# Minutes of the NGSP/IFCC Manufacturer Forum

Tuesday August 2, 2016 12:00PM-2:00PM
Sheraton Philadelphia Downtown, Philadelphia, PA

**Presenters:**
David Sacks —Chair, NGSP Steering Committee
Randie Little—NGSP Network Coordinator
Garry John—Chair, IFCC Committee for the Education in the Use of Biomarkers in Diabetes (C-EUBD)
Emma English— IFCC Committee for the Education in the Use of Biomarkers in Diabetes (C-EUBD)
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.
   - We hope to soon have another SRL in China
   - 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 a master equation and 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.
   - Number of certified methods and laboratories
     - The numbers of certified methods and laboratories have increased over the years; currently there are ~170 certified methods and ~150 certified laboratories.
     - Certified laboratories are distributed throughout the world, most are outside of the U.S.
     - Current Manufacturer Certification Criteria (2014-2016): 37/40 individual results must be within 6% of the SRL (one SRL) mean.
     - Current CAP limits (2014-2016) :Each result must be within ±6% of NGSP assigned target value (mean of 7 SRLs, multiple results from each).
   - Improvement in HbA1c testing.
     - 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 few 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): Between-laboratory CV <3.5%. We achieved this goal on the most recent survey.
     - CAP GH2 survey 2016A:
       - Pass rates:

| Specimen | NGSP Target (% HbA1c) | Acceptable Range (±6%) | Pass Rate % (Low/High) | Cumulative Pass Rate % |
|---|---|---|---|---|
| GH-01 | 5.32 | 5.0-5.7 | 71.4/100.0 | 96.4 |
| GH-02 | 9.17 | 8.6-9.8 | 76.5/100.0 | 96.3 |
| GH-03 | 5.31 | 4.9-5.7 | 88.0/100.0 | 97.8 |
| GH-04 | 12.03 | 11.3-12.8 | 66.7/100.0 | 93.0 |
| GH-05 | 5.94 | 5.5-6.3 | 83.3/100.0 | 96.5 |

*Duplicate sample

- Cumulative pass rates at the cutoff of ±6% have increased to >96% since 2008.
- Method-specific between lab CVs ranged from 1.3% to 5.9%.
- Two of the five survey samples were blinded duplicates; the mean within-lab absolute differences between duplicates by method were improved overall compared to the blinded duplicates in the 2015A survey.

- HbA1c Assay Interferences
  - New study published: C. Rohlfing, S. Hanson, C. Weykamp, C. Siebelder, T. Higgins, R. Molinaro, P.M. Yip, R.R. Little. Effects of hemoglobin C, D, E and S traits on measurements of hemoglobin A1c by twelve methods. Clin Chim Acta 2016;455:80-3.
    - We observed clinically significant differences for one or more hemoglobin variants for several methods.
    - One ion-exchange method that previously did not showed clinically significant interferences from several variants in an earlier study did show clinically significant differences for those variants in the current study. We have seen this occur before, this is why methods need to periodically be re-evaluated for variant interferences.
    - We have added the information from the current study to the NGSP web site, we also added arrows indicating whether variant intereferences cause falsely lowered or increased HbA1c results as suggested by the NGSP Clinical Advisory Committee.
- Conclusions
  - Over 100 methods and labs have been certified each year for the past 6 years.
  - There is continuous improvement in HbA1c measurement.
  - All-method /all lab CVs are now <3.5%
  - Awareness of specific method interferences is still very important

**3. AACC Update: IFCC Update—Garry John and Emma English**

- Background—Garry John
  - IFCC Task Force on Implementation of HbA1c Standardization
    - To establish a small group of clinical and scientific experts
    - To act as an advisory board to the HbA1c Reference Laboratory Network.
    - Develop scientific links between National Networks.
    - Advise manufacturers on delivery objectives.
    - To establish links with professional bodies (scientific and clinical) to enable transition of reportable HbA1c values.
    - To help implement the consensus statement.
    - Monitor the introduction of the Consensus statement globally.
    - 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
  - Delivery
    - Develop educational material; consider translating into various languages (e learning).
    - Monitor developments through surveys.

        - Attend international / National meetings to provide advice and guidance based on best practice.
        - Work with Manufacturers.
        - Work with scientific bodies to establish workshops.
        - Develop a website
        - The TF-HbA1C reported to the Executive Board through the President
    - Key Achievements—Publications
        - Hanas R, John WG; International HbA1c Consensus Committee. 2013 update on the worldwide standardization of the HbA1c measurement. Diabet Med. 2013 Jul;30(7):885-6.
        - Sacks DB, John WG. Interpretation of hemoglobin A1c values. JAMA. 2014 Jun 11;311(22):2271-2.
        - Weykamp C, John G, Gillery P, English E, Ji L, Lenters-Westra E, Little RR, Roglic G, Sacks DB, Takei I; IFCC Task Force on Implementation of HbA1c Standardization. Investigation of 2 models to set and evaluate quality targets for hb a1c: biological variation and sigma-metrics. Clin Chem. 2015 May;61(5):752-9.
    - So what next for the task force?
        - The task force was very successful and was closed
        - The final group meeting was held in June 2015
- New Committee—Emma English
    - IFCC Committee for the Education in the Use of Biomarkers in Diabetes (C-EUBD) – Madrid, March 2016
        - G. John Chair UK
        - E. English Member UK
        - R. Erasmus Member ZA
        - D. Sacks Member US
        - C. Weykamp Member NL
        - R. Hinzmann EB representative
        - Corresponding Members
            1) Nominated by National Societies.
            2) Nominated by Corporate Members
    - Updated Terms of Reference
        - 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 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.
    - Key Achievements

        - Global survey on the use of HbA1c and glucose testing – joint project with WHO and IDF: Complete and preliminary findings presented at IDF congress 2015 – paper in draft
        - Compendium of diagnostic tests for diabetes on behalf of WHO and IFCC: In final draft – external review complete
    - Achievements to date
        - Scientific Advisory Committee for Satellite Symposium on diabetes at EuroMedLab, Athens, 2017 – Under Poseidon's Eye
        - ESRC-IAA funding applied for (£7,000) to host a knowledge exchange workshop in Cape Town joint with Ethiopia
        - MRC GCRF outline submission (£360,000) Improving the understanding of the diagnosis and monitoring of diabetes in Ethiopia

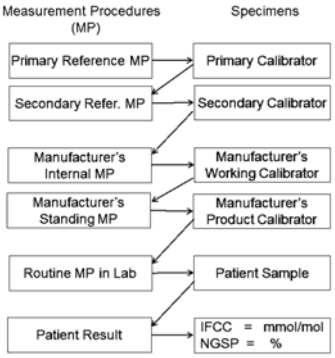
**Discussion:**

G. John and Emma English noted that standardization of HbA1c is done, the goal of the new committee is to focus more on education and availability of HbA1c testing, especially in areas with limited resources. G. John said one specific goal is to work with manufacturers in providing information that will help educate users of HbA1c methods.

**What were the goals of the global survey?**
E. English said they targeted clinical societies as well as IFCC members to provide input from the clinical and analytical side. We asked how HbA1c and glucose are used in the different countries, what kinds of methodologies are available, whether there is EQA available and if so the frequency, and what the desires of the country are in terms of moving forward with testing and what the barriers are. This way we could get a broad picture of what factors are driving diabetes testing in different countries and what improvements are needed. Some areas do not need improvement, however we found issues in some high-income countries as well as low-income countries.

**4. IFCC Reference System for HbA1c—Cas Weykamp**

- IFCC: What, Why and How
    - What
        - Results between different laboratories should be equivalent within clinically meaningful limits
        - Uniform clinical guidelines/decision limits for disease diagnosis and patient management
    - Why
        - Optimum Patient Care
        - Strengthens position in competition with other diagnostic devices (No confusion on reference values/decision limits)
    - How: Metrological Traceability
    - Traceability Chain
        - Measurement Procedures: "Assays" or "Tests"
        - Specimens: "Samples"




- Top two levels are the responsibility of the reference laboratory
- The next two levels are the responsibility of the manufacturers
- The fifth level is the responsibility of the routine laboratory
- The bottom level is the responsibility of the physician and patient
- Each step is critical to achieving optimal HbA1c testing, analogous to runners in a relay race
- The IFCC is analogous to a "coach" in the process

o Reference laboratory: IFCC network
- Worldwide network of laboratories
- Perform comparison studies twice a year via sample exchanges
- Criteria for acceptable performance
- Annual meeting of network laboratories

o Services to Manufacturers
- Calibrators to achieve Traceability
- Controls to check Traceability
- Monitoring Programme to prove Traceability
- Variant Samples (FDA Approval)
- Value Assignment Specimens
- Calibrators: Specifications
  1) Units provided: HbA1c and Total Hb, IFCC- NGSP Units, mmol/mol, %, mmol/L, g/dL HbA1c,mmol and g/dL Total Hb
  2) All are provided with expanded uncertainties (IVD Directive)
  3) Eight levels of calibrators
- Controls: Specifications
  1) Low, medium and high levels
  2) Medium provided with low, medium and high hemoglobin concentrations
  3) Units provided: HbA1c and Total Hb, IFCC- NGSP Units, mmol/mol, %, mmol/L, g/dL HbA1c,mmol and g/dL Total Hb
  4) All are provided with expanded uncertainties
- Monitoring program
  1) Panel of blind specimens
  2) Analyze and send in the results
  3) Certificate provided showing deviations from the IFCC target, reproducibility, CV, linearity, correlation coefficient
  4) New this year: Graph provided based on recent paper on quality targets published by the IFCC Task Force (Clin Chem 61:5 752-759 (2015). CV (%) plotted against bias in IFCC and NGSP units showing level of analytical performance.
- Variant samples: Collection of AS, AE, AC, AD samples in stock along with limited quantities of A2, elevated HbF and rare variants.

o Routine laboratories: EQA/PT
- Publications showing method performance based on CAP data (Clin Chem 61:5 752-759 (2015)), EQA in Germany, Belgium and the Netherlands (Clin Chem Lab Med 2016), Italy (Clin Chim Acta 459(B), 305-309 (2015)).

        - New survey EQA survey will be performed once a year beginning in October using the same fresh blood samples across Europe, findings will be presented at Euromedlab.
    - Laboratory/Patient
        - Established master equation for converting IFCC to NGSP or vice-versa prior to reporting of results
        - Equation is monitored twice a year via IFCC/NGSP network comparisons

**What is the practice in the industry regarding lots of IFCC calibrators, do manufacturers generally change lots of IFCC calibrator every time a new lot comes out?**
C. Weykamp said the IFCC produces a new batch of calibrators every year, there is some minor unavoidable fluctuations from year to year but each batch is checked against the previous batch to ensure continuity, they are also tested for commutability. Therefore it should not matter which batch manufacturers use. Some manufacturers use the same batch for three years, others use the new batch every year.

**As assays get more precise we can sometimes see the effects of small fluctuations in the IFCC calibrators, how could this impact NGSP certification?**
C. Weykamp said the NGSP does not supply calibrators, they supply samples with NGSP values. There is going to be a certain amount of uncertainty with any value assignment, the IFCC assigns values using 17 network laboratories so the uncertainty is very low. Also, patient samples are used, so there can be differences in specificity between different methods with some samples. We test each batch using five different method types to assess commutability.

**5. POC HbA1c for Diagnosis—David Sacks**

- Can HbA1c be used to diagnose diabetes?
    - Follow-up Report on the Diagnosis of Diabetes Mellitus (Diabetes Care 2003;26:3160): "… the Committee believes that it is still premature to add [Hb]A1C to the group of tests used for the definitive diagnosis of diabetes."
    - WHO/IDF 2006: "Currently HbA1c is not considered a suitable diagnostic test for diabetes…."
    - International Expert Committee Report on the Role of the A1C assay in the Diagnosis of Diabetes (Diabetes Care 2009;32:1327): "[Hb]A1c assay may be a better means of diagnosing diabetes than measures of glucose"
    - Diagnosis of Diabetes Mellitus—ADA 2010 (Diabetes Care 2010; 33 (Suppl. 1):S11):
        - HbA1c ≥ 6.5% OR FPG ≥ 126 mg/dL (7.0 mmol/L ) OR. 2-h glucose ≥ 200 mg/dL (11.1 mmol/L) during OGTT OR Symptoms of hyperglycemia and casual plasma glucose ≥ 200 mg /dL (11.1 mmol/L)
        - Unless unequivocal hyperglycemia, confirm by repeating the same test on a different day
    - WHO Position on HbA1c for Diagnosis (WHO Jan. 2011): "HbA1c can be used as a diagnostic test for diabetes"
    - 2011: WHO recommendation accepted by presidents of IDF, ADA & EASD
- HbA1c for Diagnosis: Manufacturer
    - Most clinicians who order HbA1c for diagnosis are unaware of assay used
    - FDA developed criteria to allow manufacturers to have diagnostic claim
    - Several methods now FDA-approved for this claim
- HbA1c for Diagnosis: FDA-approved
    - Bio-Rad D-100 HbA1c
    - Roche COBAS INTEGRA 800
    - Roche COBAS C 501 TINA-QUANT HBA1CDX GEN.3 ASSAY
    - Tosoh AUTOMATED GYLCOHEMOGLOBIN ANALYZER HLC-723G8
    - Abbott HbA1c on the ARCHITECT c 8000 System
    - Bio-Rad VARIANT II TURBO HbA1c Kit - 2.0
    - Abbott HbA1c on the ARCHITECT c 4000 System
    - Ortho-Clinical VITROS Chemistry Products HbA1c Reagent Kit Ongoing projects:
- ADA Guidelines: HbA1c POCT

    - 2010-2012: "Point-of-care A1C assays are not sufficiently accurate at this time to use for diagnostic purposes."
    - 2013—Present: "Although point-of-care A1C assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of POC assays for diagnostic purposes is not recommended."
- HbA1c POCT for Diagnosis
    - All approved assays in central lab
    - Alere has applied to FDA for clearance of Affinion HbA1c for diagnosis of diabetes and identifying persons at risk for diabetes
    - Applying under "moderate complexity" (currently waived for monitoring)
    - FDA held a public meeting July 22, 2016 in Gaithersburg, MD

**Discussion:**

D. Sacks said the main reason the Expert Committee recommended HbA1c for diagnosis in 2009 was improvement in the assays. He noted that in addition to clinicians being unaware of the HbA1c method used for diagnosis, the lab is generally not aware of what the test is being used for. A. Gutierrez said that the diagnosis issue in the U.S. is complex, we have a two-tier regulation. FDA regulates manufacturers while CMS, through CLIA, regulates laboratories. CLIA has a three tiers of complexity, high, moderate and waived, these categories define the requirements for the lab including laboratory director qualifications, who can perform the test, and PT. For waived laboratories, which are the vast majority in the U.S., the only requirement is that they follow the manufacturer's instructions. These labs typically do not get inspected and are not required to perform PT. Our concern at the FDA is if we have the appropriate controls in place if the test is to be used for diagnosis. The problem is that in the two-tier regulatory system of FDA and CMS, the two do not always match up. FDA is concerned with safety, effectiveness and equivalence for the stated use; CLIA waiver status is concerned with whether the test is accurate and is unlikely to produce erroneous results, it is a different standard.

**Should a manufacturer be allowed to apply for the diagnosis claim under moderate complexity when the method is already being used as a waived test?**
A. Gutierrez said this was asked at the panel meeting. FDA cannot force a manufacturer to apply under waived status, if they are approved under moderate complexity then want to get waived status for the method they need to do a separate waiver study. We can only do what is in front of us, we are not really sure yet how to approach this. Alere could have applied for FDA clearance and the waiver at the same time but there is no way for us to force them to do so, and traditionally it done as a stepwise process. It was clarified that FDA actually advised Alere to do the process stepwise.

**So if a POC test is cleared for diagnosis and is waived, does the lab still need to perform PT?**
A.Gutierrez said this cannot be addressed by the FDA, this would have to come from CLIA or one of the professional bodies. The weakness of the FDA clearance process is that we separate pre and post-market, we do not look at the manufacturer's lot release criteria or whether there is lot-to-lot variability, these are things PT generally takes care of. In this situation reliance on PT will not work, we may need to look at other ways to address the issue.

**If a POC method is NGSP-certified, it should produce the same results as a lab method.**
A.Gutierrez said that the issue is not just the method but also how the lab is performing the test; monitoring of lab performance is traditionally done through PT in the U.S. If you do not have PT you do not know if laboratories are performing the test correctly. You could argue that some of these methods are so foolproof that there is almost no chance of getting an erroneous result. That is one of the questions about the Alere method.

D. Sacks said that for moderate complexity, PT is not required if the analyte is not CLIA-regulated as long as the lab has other ways to monitor performance. A.Gutierrez said this is true but most labs perform PT if a good survey is available rather than trying to come up with their own monitoring scheme. Also, from the other side there are some waived labs that nonetheless perform PT.

There were no further questions, D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 1:30 PM.

*Minutes prepared by C. Rohlfing 8/23/16. Modified by R. Little 8/24/16. Revised by C. Rohlfing 10/17/16.*