NKDEP Manufacturers Forum
AACC Conference – Chicago, IL
July 27, 2006

Meeting Notes

LWG Members and Meeting Participants
Greg Miller, Medical College of Virginia (Chair)
Ed Ashwood, ARUP
Christa Cobbaert, EC4 EWGCS
Joris Delanghe, EC4 EWGCS
Paul D'Orazio, Instrumentation Laboratory
John Eckfeldt, University of Minnesota
Jim Fleming, Lab Corp
Elisa Gladstone, NIDDK/NKDEP
Neil Greenberg, Ortho Clinical Diagnostics
Harvey Kaufman, Quest Diagnostics
David Lacher, CDC/NCHS
Cynthia LaCivita, ASHP
Heidi Leinberger, Radiometer America
Leigh Ann Milburn, Saint Luke's Hospital (Kansas City)
Gary Myers, CDC
Andy Narva, HIS, NIDDK/NKDEP
Mauro Panteghini, IFCC
Don Parker, Bayer Diabetes Care
Karen Phinney, NIST
Dan Seymour, Beckman Coulter
David Seccombe, CEQAL
Anne Skurup, Radiometer ApS
Linda Thienpont, Ghent University
Mike Welch, NIST
Reba Wright, Olympus

IVD Manufacturer Representatives
Rob Acorn, Diagnostic Chemicals
Dave Armbruster, Abbott
Dennis Bozimowski, Abbott
Joseph DeGiorgio, Thermo Electron
Andrea DeFrance, Abbott
Glen Ehlers, Ortho Clinical Diagnostics
Mary Lou Gantzer, Dade Behring
Matt Gnezda, Roche
Ritva Kyto, Thermo Electron Corp
Jack Levine, Bayer HealthCare
Rick Miller, Dade Behring
Beth O'Connell, International Technidyne
Phil Reavy, Olympus
Sam Reichberg, Quest
Jack Zakowski, Beckman Coulter

Creatinine Standardization: Overview of Implications for the IVD Industry
Neil Greenberg started the meeting with an overview of the objectives of the Creatinine Standardization Program and its activities thus far. (The slides for this presentation are found on the NKDEP website at www.nkdep.nih.gov/labprofessionals.)

- The Creatinine Standardization Program—a collaborative effort of the NKDEP, the EC4, and the IFCC—has as its key objective improvement of the accuracy and reproducibility of the eGFR calculation based on the serum creatinine value. Optimal analytical performance of existing methods in the field must be established.

- Existing methods must try to conform to the set of specifications established by the LWG, which are centered on total error requirements to minimize the introduction of substantial additional uncertainty in the eGFR calculation.
- The LWG decided we should strive for an objective of not increasing the error in the estimate of eGFR by more than 10% within the critical range of creatinine values of 1.0-1.5 mg/dL.
- The LWG has discussed the implications for the lower analytical range, particularly in area of 0.6-1.0 mg/dL, where we also want to achieve performance comparable to that we are seeking in the range in excess of 1, particularly the 1.5-2.0 range.
- The key step to creatinine standardization is to close the gap in the calibration traceability infrastructure. This is all dependent upon availability of a commutable certified matrix reference material to manufacturers (reference material NIST SRM 967 should be available by November 2006).
- The LWG intends to address specificity issues in the future.
- Currently, instrument/method-to-method variability is substantial. The range of mean values extends over a range of more than 0.3 mg/dL. The LWG's goal is for the bias not to exceed .05 mg/dL.
- Creatinine standardization recommendations for IVD manufacturers and other groups including labs and PT/EQAS providers can be found on the NKDEP website.
- Please see Neil Greenberg's slides for other information.

NIST SRM 967, Commutability Validation

- John Eckfeldt presented the results of the commutability study that several of the manufacturers recently participated in. See the slides on the NKDEP website.

Discussion

- According to Mike Welch, the NIST reference materials should be available by November 2006.
- The College of American Pathologists does not want labs to identify LN24 as a reference material/calibrator; it is intended as a trueness control for PT/EQA.
- Sam Reichberg raised several questions of concern and would like to see criteria for commutability to address these clinical needs:
    - How many patients who may really be in stage 3 (<59) will be missed due to an error in creatinine measurement?
    - How many patients will be missed due to errors with the MDRD equation?
    - How many patients who are actually stage 2 or 1 may be classified as having stage 3 because of creatinine measurement problems.
- Andy Narva emphasized that the eGFR is a tool—doctors will interpret the results, along with other tests, to determine how to proceed. He also indicated the importance of identifying those with evidence of renal injury who are at risk of progressing. The CRIC studies may help us identify groups at highest risk (e.g., patient with proteinuria, diabetes, and a low eGFR).
- Jack Zakowski noted that patients are going to the Internet before they see a doctor; therefore, NKDEP must have the right information for patients.

Timeline for Completion of Standardization

- Greg Miller asked whether manufacturers thought it realistic that all would be using methods traceable to IDMS by the end of 2008 (assuming NIST makes the material available by November).
    - None of the manufacturers said the timeline was unrealistic.
    - Several manufacturers said the demand from customers for recalibrated methods has been high. The timeline is affected by not only availability of materials, but also budgets, FDA approvals, and the use of current inventories. Some manufacturers will have to change reagents.
    - It was pointed out that NKDEP and NIST have put manufacturers in a crisis management mode because NKDEP has raised expectations of customers (some wanting to implement eGFR with creatinine traceable to IDMS immediately). Another participant stated that "things may have gotten out of control" due to the legislation passed or proposed in several states.
- Greg Miller stated that labs do not have to wait to begin using eGFR. Rather, they should use the current equation/calculator with methods that have not had the calibration changed to be traceable to IDMS. Greg asked what the NKDEP could do to help the manufacturers communicate to laboratorians. Publications in *Medical Laboratory Observer* and *Advance* were mentioned and a participant wondered whether the *Clinical Laboratory News* article could be redistributed or reprinted (with permission of AACC). Greg emphasized that the NKDEP will do what it can to help the labs understand that full implementation of the standardization process will take time and that they do not need to wait to begin reporting eGFR.
    - Mauro Panteghini said that the risk of misinterpretation is high if labs do not use methods traceable to those used to produce the MDRD equation.
    - Discussion about the IVD directive followed, including how it could be interpreted and the issue being that of availability (of matrix reference materials from NIST). Neil Greenberg stated that he thought virtually all manufacturers were disclosing the necessary traceability-related information on their labeling.
- Greg Miller summarized that the LWG has outlined expectations of the manufacturers and that the program cannot begin until the NIST materials are available, and the NKDEP will do more to communicate with labs about timeline issues.

Recommendations for PT/EQAS Providers

Greg Miller briefly discussed the recommendations for PT/EQAS providers (see the NKDEP website for details) and told participants that a joint letter from NKDEP, IFCC and EC4 has been sent to PT/EQAS providers worldwide.

- The LWG anticipates that PT/EQAS providers will use two peer groups to accommodate labs starting to use methods traceable to IDMS and those that have not yet done so.
- Manufacturers should contact NKDEP to receive a customized letter for communicating to customers about the timeline for creatinine standardization activities.

IFCC Update

Neil Greenberg reported about IFCC's May meeting and current activities. Items included the following:

- IFCC intends to broaden their communication about the initiative, primarily via web outreach.
- Method specificity–IFCC has begun a literature review, which has proven difficult because much of the research is more than 30 years old. Advances in technology may require the implementation of studies to address the issue.
- The need to establish nomenclature around reporting values based on relevant methods.
- Changes that will need to be made in regards to serum creatinine reference ranges.
    - Mauro Panteghini reported that studies in Italy are addressing this issue and that recommended reference ranges should be available by the end of the year.

Next Steps

- Greg Miller reiterated that the implementation of creatinine standardization is in the hands of manufacturers (after they obtain NIST materials).
- NKDEP will support manufacturers as necessary to help them communicate to their customers that this process will take time. (Manufacturers should contact NKDEP to obtain a customized letter for distribution to customers.)

Other Issues/Meeting Adjourned

- Greg Miller informed the group that the NKDEP will be putting together a working group to address recommendations for calibration in whole blood systems.
    - NKDEP would like to receive contact information for manufacturers that manufacture whole blood systems and will be recruiting members for this sub-group.

Greg Miller thanked everyone, and adjourned the meeting at 12:00 p.m.