Minutes of the NGSP/IFCC Manufacturer Forum

Monday August 5, 2019 2:00—4:00PM
Hilton Anaheim, Anaheim, CA

Presenters:
Randie Little—NGSP Network Coordinator
David Sacks —Chair, NGSP Steering Committee
Cas Weykamp—IFCC HbA1c Network Coordinator
Emma English—IFCC C-EUBD

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 Update—Randie Little, NGSP Network Coordinator**
   - The NGSP Steering Committee oversees the administrative core and laboratory network. The laboratory network consists of the Central Primary Reference Lab (CPRL), which runs the original DCCT HbA1c method, 2 backup PRLs and 10 Secondary Reference Laboratories (SRLs) located in the U.S., the Netherlands, Japan and China.
   - The network is monitored monthly via comparisons between the SRLs and CPRL using 10 fresh-frozen pooled samples, and also by long-term QC specimens analyzed quarterly.
   - The NGSP has three processes
     - Calibration: Informal process to assist manufacturers/labs with calibration of their methods.
     - Certification: Formal process where manufacturer or lab certifies against a SRL via a 40-sample comparison and must pass specific criteria.
     - Proficiency testing: CAP whole blood survey, which is accuracy-based with target values assigned by the NGSP network, shows how well the harmonization process is working.
   - The NGSP network is linked to the IFCC network via a master equation that is monitored by sample comparisons performed twice a year.
   - NGSP network monthly mean between-lab CVs were all <1.6% over the past year.
   - Number of certified methods and laboratories
     - The numbers of certified methods and laboratories have increased over the years; currently there are ~260 certified methods and ~140 certified laboratories.
     - The number of certified methods continues to increase while the number of certified labs has leveled off.
     - Many of the certified methods are different variations of the same basic methodology, e.g. the same reagents used on different instruments, hemolysate vs. whole blood application on the same instrument.
     - Certified laboratories are mostly outside of the U.S., and are distributed throughout the world.
     - Level 1 laboratories are generally labs performing clinical trials where clients require level 1 certification to ensure the quality of their HbA1c results.
   - Current Limits for NGSP and CAP
     - Beginning January 2019: NGSP Manufacturer and Level II Lab Certification Criteria: 36/40 results must be within ±5% (37/40 for Level I labs)
     - CAP Survey Grading for HbA1c remain at ±6%

- Pass Rates for NGSP certification: ±6% vs. ±5%: Based on the 1st 6 months of certification data in 2018 and 2019

Certification Type	2018 ±6%	2019 ±5%
Manufacturer	92.2%	92.9%
Level I Lab	95.1%	95.9%
Level II Lab	78.6%	69.2%

- There has been much improvement in the comparability of HbA1c results since 1993 when the results of the DCCT were reported.
- Latest CAP survey (2019 GH5A)
  - A variant (HbS) sample was included in the survey.
  - Results from some methods showed a bias for HbAS when compared with a non-variant survey sample in the same HbA1c range, suggesting possible interference.
  - While the bias for HbAS was consistent with what we would expect for most methods based on our previous interference studies, two methods showed more bias than expected. The NGSP will re-evaluate these methods for variant interference.
  - 2019A CAP Pass Rates (±6%)

Specimen	NGSP Target (% HbA1c)	Acceptable Range (±6%)	Pass rate % (Low/High)	Cumulative Pass Rate % ±6%
GH-01	5.46	5.1-5.8	80.0/100.0	**94.0**
GH-02*	5.66	5.3-6.0	60.0/100.0	**87.1**
GH-03	9.31	8.7-9.9	86.7/100.0	**96.0**
GH-04	5.28	4.9-5.6	84.7/100.0	**96.3**
GH-05	7.41	6.9-7.9	89.6/100.0	**97.9**

*HbAS

  - The all-method CVs have shown an overall downward trend since 2000.
  - All-method CVs for the most recent survey ranged from 2.7-3.6% (3.6, 3.1, 3.3, 2.7%) (AS excluded).
  - Our current goal for all method CVs is <3%.
  - Cumulative pass rates were ≥94% for the non-variant samples.
  - The CV for the HbAS sample was higher than for the non-variant samples (4.4%) and the pass rate was lower (87.1%).
  - CV and bias by method type
    - Some individual methods had better CVs than others, but there were methods that performed well among all method types (ion-exchange, CE, affinity and enzymatic).
    - Mean absolute biases varied among individual methods, but overall were comparable among method types.
    - Among individual methods, some of the mean biases were positive while others were negative.
  - Method-specific, between-laboratory CV's ranged from 0.9% (Arkray HA-8180) to 4.5% (Roche Integra 400) (AS excluded).
  - 89% of laboratories are using methods with CVs≤3.5% at all four HbA1c levels (AS excluded).
- Conclusions
  - The NGSP network is still doing well with very low CVs
  - The change to tighter criteria for NGSP certification is reasonable if we want to see lower overall variability in HbA1c results for patient care.
  - Measurement of HbA1c continues to improve
  - The NGSP will continue to investigate Hb variant interferences.

Discussion:

CAP Variant Sample
D. Sacks asked if any manufacturers wanted to comment on the interferences seen with the HbAS sample; was anyone surprised? He noted that labs using methods in which there was interference were not failed based on this sample. R. Little said that her laboratory did not report a result for this sample because they know there is HbS interference for the G8 method, but most labs apparently reported results for this method. They may not have been aware that there is an interference, or they may not have felt the interference was critical since the degree of interference is relatively small in the low HbA1c range.

After the survey were manufacturers and labs notified that this sample was a variant (HbAS) sample?
R. Little and D. Sacks said yes, the information is included in the CAP report which is sent to all participating laboratories.

Inclusion of a variant sample provides important information; will CAP continue to do this in the future? It would be good if not only HbS but some other less common variants could be included as well.
R. Little said they have included variants in surveys before. It is difficult to get a sufficient amount of variant donor blood for the survey, and would be even more difficult for variants less common than HbS. D. Sacks said CAP has tried in the past to include the other common variants (C, D, E), but the supplier said it was not possible to get a sufficient number of donors. The survey is sent out to over 3,000 labs, so rare variants would be out of the question.

The focus of variant interference is on analytical interference, but there are conditions where red cell lifespan is altered and HbA1c should not be used in those patients regardless of testing methodology. There should be more focus on this.
D. Sacks said while it is true that there are conditions such as hemolytic anemia, incorporating this into a PT survey would not provide useful information to labs. The laboratory is generally not going to be aware of the clinical condition of the patient;, they will analyze the sample and report a result. Communication between clinicians and the laboratory is important, but PT is not the way to address this. R. Little added that the purpose of PT is to assess the accuracy of lab measurements, not to address the patient's condition and whether HbA1c should be used for that patient. Where variants are concerned there are a few less common variants that cause reduced red cell lifespan, but the data suggest that red cell lifespan is not significantly affected with the four most common heterozygous variants (S,C, E, D). Also, it is very difficult to measure red cell lifespan. Education of clinicians is important, we still get samples from post-transfusion and sickle-cell patients to test for HbA1c in our laboratory. It was suggested that a dry lab component could be added to the survey in order to help educate laboratories, R. Little thought that was an interesting idea. She noted that laboratories should always put information in their reports about situations where HbA1c might not be useful, although that may not necessarily always end up translating to better use of HbA1c.

3. Update on Proposed CLIA Rule—David Sacks, Chair, NGSP Steering Committee

- The number of labs participating in the CAP HbA1c survey has increased since 1993 and is now ~3500 labs (about 12% are outside of the U.S.).
- Proficiency Testing (PT)
  - Evaluation of lab performance against pre-established criteria by interlaboratory comparisons
  - Also termed EQA (external quality assessment)
  - In US all labs that measure patient samples are required by law to perform PT
  - Regulated by CMS (Centers for Medicare & Medicaid Services) through CLIA
  - CAP is largest provider of PT material
- CAP Grading
  - Initially, CAP used peer group grading for PT for GHb
  - Subsequently, introduced whole blood PT, but maintained peer group grading
  - In 2007 changed to accuracy-based grading
  - Target values assigned by NGSP network
  - +/- 15% acceptable
  - 99% pass rate

- PT Criteria Tightened
  - In 2008 acceptability reduced to 12%
  - In 2009 acceptability reduced to 10%
  - In 2010 acceptability reduced to 8%
  - In 2011 acceptability reduced to 7%
  - In 2014 acceptability reduced to 6%
- CAP 2010, 2012 & 2013 GH2A Pass Rates at ±6% HbA1c Cutoff

	2010	2012	2013
Low (5.1/5.6%/6.07)	91.0	95.8	93.4
Medium (6.0/7.2%/7.1)	91.6	92.9	95.3
High (8.4/9.4%/9.3)	88.6	92.5	94.3

- CAP Proposed Criterion 2020: ±5%
- Pass Rates for CAP 2018 GH5-A: ±6% vs. ±5%

Sample ID	±6%	±5%
GH-01	95.9	**95.9**
GH-02	97.3	**93.6**
GH-03	96.8	**95.9**
GH-04	95.6	**92.4**
GH-05	97.1	**96.1**

- How could CAP progressively tighten the criteria? Because HbA1c is not a regulated analyte.
- Summary
  - CAP progressively tightened PT grading
    - 2007 - 15%
    - 2014 - 6%
    - 2020 - 5%
  - Lab performance on CAP surveys improving due to better methods
- CLIA Proposed PT Rule
  - Hemoglobin HbA1c would become a regulated analyte
  - Criterion for acceptable performance: Target ±10%
- Effect of Change in PT
  - True HbA1c is 6.5%
  - If criterion is ±5%, acceptable value is 6.2% - 6.8%
  - If criterion is ±10%, acceptable value is 5.8% - 7.2%
- CAP Response to CLIA Proposal
  - CAP is not permitted to fail a lab if it meets CLIA criteria
  - If CLIA accepts ±10%, CAP will have to loosen acceptability from ±6% to ±10%
  - CAP has elected NOT to reduce criteria from ±6% to ±5% in 2020
- Potential Outcome of CLIA Proposal
  - Accuracy of HbA1c assays likely to deteriorate
  - Patient care likely to suffer

Discussion:

CLIA proposed PT Rule
D. Sacks said this has caused much concern. He notified R. Little as soon as he heard about the proposed rule and she notified her contacts in the various clinical organizations; they were incredulous. The major concern is deterioration of performance at the laboratory level; manufacturers still have to pass the NGSP criteria which will not change. As long as laboratories are able to pass PT they generally consider their performance to be acceptable.

What has happened subsequently is that since CMS is required to allow comments on proposed rules, many comments were submitted. Even though there were a number of analytes addressed in the rule, almost all

comments were about HbA1c and virtually all of them urged CMS not to adopt the rule as proposed. Organization including the ADA, AACC, CAP, ISPAD, and others submitted comments. We discussed this issue at our Clinical Advisory Committee meeting at the ADA in June where we learned that CMS is required to respond to every comment prior to adopting the rule. It was also suggested that representatives of the relevant organizations talk directly to CMS, so representatives from the ADA and JDRF as well as D. Nathan (Mass General Hospital) are planning to meet with CMS soon. The hope is that CMS will change the criterion but they do not have to. The latest CAP today has an article, and there was a recent editorial published in Diabetes Journal of Technology and Therapeutics, both arguing against the adoption of the current rule. It will likely be several months, if not longer, before CMS takes any action.

Would the looser requirements apply to use for diagnosis?
D. Sacks said yes, CMS is separate from FDA and does not address how the results are used.

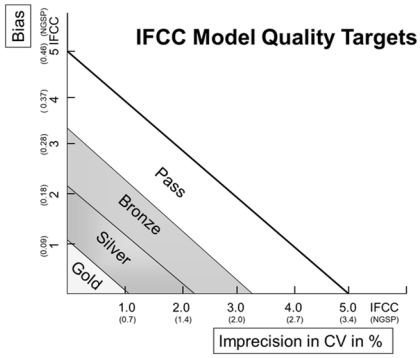
Manufacturers still have to pass FDA criterion of 6% and NGSP of 5%. Given this kind of assay performance, will the laboratories using these methods actually reach 10%?
D. Sacks said theoretically no, but labs tend to bend rules and as long as they pass PT they have no incentive to monitor their assays carefully. It is inevitable that if the PT criteria are loosened the quality of results in some labs will deteriorate.

Is there any speculation as to the motivation for the 10% criterion? Could this have just been an oversight?
D. Sacks said one hypothesis is these kinds of changes at CMS typically take a long time. It is possible that the idea of making HbA1c a regulated analyte was initially brought up years ago when the CAP criterion was 10%. We do not know if this is the case, however.

4. Update: IFCC Network—Cas Weykamp

- IFCC Roadmap to Optimum Performance HbA1c: Steps
  - IFCC Working Group
    - Reference Method
    - Global Network
    - Services Manufacturers
  - IFCC Task Force: Model Quality Targets
  - IFCC Committee: Monitoring Quality in the EU and US
- Reference Method was approved in 2001, progress report was published in Clin Chem in 2008.
- Global network of reference laboratories remains in place and continues to perform well.
- Services to Manufacturers
  - Calibrators to achieve Traceability
  - Controls to check Traceability
  - Certification Programme to prove Traceability
  - Variant Samples (FDA Approval)
  - Value Assignment Specimens
  - Monitoring Master Equation IFCC – NGSP
  - Calibrators: Specifications
    - Units provided: HbA1c: IFCC (mmol/mol) and NGSP (%) Units, mmol/L, g/dL
    - Total Hb: mmol/L, g/dL
  - Controls: Specifications
    - Low, medium and high levels
    - Medium provided with low, medium and high hemoglobin concentrations
  - Manufacturer Certification: certificate is provided showing how the method performed compared to quality targets.
  - Variant samples: Collection of AS, AE, AC, AD samples in stock along with limited quantities of A2, elevated HbF and rare variants.
  - Monitoring Master Equation IFCC – NGSP
    - NGSP = 0.0915 x IFCC + 2.15
    - Sample comparisons between the networks are performed twice a year.
    - The ME is monitored over time and has been shown to be stable over time since 2001.

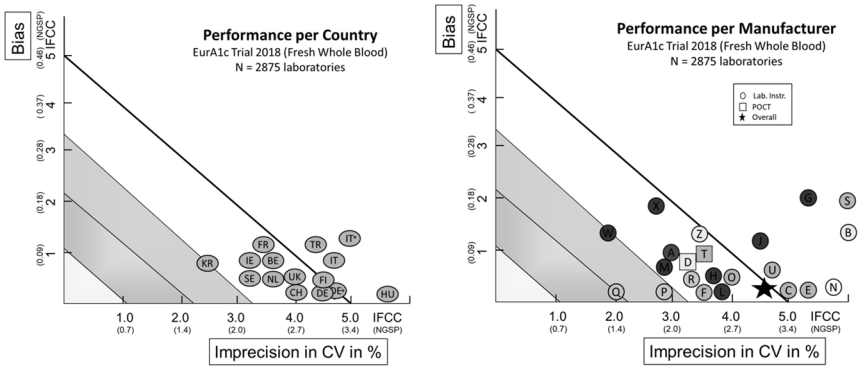
- Model Quality Targets: IFCC Task Force, published in Clinical Chemistry in 2015 (Clin Chem. 2015 May;61(5):752-9).
- Monitoring Quality— IFCC C-EUBD (IFCC Committee Education in the Use of Biomarkers in Diabetes)
  - Manufacturer Certification: Changes
    - Certificate format: Now reflects performance compared to the IFCC quality targets.
    - Monitoring: Change from 12 duplicate samples analyzed over the course of a year to 24 individual samples measured all at once.
    - New generation web site: Was www.ifcchba1c.net, now is www.ifcchba1c.org.
  - Reasons for changes: Critical questions/remarks
    - "Imprecision from duplicates sensitive to fraud"
    - "Assays covering a year: outdated data"
    - "Too optimistic – differences individual patients"
    - "Criteria and reference not clear"
  - Redesigned certification
    - Include bias
    - Include imprecision
    - Cover concentration range
    - Address differences in individual patients
    - Prevent fraud
    - Base on recent data
    - Traceable to published criteria (IFCC Model Quality Targets)



  - Options: Bias and imprecision
    - 24 measurements of 1 sample
      a. Bias: Yes
      b. Imprecision: Yes
      c. Concentration range: No
      d. Specificity: No
      e. Fraud possible: Yes
      f. Recent data: Yes
      g. Sound Criteria: Yes
    - 24 measurements of duplicates over a year
      a. Bias: Yes
      b. Imprecision: Yes
      c. Concentration range: Yes
      d. Specificity: No
      e. Fraud possible: Yes
      f. Recent data: No
      g. Sound Criteria: ?
    - 24 measurements in 24 samples
      a. Bias: Yes
      b. Imprecision: Yes
      c. Concentration range: Yes
      d. Specificity: Yes

    e. Fraud possible: No
    f. Recent data: Yes
    g. Sound Criteria: Yes
- Certificate indicates performance in terms of bias and imprecision compared to quality targets
- New Certification—New Questions
  - Mathematics of the Calculation
  - Impact Uncertainty on Score
  - Discrepancy between Certificate and Daily Life
  - My performance vs. competitors
- Mathematics of the Calculation
  - Bias calculated based on the differences from the true values
  - Imprecision is estimated based on the deviations of the individual points from the regression line.
  - Reference: Statistics for Biologists (Cambridge University, first published 1967)
- Impact of Uncertainty
  - Uncertainty is reduced by increasing the number of measurements
  - How many assays for each value assignment?
    a. IFCC Certification Frozen Whole Blood: 16 labs – each 4 assays = 64
    b. IFCC Certification Fresh Whole Blood: 3 methods – each 2 assays = 6
    c. Comparison CAP: 8 labs, each 6 assays = 48
    d. NGSP Certification: 1 lab, 2 assays = 2
- Discrepancy between Certificate and Daily Life
  - This can be seen by comparing the plots showing method performance in PT surveys to performance indicated on the manufacturer certificate.
  - Generally method performance is worse on the PT surveys than performance in the hands of the manufacturer.
  - If the performance of a method is acceptable in the hands of the manufacturer but is not acceptable on PT surveys, ways to improve the performance may include:
    a. Batch Management Reagents, Software, Calibration
    b. Maintenance Instrument (Lab/Manufacturer)
    c. Education (Lab/Manufacturer)
    d. Priority Quality (Lab/Manufacturer)
  - Discrepancies between manufacturer and PT performance vary between countries.
- My performance vs. competitors
  - Can be seen on the PT quality target plots showing individual methods
  - 2018 data: Number of labs in each category
    a. Gold: 0
    b. Silver: 54
    c. Bronze: 27
    d. Pass: 25
    e. Fail: 14
    f. Information can be found at www.ifcchba1c.org
- EurA1c: Project of the IFCC C-EUBD and 15 national EQA organizers.
  - Purpose: Global overview of HbA1c performance (E.S. Kilpatrick. Toward a Global Overview of HbA1c Test. ClinChem2018;64:1131-2).
  - Concept: Once a year the respective European EQA/PT Organizers use the same 2 samples
  - Eurocentric at the start of 2016, in 2018 participation from Korea, Thailand, Mexico, Africa, name changed to EurAAA1c.
- EurAAA1c
  - Concept: Once a year the respective EQA/PT organizers use the same 2 samples.
  - Information
    a. Overall performance in Europe (World)
    b. Performance per country
    c. Performance per manufacturer
    d. Performance per country per manufacturer

- Samples EurA1c
  - Fresh whole blood
    a. Advantage: Commutable and suitable for all methods
    b. Disadvantage: Limited stability
  - Lyophilized hemolysate
    a. Advantage: Stable
    b. Disadvantage: Not commutable for all methods, not suitable for some POCT instruments
    c. Choice: National EQA organizers: Logistics in the country
  - Prepared from the same initial specimens: Allows us to see impacts of matrix effects.
- Participation in EurA1c
  - 2016: 17 EQA/PT organizers, 2166 laboratories
  - 2018: 25 EQA/PT organizers, 3983 laboratories
- Results Fresh Whole Blood: Example



- EurA1c Activities
  - EurA1c 2018: Report released 30 September 2019 (Manufacturers sponsoring the IFCC network get the report EurA1c 2018 on request)
  - EurAAA1c 2019: Running October 2019 – April 2020
  - Presentations
    a. EurMedLab May 2019; Barcelona
    b. AACC August 2019; Anaheim
    c. Colabiocli September 2019; Panama
    d. IFCC WorldLab May 2020; Seoul (IFCC C-EUBD: 2 Symposia)
  - Scheduled 2020/21: paper reviewing trials 2016 – 2019
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Discussion:

C. Weykamp noted that this year is the 25th anniversary of IFCC HbA1c standardization efforts and the 50th anniversary of the discovery of HbA1c.

EurA1c

Will the U.S. be included in EurA1c in the future?

C. Weykamp said the U.S. already has the CAP survey and including the U.S. would involve a substantial number of additional labs. They may look at ways of comparing data from CAP and EurA1c.

5. Update on the activities of the IFCC C-EUBD 2018-2019 —Emma English, IFCC C-EUBD

- Members
  - Garry John Chair UK
  - Emma English Secretary UK
  - Asako Sato Member JP
  - David Sacks Member US
  - Cas Weykamp Member NL
  - Consultant: Erna Lenters (POCT)
- Corresponding Members, Nominated by National Societies
  - D. Aslan Turkish Biochemical Society (TBS)
  - W. Cheneke Gebisa Ethiopian Medical Laboratory Association (EMLA)
  - A. Mosca Italian Society of Clinical Chemistry and Clinical Molecular Biology (SIBioC)
  - P. Gillery Société Française de Biologie Clinique (SFBC)
  - A. Coj Lithuanian Society of Laboratory Medicine
  - R. Kumar Dubey Nepalese Association for Clinical Chemistry (NACC)
  - B. Kumar Yadav Nepalese Association for Laboratory Science (NAMLS)
  - B. Okesina Association of Clinical Chemists Nigeria (ACCN)
  - R. Nanda Association of Medical Biochemists of India (AMBI)
  - E. Schleicher Deutch Gesellschaft fur Klinische Chemie und Laboratoriumsmedizin e.V. (DGKL)
- Corresponding Members, nominated by Corporate Members
  - S. Baraldi A. Menarini Diagnostics
  - R. Molinaro Siemens Healthcare
- Educational Events 2018/2019
  - Peru and Chile: Cas Weykamp
  - Vietnam: Andrea Mosca
  - Dubai and China: Emma English
  - Hong Kong and India: Garry John
  - China and ADA: David Sacks
  - Indonesia, China, Iran: Erna Lenters
  - Tunisia: Okesina
  - Thank you to all of the manufacturers who have facilitated these events over the past year!
- Upcoming Symposia
  - 2019: COLABIOCLI Regional Congress, Panama, September 10 – 13
  - 2020: IFCC WorldLab, Coex, Seoul, Korea 24-28 May
- Current Projects
  - Continue EurAAA1c project – expanding the global reach
  - Continue partnership with the Chinese Diabetes Society to improve quality of testing in China
  - Initiate project with Manufacturers on calibration and best practice.
  - Improving diabetes testing across Africa project
- The Africa Project—We Need Your Help
  - Aims: Improve Access to and Quality of Diabetes Testing in Africa
  - Partnerships: WHO, IDF, IFCC, NGOs, Individual Country Associations, Manufacturers
  - Progress to date
    - Joint global survey between WHO, IDF and IFCC – completed and presented data at IDF congress, Vancouver
    - Obtained UK government funding for knowledge exchange workshop in Africa to explore barriers to diabetes testing

        - Obtained further UK government funding to follow up the global survey and explore policy and practice issues around diabetes testing in Africa
        - Prof John and Dr English are consultants on the upcoming WHO Priority Medical Devices for Stroke, CVD and Diabetes
    - Next Steps
        - Finalise draft policy overview for diabetes testing in Africa
        - Further develop collaborations with key partners to develop low cost reliable HbA1c testing for Africa
    - How can you help? Understanding the manufacturer's perspective
    - Post forum follow up
        - We would like to talk to you – we would like to understand the barriers to implementing diabetes testing in low income settings and explore ways to overcome these
        - We will send out invitations to participate via the registered contact details provided for the forum or contact me: emma.english@uea.ac.uk
- Contact Details:
    - Prof Garry John; Chair: g.john@nnuh.nhs.uk
    - Dr Emma English: emma.english@uea.ac.uk
    - Dr Cas Weykamp: c.w.weykamp@skbwinterswijk.nl
    - Dr David Sacks: david.sacks2@nih.gov
    - Prof Asako Sato: sato.asako@twmu.ac.jp

Discussion:

IFCC C-EUBD
E. English said what they need from manufacturers is information regarding what barriers they face in Africa and other parts of the world, and how the IFCC C-EUBD may be able to assist in addressing these issues in order to improve the quality of HbA1c testing.

D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 4:00PM.

Minutes prepared by C. Rohlfing 10/10/2019. Modified by R. Little 10/11/2019 and D. Sacks 10/16/2019.