Minutes of the NGSP/IFCC Manufacturer Forum

Monday July 27, 2015 10:00AM-12:00PM
Hyatt Regency, Atlanta, GA

Presenters:
David Sacks —Chair, NGSP Steering Committee
Randie Little—NGSP Network Coordinator
Garry John—Chair, IFCC Task Force on HbA1c Standardization
Cas Weykamp—IFCC HbA1c Network Coordinator
Alberto Gutierrez—FDA

Present were members of the NGSP Steering Committee and representatives from various manufacturers, laboratories and agencies.

1. **Welcome and Introduction— David Sacks, Chair, NGSP Steering Committee**
   - D. Sacks welcomed those in attendance on behalf of the NGSP and IFCC.
2. **NGSP Progress Report—Randie Little, NGSP Network Coordinator**
   - The NGSP is overseen by a Steering Committee and includes a administrative core and a laboratory network consisting of Primary and Secondary Reference Laboratories (PRLs and SRLs) located in the U.S., the Netherlands and Japan.
   - The SRLs certify manufacturers and laboratories, they are monitored against the Central Primary Reference Lab (which is the original DCCT method) monthly via sample comparisons.
   - The network is linked to the IFCC network via sample comparisons performed 2X/year.
   - The function of the NGSP is to standardize HbA1c and ensure that results from clinical laboratories match those of the DCCT.
   - The NGSP assists manufacturers with calibrating their assays, has a formal certification process and monitors performance of HbA1c testing in the field via the CAP survey which uses fresh whole blood.
   - NGSP Update
     - The numbers of certified methods and laboratories leveled off the previous year but again increased over the past year to ~150 methods and ~170 laboratories.
     - Certified laboratories are distributed throughout the world, most are outside of the U.S.
     - Level II labs are certified using the same criteria as manufacturers, Level 1 labs are certified using stricter criteria and are also required to perform quarterly monitoring.
     - Current Manufacturer Certification Criteria: 37/40 individual results must be within 6% of the SRL (one SRL) mean.
     - Current CAP limits (2014-2015): Each result must be within ±6% of NGSP assigned target value (mean of 7 SRLs, multiple results from each).
   - Status of HbA1c Measurement
     - There has been much improvement in the comparability of HbA1c results since 1993 when the results of the DCCT were reported. The improvement has been more subtle over the last 3-4 years.
     - The all-method CVs have shown a downward trend since 2000.
     - 2011 Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus (Reviewed by ADA, AACC, NACB)
       - Within-laboratory CV <2%: Many methods have <2% CV
       - Between-laboratory CV <3.5%: We are close to this goal, CVs were 3.4-3.6% on the most recent survey
     - CAP GH2 survey 2015A:
       - Pass rates:

Specimen	NGSP Target (% HbA1c)	Acceptable Range **(±6%)**	Pass Rate % (Low/High)	Cumulative Pass Rate %
GH-01*	6.79	6.3-7.2	77.1/100.0	94.3
GH-02	10.28	9.6-10.9	62.9/100.0	93.3
GH-03*	6.82	6.4-7.3	62.9/100.0	94.2
GH-04	8.63	8.1-9.2	67.9/100.0	94.0
GH-05	5.32	5.0-5.7	67.9/100.0	96.3

*Duplicate sample

- Cumulative pass rates at the cutoff of ±6% have increased since 2008.
- Method-specific, between-laboratory CV's ranged from 1.3% to 8.4%.
- Over 76% of laboratories are using methods with CVs <3.5% at all five HbA1c levels.
- The overall pass rates for this survey were ~93-96%.

o Conclusions
- Over 100 methods and labs have been certified each year for the past few years.
- There is continuous improvement in HbA1c measurement although the changes over the last few years have been subtle.
- All-method /all lab CVs hover around 3.5%
- CAP pass rates at the current ±6% acceptance level have increased to almost 95%.

3. CAP Update—David Sacks

- CAP Proficiency Testing
  - In USA labs that perform patient testing are required by law to participate in PT
  - Historically, CAP sent out 2 PT surveys annually for HbA1c
  - Each survey contains 3 samples
  - Originally artificial, now whole blood
  - Participation in the survey increased from ~2500 labs in 1998 to ~3500 today
- Regulated analytes
  - CLIA mandated 86 analytes ("regulated") that require PT
  - Mainly diagnostic tests regularly performed whose results are "important to health care treatment decisions"
  - HbA1c is not included i.e., not a "regulated analyte"
- Regulated analytes—Future
  - CMS (Centers for Medicare and Medicaid Services) and CDC are examining a list of non-regulated analytes
  - Plan to add more to mandated list requiring PT – when?
  - Commission on Laboratory Accreditation (LAP) suggested increased frequency of monitoring
  - Selected tests "critical to patient safety"
  - Analytes: BNP/NT-proBNP, Troponin, HbA1c
  - Increased frequency of PT to 3 mailings per year, with 5 samples in each shipment
  - Require 4/5 correct (i.e., +/- 6%) to pass
  - Optional - labs can choose whether to participate in the new 5 sample GH5 survey or the 3 sample GH2 survey (for now)
- PT Failure
  - In past, CAP worked with labs that failed PT
  - CMS recently reminded CAP to adhere to CLIA mandate
  - If lab has repeat unsuccessful performance in PT for a regulated analyte, it is required to cease testing for 6 months (fail either 3 consecutive or 3 of 4 surveys)

Discussion:

How does CLIA-waived vs. moderate or high-complexity testing relate to CLIA regulated vs. non-regulated analytes? There are CLIA-waived methods that appear on the PT surveys, will there ever be an attempt to address the issue of why these tests may be moderate complexity in one setting and waived in another?

D. Sacks noted that users of test methods that are CLIA-waived are not required to participate in PT. One example is glucose meters, most are CLIA-waived, also there are a number of POC HbA1c methods that are waived. A. Gutierrez said he will address the topic of waived vs. moderate complexity. It was noted that for the analytes other than HbA1c that may be regulated in the future, the surveys currently use processed materials and there are no assigned target values so grading is based on peer groups.

Will NGSP and/or CAP tighten the current limits of ±6%? This is important for manufacturers, our product life cycles are generally several years.
R. Little and D. Sacks said there are currently no plans to further tighten the criteria. When the criteria are tightened we generally give manufacturers at least a year's notice, and we provide manufacturers with reports in the interim showing how their method(s) perform under the new criteria.

4. IFCC Task Force on HbA1c Standardization—Garry John

- Successes
  - Several Publications including:
    - JAMA
    - Clinical Chemistry
    - Clinical Chemistry and Laboratory Medicine
- Collaborations:
  - International Diabetes Federation
  - World Health Organisation
- Ongoing projects:
  - IFCC/IDF/WHO International questionnaire on diabetes clinical practices
  - WHO Handbook on Laboratory aspects of Diabetes Monitoring and Diagnosis.
- The Next Stage
  - To maintain and further develop the network of reference laboratories for the measurement of HbA1c (through collaboration with C-TLM)
  - To work in partnership with WHO and IDF to continue to promote the reporting of HbA1c in line with the consensus statement
  - To work in partnership with WHO and IDF to facilitate the development and implementation of international guidelines for the use of HbA1c in the diagnosis of diabetes
  - To work with IFCC Corporate Members to develop a consensus position on the information to be included in the Instructions for Use (IFU) as it relates to the clinical use and interpretation of HbA1c methods
  - Develop quality targets for the measurement of HbA1c and other biomarkers, and on the basis of these targets, and in conjunction with professional bodies, advise on the use of biomarkers for monitoring, diagnosis and screening of diabetes and glucose intolerance.
  - To work with WHO and TF-POCT to recommend best practice in the use of POCT methods for the measurement of HbA1c
  - To evaluate the clinical value of emerging biomarkers (e.g. glycated albumin) for the management of patients with diabetes and to establish whether there is a case for method harmonisation of effective new biomarkers
  - To evaluate the emerging importance of post translational modification derived products (PTMDPs), and especially Advanced Glycation End-Products (AGEs), and work with professional bodies on the best way of developing these for use in diabetes.
  - To monitor the literature and advise on best practice in relation to laboratory aspects of diabetes.

Discussion:

G. John said the IFCC Task Force goal is shifting its focus more toward global education efforts, especially in developing countries where knowledge of HbA1c testing is limited. We want to work with clinical organizations and manufacturers to achieve this.

Are there specific biomarkers besides HbA1c that the TF will be looking at, and is standardization of these analytes a concern?

G. John said right now they are looking at glycated albumin and 1,5 AG but they are also interested in others that may come along. Standardization of these analytes will be important if they eventually are to be more widely used.

Does the TF expanded scope include gestational diabetes?
G. John said yes, the situation with gestational diabetes is currently in flux and new criteria are being discussed but it's something we will need to address.

5. IFCC Reference System for HbA1c—Cas Weykamp

- IFCC Reference System for HbA1c
  - Mission of the IFCC Network is to warrant continuity of the IFCC reference measurement procedure and make HbA1c assays worldwide traceable to it.
  - Network laboratories:
    - There are approved laboratories in the US, Europe and Asia
    - There are currently two candidate laboratories (Brazil, Europe)
    - Network laboratory members participate in annual meetings to discuss network activities and issues that arise.
  - Services for Manufacturers
    - Calibrators to achieve traceabililty
      1) Provided with HbA1c results in IFCC (mmol/mol Hb) and DCCT (%) units, also mmol/L and g/dL.
      2) Provided with total hemoglobin in mmol/L and g/dL.
      3) All are provided with expanded uncertainties.
    - Controls to check traceability
      1) Low, middle and high levels
      2) Middle level is provided with low, normal and elevated total hemoglobin
      3) Units provided
         - HbA1c and Total Hb
         - IFCC- NGSP Units
         - mmol/mol, %, mmol/L, g/dL HbA1c
         - mmol and g/dL Total Hb
         - All are provided with expanded uncertainties
    - Monitoring to prove traceability
      1) Set of frozen whole blood samples, including blind duplicates, to be analyzed throughout the year
      2) Once a year mean deviations from the targets, imprecision and linearity are calculated
      3) Certificates of traceability are provided
    - Variant samples
      1) Collection of the "big four": AS, AC, AD, AE
      2) Limited quantities of A_2, elevated HbF, rare variants
    - Over 30 manufacturers collaborate with the IFCC Network
  - Questions from Manufacturers.
    - Master equation IFCC—NGSP
      1) NGSP maintains traceability to the DCCT, the IFCC maintains metrological traceability
      2) ME: NGSP=(0.915*IFCC) + 2.15
      3) Monitoring validity of the ME
         - Twice a Year a Study
         - 5 Samples
         - All IFCC Network labs
         - All NGSP Network labs
         - Relation calculated
         - Relation used to calculate NGSP% at IFCC = 53 mmol/mol
         - Result is plotted over time
         - 27 Studies from 2001 to 2015

4) Results show ME has remained stable.

- Quality Targets
  1) IFCC Task Force HbA1c: "Develop quality targets for the measurement of HbA1c, and on basis of these targets, and in conjunction with professional bodies, advise on the use of HbA1c for monitoring, diagnosis and screening of diabetes and glucose intolerance"
  2) IFCC TF: Investigation of 2 models to set and evaluate quality targets for HbA1c: biological variation and sigma-metrics. Clin Chem. 2015 May;61(5):752-9.
     - Small errors in terms of imprecision and/or bias can have a high impact on interpretation when HbA1c is used to diagnose diabetes (low risk vs. increased risk for diabetes vs. diabetes)
     - Basics of the model
       i. An Allowable Error is defined: "Results should not differ more than 5 mmol/mol from the true value"
       ii. Risk of not meeting the criterion is defined: "It is acceptable that 1 out of 20 results will not meet the defined criterion"
       iii. Application: Lab – Manufacturer - Country
     - Results:
       i. Combination of bias and CV: Bias of 5mmol/mol and 0%CV, or bias of 0 and 5% CV are acceptable.
       ii. CAP survey 2014A:
           - When model is applied to all laboratories/methods combined the criterion is not met.
           - When applied to individual laboratories about half are within the acceptable limits.
           - For some methods bias is the main issue, this could probably be resolved by calibration adjustment.
           - The 2015A results look better.
  3) HbA1c for diagnosis: Focus on quality, improve:
     - Traceability to the Reference system
     - Quality of the Test itself
     - Storage Conditions Reagents/Calibrators
     - Batch Management Reagents/Calibrators
     - Internal Quality Control Customers
     - Instructions Customers
     - Maintenance Instrument
     - Or introduce a new test

Discussion:

According to the graph if the bias is 0 the allowable CV is much higher than 2% at 2σ.
C. Weykamp acknowledged that this is true.

What is the significance of the different colors on the graph of individual method?
C. Weykamp explained that the different colors indicate the different method types (ion-exchange HPLC, boronate affinity, capillary electrophoresis, immunoassay, etc.).

Should labs mainly focus on the performance of their method within their lab or should they look at the CAP survey as well?
C. Weykamp said both. Monitoring of internal controls is very important and a good EQA survey indicates how the method is performing overall in the field. For example, if your method performs poorly the survey results can tell you if the problem is with the method itself or specific to your lab.

6. FDA Diagnostic Claims for HbA1c— Alberto Gutierrez

- HbA1c is regulated as a class II device. This means that HbA1c testing methods submitted to the FDA are cleared as long as the method can show equivalence to a method previously approved, even if it is decades old.
- When HbA1c was recommended for use in diagnosing diabetes as well as monitoring, this represented a new intended use. This meant we did not have to use substantial equivalence for devices submitted for a diagnostic claim, we were able to write special controls containing stricter requirements.
- One of these special controls requires initial and annual standardization to a certified body (e.g. NGSP). Thus, if a manufacturer method fails annual re-certification they are out of compliance and have to stop marketing the device.
- Other special controls specify total error and other performance requirements.
- There have been seven devices approved for the diagnostic claim so far.
- Information regarding the special controls for the diagnostic claim is available on the FDA web site, manufacturers are also welcome to contact the FDA with questions or concerns.
- CLIA classification
    - In the U.S., testing that is not performed in a formal laboratory (e.g. physician offices) can only be performed using methods that are CLIA waived.
    - Categorization of tests (high complexity, moderate complexity, waived) is done by the FDA.
    - If CLIA-waived PT testing is not required.
    - Ways tests can be waived
        - If FDA cleared for OTC use by lay-users it is automatically CLIA waived.
        - By regulation (e.g. urinanalysis)
        - If the manufacturer can demonstrate to the FDA that the test is accurate and easy to use.
    - Issue with POC HbA1c testing: Some methods that were previously waived for monitoring are not suitable for use in diagnosing diabetes.

Discussion:

Does the FDA or any government agency have any idea how many POC HbA1c analyzers are operating in waived laboratories as opposed to laboratories that participate in PT?
A. Gutierrez said he does not think anyone knows. There are almost 200,000 waived laboratories, no one keeps data on what tests are being performed by which labs.

We know that waived POC HbA1c devices are being used for screening/diagnosis in physician offices, etc., do you believe that CMS will at some point issue a memo proposing a higher level of complexity for this use similar to the recent memo regarding glucose meters?
A. Gutierrez said that most glucose meters were cleared for OTC use, but hospitals began using them off-label in patient populations for which the devices had not originally been tested/cleared. CMS therefore issued a memo to healthcare institutions noting that off-label use means the test automatically goes from waived status to high-complexity, meaning that there are much stricter requirements in terms of personnel, documentation, PT, etc. If the situation is similar with HbA1c, and a POC method that has not been cleared for diagnosis is being used for that purpose, we probably could get CMS to issue a memo.

Is there any way to make a distinction between screening and diagnosis? A device that may not be good enough for diagnosis might still be useful for screening as long as the subsequent diagnosis is made using a suitable test.
A. Gutierrez said the FDA does try to make those distinctions when manufacturers wish to make a claim. One problem the FDA has faced is that many tests were grandfathered in, and labs were not always exact in terms of what claims were made and how the methods are used. For example, with glucose meters the intended use was only for monitoring diabetes. Over the last 10-15 years the FDA has tried to ensure that intended uses are more carefully crafted and worded to make sure they are well-defined. Troponin is an example where the FDA allowed it to come into the market as a Class II device based on equivalence to older cardiac markers, but then it began to be used very differently. Manufacturers were controlling for a high cutoff, but labs began using the limit of detection where manufacturers did not know what was going on. This resulted in recalls and adverse events.

There were no further questions, D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 11:25AM.

Minutes prepared by C. Rohlfing 8/18/15, reviewed by R. Little.