



## Minutes of the NGSP/IFCC Manufacturer Forum

Monday, July 16, 2012 10:00AM-12:00PM  
Westin Bonaventure, Los Angeles, CA

### Presenters:

David Sacks —Chair, NGSP Steering Committee

Randie Little—NGSP Network Coordinator

Curtis Parvin—NGSP Steering Committee

Cas Weykamp—IFCC HbA1c Network Coordinator

Garry John—Chair, IFCC HbA1c Integrated Project

Jack Zakowski—Beckman Coulter, Inc. for the Advanced Medical Technology Association (AdvaMed)

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 in the U.S., Europe and Japan.
- The network is tied to the IFCC network via sample comparisons performed 2X/year.
- 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.
- Status of HbA1c measurement
  - The numbers of certified methods and laboratories continues to increase (currently 110 methods and 110 laboratories are certified).
  - Certified laboratories are distributed throughout the world.
  - There has been much improvement in the comparability of HbA1c results since 1993.
  - All-method CVs on the CAP surveys have dropped from ~7% to 3.5% in the normal range (4-6% HbA1c) since 2000. The CVs have also declined, albeit to a lesser extent, in the middle and high range as well.
  - CAP GH2 survey 2012A:
    - The method-specific means were all within 0.45 at all levels. Eight methods showed a bias >0.35% HbA1c (not all in the same direction).
    - Method-specific, between-laboratory CV's ranged from 1.2% to 7.0%! All but 4 methods had CVs below 5% for all 3 HbA1c levels..
    - Approximately 97% of laboratories were using methods that had between-lab CVs<5%. But only 20% of labs use methods with between-lab CVs <3% at all three levels.
    - Most individual methods show between-lab CVs<3.5% but some, including two methods with a significant number of users, show higher CVs.
    - Only a few methods had pass rates <90%.
- Tightening the NGSP criteria
  - Current criteria: 95%CI of differences must be within  $\pm 0.75\%$  HbA1c
  - Current CAP limits: Each result must be within  $\pm 7\%$  of the NGSP target (Note: at 7% HbA1c, limit is 0.49% HbA1c)
  - Considerations in Choosing the New Certification Criteria
    - Fixed limits or percent:
      - (a) Tighten to  $\pm 0.70\%$  HbA1c (or tighter)
      - (b) Use % limits as used for CAP grading

- Comparison with CAP criteria
      - (a) 2/3 or 3/3 passing on CAP
      - (b) Within 7% (current), 6% (future)
    - Comparison with current certification criteria
    - Certification protocol: Single result or duplicates
  - New certification criteria
    - Use percent rather than fixed criteria
      - (a) Smaller % HbA1c limit at diagnostic and decision levels
      - (b) Easier to compare with CAP criteria
    - Compare to 3/3 passing on CAP: We should expect labs to pass all 3 levels for optimal clinical value; 7% is reasonable at all levels
    - Comparison with current certification criteria
      - (a) Should be more stringent, especially at critical levels
      - (b) Should not be so tight as to fail too many methods
    - Use single results
      - (a) Same as for patient care and diagnosis
      - (b) Single results used for CAP survey
  - New Manufacturer Certification Criteria
    - 37/40 results must be within  $\pm 7\%$  of the NGSP SRL HbA1c; comparable to passing 3/3 on CAP ( $\pm 7\%$ )
    - Based on the past year's certification data, more than 95% of methods that passed with the current criteria would pass with the new criteria
  - New Level 1 Laboratory Certification Criteria
    - 38/40 results must be within  $\pm 7\%$  of the NGSP SRL HbA1c
    - Based on the past year's certification data, more than 93% of Level I laboratories that passed with the current criteria would pass with the new criteria
- Summary
  - HbA1c measurements continue to improve.
  - In an effort to further decrease the variability in HbA1c measurement, the NGSP will tighten manufacturer certification criteria (effective September 2012).
  - The new criteria are comparable to the CAP criteria 3/3 passing at  $\pm 7\%$ .

### 3. Analyses and Comparisons of Certification Criteria—Curtis Parvin

- Analysis Approach: Current NGSP Criteria
  - 40 samples are tested in duplicate by the lab and a reference lab. The 95% CI is computed for the differences between lab and reference lab duplicate averages. If the 95% CI is within  $\pm 0.75\%$  HbA1c the lab passes, otherwise the lab fails.
  - The CV of the average of duplicates for a reference lab is  $CV = 100 \sqrt{\frac{\sigma_{SRL}^2 + \sigma_{DAY}^2 + \frac{\sigma_{REP}^2}{2}}{\mu_{Samp}}}$
  - Based on past data the CV of the average of duplicates for a reference lab is set to 1.5%
  - Given Lab Bias (%) and CV (%) compute the probability that the lab fails the current NGSP criterion
  - Computer simulation: 40 samples uniformly distributed based on the NGSP certification ranges were randomly generated, then the required CV/bias combinations required to pass the  $\pm 0.75\%$  limit were determined based on 5%, 1% and 0.1% probabilities of failure. One million simulations were performed in order to obtain accurate estimates.
- Analytical Approach: CAP criteria
  - Simulation was not required, the criteria can be considered concentration independent so the estimates could be derived mathematically
  - 3 samples are tested by the lab. The assigned values are obtained from 7 SRLs testing each sample on 2 days in triplicate. If 2 or 3 of the lab's results are within 7% of the assigned values the lab passes, otherwise the lab fails.
  - CV of the assigned values for the average from 7 SRLs testing each sample on 2 days in triplicate is  $CV = 100 \sqrt{\frac{\sigma_{SRL}^2}{7} + \frac{\sigma_{DAY}^2}{7 \times 2} + \frac{\sigma_{REP}^2}{7 \times 2 \times 3}} / \mu_{Samp}$
  - Based on past data the CV of the assigned values is set to 0.5%.
  - Given Lab Bias (%) and CV (%) compute the probability that the lab fails the CAP criterion
    - $>1$  of 3 lab results differ by  $>7\%$  from their assigned values (CAP 2/3)

- $\geq 1$  of 3 lab results differ by  $>7\%$  from their assigned values (CAP 3/3)
  - Analysis Approach: New NGSP criteria
    - 40 samples are tested once by the lab and in duplicate by a reference lab. If N (N = 37 or 38) or more of the lab's 40 sample results are within 7% of the reference lab's average value then the lab passes, otherwise the lab fails.
    - As before, based on past data the CV of the average of duplicates for a reference lab is set to 1.5%
    - Given Lab Bias (%) and CV (%) compute the probability that
      - $\leq 3$  of 40 lab results are  $>7\%$  from the reference averages (NGSP 37/40)
      - $\leq 2$  of 40 lab results are  $>7\%$  from the reference averages (NGSP 38/40)
  - Comparing Different Criteria
    - Determine contours for combinations of lab bias and CV that give a specified probability of failing a given criterion
      - Contours for failure rates of 0.1%, 1%, and 5%
      - Overlay the contours to compare criteria
  - Results
    - Current NGSP vs. CAP 2/3 within 7%
      - Labs that have a 99% probability of passing the current NGSP criteria also have ~99% probability of passing CAP 2/3.
      - CAP is more stringent than NGSP at a 99.9% probability of passing and less stringent than NGSP at a 95% probability.
    - Current NGSP vs. CAP 3/3 within 7%: CAP (3/3) within 7% is more difficult to meet than the current NGSP criterion.
    - NGSP 37/40 single examinations vs. CAP 3/3 within  $\pm 7\%$  of reference average
      - At zero bias NGSP 37/40 and CAP 3/3 within 7% are very comparable at a 95% probability of passing; at higher probabilities of passing CAP 3/3 is more stringent.
      - The NGSP criteria are less tolerant of bias than CAP.
    - NGSP 38/40 single examinations vs. CAP 3/3 within  $\pm 7\%$  of reference average: The NGSP contours move downward such that NGSP and CAP are comparable at 99% and 99.9% probabilities of passing at zero bias.

**Discussion:**

It was noted that C. Parvin's analyses bear some resemblance to six sigma although the purpose is different. D. Sacks noted that the analyses will be published, a draft manuscript has already been completed.

***Were the analyses performed comparing NGSP to CAP criteria of  $\pm 6\%$ ?***

C. Parvin said that this was done and the results were shared with the Steering Committee.

**4. CAP Grading: Future Plans—David Sacks**

- In the past peer group grading was used for HbA1c
- In 2007 CAP switched to accuracy grading using the DCCT target
  - Initial limits were  $\pm 15\%$
  - 99% pass rate
  - The limits were tightened to  $\pm 12\%$  in 2008,  $\pm 10\%$  in 2009, and  $\pm 8\%$  in 2010.
  - Plan was to reduce to  $\pm 6\%$  in 2011 but  $\pm 7\%$  was selected and this was kept for 2012.
  - CAP 2010 GH2A Pass Rates at  $\pm 8\%$  and  $\pm 6\%$  (projected) HbA1c cutoff:

	At $\pm 8\%$	At $\pm 6\%$
GH2-01 (5.1%)	95.5	91.0
GH2-03 (6.0%)	95.4	91.6
GH2-02 (8.4%)	95.2	88.6

- CAP 2010 GH2A Pass Rates at  $\pm 7\%$  and  $\pm 6\%$  (projected) HbA1c cutoff:

	At $\pm 7\%$	At $\pm 6\%$
Low (5.6%)	95.6	95.6
Medium (7.2%)	96.2	92.9
High (9.4%)	94.9	92.5

- CAP 2010 & 2012 GH2A Pass Rates at  $\pm 6\%$  (projected) HbA1c Cutoff

	2010	2012
Low (5.1/5.6%)	91.0	95.8
Medium (6.0/7.2%)	91.6	92.9
High (8.4/9.4%)	88.6	92.5

- PT Criteria Will Be Tightened: The CAP limits will be reduced to  $\pm 6\%$  beginning in 2013

#### Discussion:

##### *Given the FDA concerns regarding diagnosis will $\pm 6\%$ be the end goal?*

D. Sacks said that he is not sure that the FDA has decided what the goal(s) will be. C. Benson (FDA) said that the FDA does not have set criteria for a diagnosis claim, there will be an open workshop on August 16 to discuss this.

##### *Will the FDA ever consider the use of HbA1c for the diagnosis of pre-diabetes?*

C. Benson said that the mission of the FDA is to promote public health, they are always open to ideas that help advance patient care.

##### *For an individual laboratory what is required to pass CAP (2/3 vs. 3/3)?*

D. Sacks said CAP considers 90% of labs passing to be good and 95% as very good. On the surveys the requirements depend upon whether the analyte is regulated or not, this decision is not made by CAP. For most analytes, 2 out of 3 samples must be within the limits to pass the survey. However, documentation indicating why one sample failed and corrective action must be submitted to CAP.

#### 5. IFCC Network and Integrated Project—Cas Weykamp and Garry John

- Mission of the IFCC Network is to warrant continuity of the IFCC reference measurement procedure and make HbA1c assays worldwide traceable to it
- Services for Manufacturers
  - Calibrators to achieve traceability
    - Provided with HbA1c results in IFCC (mmol/mol Hb) and DCCT (%) units, also mmol/L and g/dL.
    - Provided with total hemoglobin in mmol/L and g/dL.
    - All are provided with expanded uncertainties.
  - Controls to check traceability
    - Low, middle and high levels
    - Middle level is provided with low, normal and elevated total hemoglobin
    - Units provided
      1. HbA1c and Total Hb
      2. IFCC- NGSP Units
      3. mmol/mol, %, mmol/L, g/dL HbA1c
      4. mmol and g/dL Total Hb
    - All are provided with expanded uncertainties
  - Monitoring to prove traceability
    - 24 frozen whole blood samples per year to be analyzed throughout the year
    - Once a year mean deviations from the targets, imprecision and linearity are calculated
    - Certificates of traceability are provided
    - Many manufacturers have been participating in the program for many years.
- Commutability
  - To link the reference system to the manufacturer assay methods a commutable material is required
  - Fresh whole blood is the most commutable, and will work with POCT systems, but is not stable
  - Frozen whole blood is stable but may not be commutable with some methods, especially POCT methods
  - The network therefore can provide panels of either fresh or frozen whole blood

- Commutability can be assessed two ways
  - CLSI C53-P
  - Divide fresh whole blood into two aliquots, store one overnight at 4 degrees C and freeze the other then test both together
- Sustainability: Each time a batch of calibrators is produced:
  - Assay 10 patients on 4 different instruments calibrated with 4 batches of calibrators
  - Evaluate calibrated HbA1c results within and across instruments
- Network Laboratories
  - Laboratories in China and India have recently been approved
  - There is a candidate laboratory in Korea, and a laboratory in Brazil has shown interest
- Master Equation IFCC-JDS
  - The IFCC-NGSP relationship has remained stable over the duration of the 31 studies
  - The IFCC-Sweden (Mono S) relationship has also been stable
  - The IFCC-JDS relationship has shown a trend. Hypothesis of Dr. Umemoto:
    - HbA1c is formed in a reaction between glucose and the amino terminus of the beta chain, first in a reversible reaction (labile) then the stable product (HbA1c) is formed after Amadori rearrangement.
    - There can be a further reaction with glucose in the sample at the beta 66 lysine residue where a reversible (labile) product (HbA1cβ66 Labile) is formed that can go on to form a stable product (HbA1cβ66 Stable).
    - Any hemoglobin that is glycosylated at the n-terminus of the beta chain, including HbA1cβ66 Labile and Stable, is included in the HbA1c fraction in the IFCC reference method. However, the JDS KO500 method separates HbA1cβ66 labile and stable from the HbA1c fraction.
    - The wash/dialysis step normally performed with fresh blood prior to KO500 analysis returns HbA1cβ66 labile (~2% of HbA1c) back to the HbA1c fraction and also gets rid of any interfering substances in the plasma.
    - Recent sample comparisons between the IFCC and JDS systems have used frozen whole blood so the wash/dialysis steps could not be performed prior to analysis on the KO500.
    - Thus, the KO500 produced lower results that would be the case if fresh blood samples were washed and dialyzed prior to analysis.
  - Two subsequent IFCC/JDS exchanges that utilized fresh blood have confirmed this hypothesis and the IFCC/JDS relationship is now back to where it should be.
- IFCC Integrated Project Update
  - After the tasks they had been assigned to had been successfully completed the IFCC Working Group on HbA1c Standardization was disbanded.
  - Subsequently the IFCC Integrated Project was formed to monitor and help implement global standardization of HbA1c.
  - Recently met with the President of the Japanese Diabetes Society to discuss how Japan will move forward in reporting HbA1c
  - We are working on a review article summarizing where HbA1c is now and where it will be going in the future.
  - Presentations are planned for the Brazilian Congress of Clinical Pathology and the IDF Western Pacific Meeting
  - Attended consensus meeting in association with the IDF meeting in Dubai last year.
    - Updated consensus statement
      1. Reinforced dual reporting (but recognizes that some countries will not adopt this)
      2. Encourages journals to ask for dual reporting in publications
      3. Establish web based calculator for conventional results
      4. Next IDF meeting (Australia) dual reporting in posters
      5. Workshops to explain the value of standardization in countries where it is limited or does not exist
  - Sent out a HbA1c questionnaire to all IFCC member countries.
    - Due to an error that occurred when the survey was transferred to the internet we do not currently know which countries responded, we are trying to identify them based on IP addresses.

- 40 countries responded
- Survey questions
  1. Is HbA1c widely available in your countries? (95% Yes, 5% No)
  2. Is testing mainly performed in laboratories (70%), POCT (0%), both (30%)?
  3. Are the assays calibrated? (92.5% Yes, 7.5% No)
  4. If calibrated, by IFCC (45.7%), NGSP (34.3%), Unknown (20%)?
  5. How are results reported? SI (mmol/mol) (10%), NGSP(%) (55%), both (35%)
  6. How will results be reported in the future? SI (38.9%), NGSP (25%), both (36.1%)
  7. What date will the change be implemented? (Wide range of responses)
  8. Is there national QA or proficiency testing? (59% Yes, 41% No)
  9. How often is EQA performed? (Ranged from 1x/year to monthly)
  10. How many samples per distribution? (Ranged from one to five)
  11. What type of material is used for EQA? (Processed liquid 11.8%, processed lyophilized 35.3%, whole blood 52.9%)
  12. Are target values assigned? (Yes 90.5%, No 9.5%)
  13. How are target values assigned? (Responses varied)
  14. Do you currently use HbA1c for diagnosis? (Yes 40.6%, No 59.4%)
  15. If not are there plans to use HbA1c for diagnosis (Yes 65%, No 35%)
  16. If yes to either previous question will you use only 48 mmol/mol (6.5%) for diagnosis? (Yes 76.2%, No 23.8%)
  17. Will other cutoffs be used (Responses varied)
  18. Would you be willing to answer additional questions arising from these responses (Yes 87.1%, No 12.9%)
- Concerns
  1. A number of countries that are not calibrating
  2. A number of countries have no EQA
- Education and training are needed: We hope to be able to obtain help from manufacturers in parts of the world where there are deficiencies.

### Discussion:

D. Sacks noted that it is very clear that all countries will not be reporting the same numbers, and journals will be requiring reporting in both IFCC mmol/mol and NGSP %. The NGSP will be putting a calculator on the NGSP web site that will allow conversion between IFCC, NGSP and eAG units. It will also have a calculator to convert change or sd between units.

### 6. Scientific Workshop: Exploring Challenges and Opportunities for HbA1c In Vitro Tests for Diagnosis of Diabetes Mellitus—Jack Zakowski

- AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems.
- AdvaMed member companies produce the medical devices, diagnostic products and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments.
- Objective: An open discussion on the use of HbA1c for diagnosis of diabetes
- Format
  - Interactive, 1-day workshop
  - Speakers and panel discussions with:
    - Clinicians and academicians
    - IVD industry
    - Standardization bodies (including NGSP)
    - Regulatory agencies (including FDA)
    - First come, first served
- Key Questions and Topics
  - What is needed to evaluate an HbA1c in vitro diagnostic test for a diagnostic claim?

- Clinical need
- Study design considerations
- Analytical performance characteristics
- What are acceptable performance limits/criteria for studies supporting a diabetes diagnostic indication?
- How would results be interpreted from both a clinical and statistical perspective?
- Certification/Standardization Needs
- Point of Care Assays
- Workshop will be held August 16, 2012 from 8:00 am to 4:30 pm at the Offices of Arnold & Porter, Paul Porter Conference Room, 555 12th Street, NW, Washington, DC 20004
- Meeting contact: Ellen Bielinski, Advamed (ebielinski@advamed.org)
- Registration Link: <http://advamed.org/MemberPortal/Issues/FDA/Scientific+Workshop+-+August+16+2012.htm>

**Discussion:**

D. Sacks thanked Advamed for putting the workshop together, and asked if it will be set up where people can listen in via a webinar or something similar if they cannot attend. Pratul Deshmane (Bio Rad Laboratories) said that he spoke with Advamed and they said this would be difficult. J. Zakowski said that if the meeting space fills up and many people are still needing to register they will look into alternatives. D. Sacks said this meeting is very important and encouraged everyone to attend, he hopes that this will facilitate the development of clear guidelines for diagnostic claims. The goal is to make sure this serves patients well.

***With the new NGSP criteria the limits are very tight in the lower HbA1c range, was consideration given to having a different percentage at the lower vs. the upper range of HbA1c?***

D. Sacks responded that in considering the clinically important range of HbA1c the diagnostic threshold of 6.5% is obviously very important but values below this level are also important. The ADA has recommended that 5.7-6.4% be used to diagnose pre-diabetes, and it is becoming clear that differences in HbA1c levels in the normal range, at least down to 5.0% are indicative of cardiovascular risk.

D. Sacks thanked everyone for their attendance, the meeting was adjourned at 11:50 AM.

*Minutes prepared by C. Rohlfing 7/31/12. Modified by R. Little 7/31/12.*