in its proposed pilot project to develop standardized SNOMED® response coding sets for selected assays. Currently, work is being done with enzyme-linked immunosorbent assays (ELISA) and qualitative polymerase chain reaction (PCR)-based assays to define a standard response set that would be applicable across a large number of devices that use the same technology. Dr. Gitterman stressed that this effort reflects nothing fundamentally unique. He also emphasized that this is not an FDA regulatory initiative. In conclusion, he listed stakeholders and reviewed potential issues, all of which he said are solvable.

Committee Discussion

- The Chair requested further information about the meaning of extensibility. She also pointed out there is often a reagent component of test systems, which can differ on the same instrument, that must be considered. Dr. Gitterman replied that if a laboratory runs a test that is not FDA-approved, for example, the laboratory uses different reagents than cleared for a certain instrument making it an off-label use, the

laboratory reporting that result would want to be able to extend the initial UDI file to allow for that possibility. The idea that if the files that define each device come from a central place, since certain things may be customized for local use, there may be a need to extend that file to ensure it gets fully used. Semantic interoperability would still be extended even though there may have to be control over it from a centralized perspective.

- A member noted that patients were missing from the list of stakeholders. In thinking about standardization, it is important to recognize that patients now have portals and can log in to see their own test results. Thinking about end users, such as clinicians and patients, it is important to consider standardization of how abnormal results are flagged. Another member pointed out that the other extreme is over-flagging. Sometimes an abnormal result is not significant, but it is difficult to explain to the patient that it does not matter. Dr. Gitterman emphasized that in order to build good clinical decision support on a hospital wide, community wide, and national basis, good semantic interoperability is necessary at many levels.

CLIAC Discussion
Paula Santrach, M.D.
CLIAC Chair

At this time, Dr. Santrach posed two questions for members to consider and discuss. Committee suggestions follow each question:

1) How can HHS support the harmonization and interoperability of nomenclature, such as LOINC®, SNOMED®, and UCUM?

   - ❑ Include other stakeholders to help the NLM collate information and conduct necessary activities: manufacturers, CLSI, International Federation of Clinical Chemistry and Laboratory Medicine, and others involved in setting standards.
   - ❑ Use package inserts as a way to help standardize.
   - ❑ Identify early what the right codes are related to a test.
   - ❑ Drive people to adopt a standardized approach through Meaningful Use and other initiatives.
   - ❑ Rather than imposing regulations, consider developing guidelines and best practices; however, the ability to achieve the highest possible standard may be limited if there are not regulatory requirements.
   - ❑ Consider an international forum since manufacturers sell their products worldwide.

2) Who should be responsible for sustaining nomenclature for clinical laboratories? Are there existing successful models?

   - ❑ Review successful models, and use existing accreditation or other standard-setting organizations.
   - ❑ Support sustaining efforts that currently exist in terms of the group working through the LOINC® codes.

- Consider making this an NLM core function to ensure stable sustainability.
- Ultimately, someone has to take responsibility for standardizing the nomenclature and aligning the incentives:
  - This currently appears to be through building requirements into Meaningful Use, but consideration must be given to how to do this over the long-term.
  - The legal foundation of Meaningful Use is based on the practice and medical record—there is no requirement for senders, but this would be helpful.

International Consortium for Harmonization of Clinical Laboratory Results

Greg Miller, Ph.D.
Professor of Pathology
Director of Clinical Chemistry
Director of Pathology Information Systems
Virginia Commonwealth University

Addendum 15

Dr. Miller discussed a project initiated by the American Association for Clinical Chemistry (AACC) to create a new organization, the International Consortium for Harmonization of Clinical Laboratory Results. He explained that in the context of his presentation, "harmonization" would mean that if a patient's blood sample is sent to several different laboratories, each of which is using several different measurement procedures, the results would be the same (e.g., getting the same answer for the same patient sample, irrespective of where it is measured). He discussed the importance of achieving comparable results and traceability in laboratory medicine. To illustrate traceability, Dr. Miller shared and explained in detail several diagrams of a laboratory medicine "reference system." He said that metrologists use the term "measurand" to describe the analyte being measured. He also discussed commutability, an extremely important concept in the traceability scheme, which means that values measured for a calibration material and representative clinical samples have the same relationship between two or more measurement procedures for the same measurand. A current problem in the clinical laboratory is that many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures. Dr. Miller explained the historic reason for this and stressed that clinical laboratory practice must be changed to require commutability validation for reference materials intended for use with manufacturer's standing procedures or directly with routine clinical laboratory procedures.

Given this background, the AACC organized a conference in October 2010 called, "Improving Clinical Laboratory Testing through Harmonization: An International Forum." Key barriers to global harmonization were recognized during this conference and were published in 2011 in *Clinical Chemistry*. Given the fundamental barriers, the recommended roadmap included developing an infrastructure to coordinate harmonization activities worldwide. To that end, the International Consortium for Harmonization of Clinical Laboratory Results was established. It includes five organizational partners with AACC serving as the secretariat for administration of the

program. Further information on the Consortium can be found at: http://www.harmonization.net.

CLIAC Discussion
Paula Santrach, M.D.
CLIAC Chair

At this time, Dr. Santrach posed the following questions for members to consider and discuss:

1) How will clinical laboratories be impacted by efforts to harmonize individual analytes for comparability?

   - ❑ CLIAC members agree that this is an important issue; customers want it and it is good for patient care.
   - ❑ This will be a major issue for clinical laboratories as they try to adopt it; given the potential difficult challenges, duplicative reporting may be necessary for some period of time.
   - ❑ Availability of reference materials will be key to success, and consideration must be given to the cost of such reference materials.
   - ❑ Hospital information systems and EHR vendors must be on board, given that connection to the hospital information system/EHR is key to driving this effort.
   - ❑ Change management must occur.
   - ❑ Manufacturers should be involved and support the idea of having a standard.

2) Is there a role for HHS to support clinical laboratories with harmonization of individual analytes for comparability?

   - ❑ HHS could potentially support this effort by serving as a clearinghouse for harmonization materials, although Dr. Miller reported that the Consortium is serving in that role and AACC is currently compiling a list of useful information.
   - ❑ With other harmonization efforts, FDA has encouraged manufacturers to declare on labels whether there is harmonization; eventually, this becomes the way to do business.
   - ❑ One role for CLIAC could be to assist with prioritization from the perspective of a customer.
   - ❑ Dr. Miller suggested that the strategic partners group may be a place for CLIAC to have representation, although he reminded the Committee that this is an international initiative and not restricted to the US.
   - ❑ CLIAC should engage in further discussion directly with the leadership of the International Consortium for Harmonization of Clinical Laboratory Results to better understand what role (formal or passive) the Committee can play in helping to advance this effort.
   - ❑ Once there is more clarity about CLIAC's role, the Committee can advise HHS on how they can support that role.

ACRONYMS *Addendum 16*

NOMINATION FOR CLIAC INSTRUCTIONS *Addendum 17*

PUBLIC COMMENTS

- **Virginia Commonwealth University, Greg Miller, Ph.D.** *Addendum 18*
- **Virginia Commonwealth University, Greg Miller, Ph.D.** *Addendum 19*

ADJOURN

Dr. Santrach acknowledged the staff that assembled the meeting program and thanked the CLIAC members and partner agencies for their support and participation. No Committee recommendations were passed during this meeting.

Dr. Santrach announced the fall 2013 CLIAC meeting dates as August 21-22, 2013, and adjourned the Committee meeting.

I certify this summary report of the March 6-7, 2013, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.

_____ Dated: 05/15 /2013

Paula Santrach, M.D., CLIAC Chair