NKDEP Lab Working Group Conference Call
October 25, 2005

Members in Attendance
Greg Miller, Virginia Commonwealth University (Chair)
John Eckfeldt, University of Minnesota
Elisa Gladstone, NIDDK
Neil Greenberg, Ortho Clinical Diagnostics
David Lacher, CDC
Timothy Larson, Mayo Clinic Renal Laboratory
Leigh Ann Milburn, St Luke's Hospital (Kansas City, MO)
Marva Moxey-Mims, NIDDK
Gary Myers, CDC
Michael Welch, National Institute of Standards and Technology

Guests
David Armbruster, Abbot Laboratories
Dennis Bozimowski, Abbott Laboratories
Phil Deemer, Abbott Labs
Matt Gnezda, Roche
Chandra Jain, Beckman
Tina Kristensen, Radiometer Medical Aps
Rick Miller, Dade-Behring
Anne Skurup, Radiometer Medical Aps
Melanie Swartzentruber, Roche
Joann Walter, Dade-Behring
Reba Wright, Olympus America

The group met to review materials that will be posted on the Lab Professionals section of the NKDEP website. The materials were developed or revised as a result of the July meeting in Orlando and include creatinine standardization-related recommendations for stakeholder audiences. The recommendations are updated versions of those found in the Lab Working Group's (LWG) manuscript to be published in the January 2006 issue of *Clinical Chemistry*.

Recommendations for pharmacists

Question: Should the LWG make a recommendation to pharmacists to do any type of calculation or correction of creatinine to use with Cockcroft-Gault or other estimating equations embedded in pharmacy practice? The group discussed the following:

- Recalibration will result in slightly lower serum creatinine values. This has implications for pharmacists' interpretation of serum creatinine values and dosing practices, particularly for drugs, although few, that are prescribed based on absolute serum creatinine values (e.g. Glucophage/metformin, which is to be avoided with females with serum creatinine values greater than 1.4 and males with values greater than 1.5). After recalibration, 1.3 may be "equivalent" to these threshold values.

- Pharmaceutical companies typically give dosing recommendations based on Cockcroft-Gault or a measured creatinine clearance.
- It would be overly complex to try to propose to pharmacists some type of correction process because it could lead to more errors. In addition, the correction may not be linear.
- Consider reaching out to pharmaceutical manufacturers so they can adjust recommendations for dosing/labeling.
- IVD manufacturers must be clear with customers/pharmacists about what to do when the calibration change is introduced—they must communicate the relationship between the old and new values. Manufacturers must provide factors for a serum creatinine value in the event that customers need to go back to older values for purposes of medication dosing. Manufacturers must describe the impact on quantities throughout the range of interest—.4-.5 level to the 2.0 to 3.0 level. Providing advice on conversions will require good data that covers the range of interest.
- Neil Greenberg drafted and read a proposed statement (See revised recommendations).
- Leigh Ann Milburn asked (on the last point on the second page) if we should be using the MDRD equation for drug dosage adjustments when most drug dosing recommendations are based on Cockcroft-Gault or measured creatinine clearance. Greg stated that it is realistic that pharmacists are not going to change from Cockcroft-Gault at this time. It's going to take a couple of years for pharmaceutical industry to adopt this change. In the meantime, the LWG will try to initiate thinking about it at this time, provide pharmacists with information about the relationship between new and old creatinine results, and continue to work with pharmacists.
- Greg shared that Leigh Ann arranged for a Dec 6 meeting at the annual meeting of the American Society of Health-System Pharmacists (ASHP) to engage them in discussion about NKDEP, lab issues, and how they affect pharmacy. Greg will speak to this group to initiate dialogue and engage interested parties to help us reach out the to pharmacy community.
- The LWG will delay the posting of pharmacy recommendations until after this meeting and/or it is comfortable with recommendations. (See below for more information on posting recommendations.)
- Greg to make changes to pharmacy recommendations (as well as related changes to recommendations for IVD manufacturers and labs).

Recommendations for IVD Manufacturers

- The recommendations are based on those to appear in the LWG's *Clinical Chemistry* article, which will be published in January 2006 and available online in December [at the time of this meeting, the LWG anticipated December publication]. When we post new recommendations, we will identify them as "updated recommendations," built upon those in the article.
- Neil recommended adding the following statement: "It is expected that manufacturers will provide more detailed information about the nature and impact of the calibration changes for their particular devices." The group discussed using language to indicate that values "may change" – to avoid stating "higher" or "lower" because the direction of change may be different for different methods. (See revised recommendations for new language.)
- The group discussed the need to be careful with language because of the challenges presented by manufacturers that may have already recalibrated without addressing clinical implications with their customers.

- The group discussed the website having links to the article and Andy Levey's American Society of Nephrology (ASN) meeting abstract. [NKDEP has since received permission from ASN to post the abstract on the website, and *Clinical Chemistry* will allow NKDEP to post a special access link to the online version of the article when it becomes available.]
- The group discussed the text on total error. We will end up with a (revised) total error statement for creatinine, not just a bias and imprecision statement. The bias and imprecision (numbers) are numbers that fit within that total error curve. Greg will also add the rationale for the total error graph—that it does not cause more than a 10% change in the eGFR value. The group also discussed the benefit of using concentration units. Greg will revise language to make it more clearly stand on its own and distribute for comment.
- Greg stated that numbers 5, 6 (optimum method performance should be targeted at 1.0), and 7 (would like to extend to lower values but don't have enough data to make a recommendation) are compromised statements that need to be revised.

Recommendations for Clinical Laboratories

- Overall, changes will be similar to those discussed above but geared toward clinical labs.
- Item 5, about communicating to health care providers, needs to be revised similar to the manufacturers' recommendations and reflect what we discussed regarding pharmacy issues—separating out measured creatinine clearance, from estimating equations, and from reference interval changes, and making each item their own separate bullet.
- Bullet 3: "Communicate to pharmacy…" must be clarified more, based on earlier discussion. Greg will consider making this a separate item because it is a complicated issue, with several supporting points.
- Number 6 will be changed as discussed for IVD manufacturers (see revised recommendations for text).

Recommendations for LIS Vendors (or "Providers of software developed for laboratory information systems")

- We need to point out that Cockcroft-Gault isn't going away, that MDRD should be provided as an option, and users need to be given options to select the equations that are most appropriate for their practices.
- The group discussed that there may be an opportunity here for LIS to build in capability for pharmacy to adjust new creatinine values back to old values to support use of legacy tables for dosing schedules. The group also discussed suggesting to LIS vendors that they consider offering that as another feature/capability at the LIS level, where those conversions can be made to support pharmacy applications.
- To support some type of correction process to use legacy tables or algorithms, labs need to know, on average, for their system, the function that describes the difference between old and new creatinine values. Neil stated, however, that site-specific variables would also creep into the process. Labs may have already employed some other type of correction factor to go from system A to system B. LIS must provide some additional flexibility to support further conversion of creatinine values to the previous methods or other methods. Greg cautioned the group to keep in mind that there is a range of calibrations in current practice (may vary as much as 20 percent) and that we must be careful about too many opportunities for making errors in corrections.

Recommendations for National Metrology Institutes, reference laboratories, and JCTLM organizational members

- NKDEP will post a link to the JCTLM listing of reference laboratories that can provide IDMS values.
- Currently there is no U.S. lab.
- "Reference labs are needed" will become a separate item. (A participant emphasized the importance of SRM 967 availability since we don't have reference labs readily available to us.)

Recommendations for PT and EQA providers

- The group discussed that we need a mechanism for manufacturers to notify PT providers that the recalibration transition will start on X date (and last about Y months), and in the interim, we need PT providers to recognize this when they collect/analyze the data (e.g. new method codes).
    - CAP has already agreed to create new peer groups.
- Strategies for informing labs about implications for PT testing during the transition:
    - Requesting CAP to post on website (information coming from various sources and stakeholders may make the transition easier).
    - Publishing an article/announcement in *CAP Today*, *Clinical Laboratory News*, and *IVD Technology* to inform parties about the transition, and the implications and instructions for testing.
- Add to the recommendations that PT/EQA providers should instruct participants that creatinine calibration will be changing and they need to be in close communication with their manufacturer. PT/EQA providers should include information in instructions to participants, relative to the issue of having recalibrated or not.
    - CAP has agreed to do this more than one year ago. NKDEP hasn't communicated with other PT/EQA providers and will need to communicate to as many of them as we can find. (The IFCC can take an NKDEP communication and distribute it to PT/EQA providers overseas.)
- The group discussed that it will be the manufacturers' responsibility to contact the PT/EQA providers. Greg will add this to recommendations for manufacturers. (Greg also added to his notes for labs that they must be aware of this so they get the right information.)

Timing of communications and availability of NIST reference material

- The original intent was to get information on the website as soon as the LWG is comfortable it has the proper set of recommendations. Chandra Jain shared her concern, however, that if information is made public, it will lead to an increase in lab inquiries to manufacturers about when the recalibration will occur (calls are already coming in). Perception was that IVD manufacturers' hands are tied if SRM 967 is not available.
    - The group discussed that labs can, at this time, recalibrate by referencing back to IDGCMS method, before a new reference material is available. Labs have the option of contacting a lab that provides reference lab services for creatinine and do patient comparison studies or whatever is appropriate for their technology—and make adjustments accordingly. (LN 24 would not be useful for this at this time because its commutability has not been validated. It is being evaluated at the same time as SRM 967.)

- John Eckfeldt was asked to provide an update on the commutability study for SRM 967.
    - At this time, the study hasn't progressed very far because they haven't collected enough samples yet (study calls for 3-4 tubes of blood from patients with renal failure/CKD) and it was difficult to obtain IRB approval. The research has recently been approved, but they haven't collected any/many samples as of now. They need IDMS values on the samples. The study should not take long once samples are collected. John is aiming to collect 40 samples, with a subset of 20-25 to cover the range of 0 to 5. Mike Welch said NIST could analyze 20 samples.
- Mike Welch was asked to provide an update on the status of release of the NIST material and outline the timeframe for analyzing clinical samples for the commutability study. The group discussion covered:
    - NIST is currently doing the GCMS (have had LCMS values) and expects to have measurements completed in a month's time.
    - Regarding the release, Mike was hoping we'd be further along. The commutability study data need to be included when NIST releases the SRM.
    - Commutability will be method-specific. Manufacturers that have expressed interest in participating in the commutability study first round will be able to be included in the certificate of analysis that indicates which methods have been shown to be commutable. The group agreed that NIST labeling should also list systems found to be non-commutable.
        - Seven or 8 manufacturers have stepped forward expressing interest in participating—this provides sufficient critical mass, at least in the U.S., and will cover 90% or more of participants in typical CAP surveys. This will go a long way toward saying that the product has commutability characteristics for these methods. Others can be dealt with as an update process.
    - Mike said he hopes that SRM 967 will be available in the 1st quarter next year. We need to get the study going and get the data back. Then it's a matter of pushing through the system at NIST as quickly as possible.
    - Regarding the status of LCMS: NIST has done measurements necessary, but hasn't compared results to GCMS to verify if they get the same values. Mike is confident NIST will get close to the same answers but will not know for certain until NIST sees the GCMS results on the new material.
    - If it is true that LCMS (which is commercially available to IVDs) is equivalent to GCMS, it will be more practical to do patient sample comparisons to LCMS due to throughput capability. LCMS is not yet on the JCTLM list, but it will be nominated. JCTLM qualifies the *method*—and once approved, it doesn't have to be nominated in each individual lab that performs the assay.
- The discussion returned to the issue of making this information available via the web—that an IDMS traceable equation for MDRD calculation exists, that we're expecting manufacturers to move to new calibrations, etc.—which will result in customers calling to ask when IVDs are going to make the change. Premature web publication may appear that manufacturers are delinquent; but, in fact, they/we don't have the resources/infrastructure in place to support these changes until first part of 2006.
    - The group agreed and discussed the possibility of delaying the posting of information until the LWG has a better idea about when the 967 will be released. (Manufacturers are already receiving inquiries about their timelines).
    - NKDEP will post a message on the website that addresses the issue of timeline. Greg offered that they might want to post that the program will be starting some time in '06, but it is pending the availability of a reference material. Others agreed

with the need to post something that people can find/relate to and answer their questions, including a statement that transitions will begin when the NIST reference material is available.

- The group discussed that the commutability piece is key—must get completed or at least understood for a significant number of key methods before we can say we are ready to make 967 available.
    - Gary Myers reminded the group everything does not rest on 967—that some manufacturers have already completed comparisons with one of the reference labs and recalibrated. That option is still available if the manufacturer wants to pay for and do that. The group noted that this is not the most efficient way to do things.
    - The group discussed that the transition process will take up to 2 years (not 18 months) for manufacturers to establish proper traceability and get all field methods recalibrated.
- NKDEP has received a couple of questions about the Roche assay.
    - John said that data from the CAP LN survey and other sources say that they [Roche] are (pretty much) traceable to IDMS. Anyone using the Roche assay should be using the new IDMS traceable MDRD equation. Now that the equation is available and ready for release (at ASN meeting in November 2005), labs can be given the correct instructions.
    - In anticipation of receiving additional questions about the Roche assay, the NKDEP will collaborate with Roche to write a FAQ item for posting on the website. Melanie Swartzentruber, Roche representative on the call, will react to something written by the NKDEP. NKDEP will send something in the near future.

Closing

- Next steps include Greg's revision of recommendations, which will be circulated for review and comment. The next call will likely be scheduled for early December.
    - Greg summarized that he heard the group identify that it should not rush information/recommendations onto the website—we should take our time to make sure we've got it right.
    - Greg emphasized the group believes that the SRM 967 value assignment and commutability studies are key—we need to encourage our colleagues to complete those studies and analyses.
- Since the group didn't have time to discuss the NKDEP lab survey and *Suggestions for Laboratories*, members should review and send comments to Elisa. The latter will go on the website after the ASN meeting, when the new equation is presented. We'd like to time the availability of the piece with the ASN meeting.
- Elisa will canvass the group for preferred times to meet in early December.
- Meeting adjourned.