



Meeting of the NGSP Steering Committee Minutes

Sunday July 31, 2016 2:00 PM – 4:30 PM
Sheraton Philadelphia Downtown

Participants:

*David Sacks—NIH, Chair, NGSP Steering Committee
*Randie Little—Univ. of MO, NGSP Network Coordinator
*Philippe Gillery-University Hospital of Reims (FR), IFCC Scientific Division
*W. Greg Miller—Virginia Commonwealth Univ.
*Ross Molinaro—Siemens Diagnostics
*Michael Steffes—University of Minnesota
*Hubert Vesper—CDC
*Cas Weykamp—Queen Beatrix Hospital (NL), IFCC Network Coordinator
*Member of the NGSP Steering Committee

Susanne Adams—Roche Diagnostics
Valerie Arends—University of Minnesota
Shawn Connolly—Univ. Of MO, NGSP
Emma English--IFCC
Kuanysh Kabytaev—Univ. of MO
Erna Lenters—Isala (NL);IFCC;NGSP
Curt Rohlfing—Univ. of MO, NGSP

Scott Ruetten—Abbott Diagnostics
Violeta Raneva-- Ref. Material Inst for Clin Chem Standards
Amy Saenger—University of Minnesota
Rick San George--Alere
Mark Schmid—Roche Diagnostics
Louisa Shen—Roche Diagnostics
Carla Siebelder—Queen Beatrix Hospital (NL);IFCC;NGSP
Toshie Takoura—Tosoh Bioscience
Carla Terry—Tosoh Bioscience
Hirohito Umemoto—Ref. Material Inst for Clin Chem Standards (ReCCS)

Steering Committee members not present:

Robert Cohen—University of Cincinnati
David Nathan—Massachusetts General Hospital
Curtis Parvin—Bio Rad Laboratories
Tony Prestigiacomo—Thermo Fisher
Elizabeth Selvin—Johns Hopkins University

1) **Welcome and Introduction—David Sacks, Chair, NGSP Steering Committee**

D. Sacks welcomed those in attendance. Those present introduced themselves.

2) **The 2015 Steering Committee minutes were approved by the members present.**

3) **Dr. Masao Umemoto**

D. Sacks noted the untimely recent passing of Dr. Masao Umemoto who was President of the Reference Material Institute for Clinical Chemistry Standards (ReCCS) in Japan. Dr. Umemoto was the head of one of the NGSP network laboratories and was very actively engaged with the NGSP as well as numerous laboratories in Japan, his presence will be missed. D. Sacks then introduced Dr. Umemoto's son Hirohito Umemoto who was elected President of ReCCS in April. H. Umemoto noted that his father passed away April 4 at the age of 65 and that he is grateful for the kindness shown to his father during his term as President of ReCCS. M. Umemoto made great contributions to the standardization of clinical chemistry testing. He worked very hard to develop definitive reference methods and certified reference materials, and successfully established their general use in clinical practice in Japan. Most of the reference materials used in clinical chemistry testing in Japan are supplied by ReCCS. Dr. Umemoto also contributed significantly to the standardization of HbA1c over the last 15 years. ReCCS has maintained a NGSP backup PRL (APRL) as well as a SRL (ASRL#1) and has performed numerous NGSP certifications of manufacturers and laboratories in Asia. When it was decided that Japan would change from reporting JDS %HbA1c values to NGSP %HbA1c, Dr. Umemoto helped to facilitate this by assigning NGSP as well as JDS values to reference materials. He also was a core member of the IFCC HbA1c laboratory network and contributed to international HbA1c standardization. We at ReCCS plan to continue his work and ask for your continued support in these activities. D. Sacks thanked H. Umemoto for his words and for continuing to work with the NGSP.

4) **NGSP Progress Report—Randie Little , NGSP Network Coordinator**

- NGSP Network Monitoring
 - The PRLs and SRLs continue to demonstrate excellent comparability (May between-lab CVs were 1.2% and 0.94% for the PRLs and SRLs, respectively).
 - In addition to monitoring the SRLs against the CPRL, we monitor the SRLs against each other using an acceptance ellipse which is based on the slope and intercept of the differences between the individual SRLs results and the medians of all SRLs (limits based on historical data).
 - Monthly between-lab CVs for the NGSP network were all <1.8% over the past year.
- Certification
 - The number of certified methods continues to increase, while the number of laboratories has leveled off recently.
 - There are ~150 methods and ~170 laboratories currently certified.
 - Most certified labs are Level I and are outside of the U.S.
 - There are clusters of certified labs in South Africa, Columbia and various locations in Asia.
- CAP Data
 - Current CAP limits (2013-2016) : Each result must be within $\pm 6\%$ of NGSP assigned target value (mean of 7 SRLs, multiple results from each).
 - There has been much improvement in within and between-lab variability since 1993.
 - 2016A survey
 - 5 samples, 2 were duplicates.
 - The worst methods are used by very few labs (83 out of ~3500).
 - Individual method pass rates varied from 66.7% to 100%.
 - Overall pass rates were 93.0-97.8%.
 - Cumulative overall pass rates at the current cutoff of $\pm 6\%$ have increased from 2008 to 2016.
 - For the first time the all-method CVs for all three samples between 4 and 10% HbA1c were all <3.5% (2.8-3.1%), which has been our goal.
 - The mean absolute differences between the duplicate samples for individual methods were <0.15% HbA1c for all but one method, which is improved over last year.
- HbA1c assay interferences
 - New variant interference 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.
 - One ion-exchange method that previously did not show clinically significant interference from HbS or HbC now shows significant interference, we have seen this before, especially with ion-exchange methods.
 - We have updated the NGSP web site to reflect the most current data, we have also added arrows to the table to indicate whether a given interference causes a lower or higher result based on a recommendation made at the last Clinical Advisory Committee meeting.
 - There are still methods with interference from common Hb variants.
 - These interferences can change for ion-exchange HPLC methods; these must be reevaluated periodically.
- Requirements for New SRLs and New SRL Method Certification Criteria
 - Candidate SRLs that have not previously participated in the NGSP network must be able to fulfill the following requirements:
 - Must be able to participate in monthly monitoring (10 samples/month) by CPRL.
 - Have experience with and be able to communicate with interested manufacturers and laboratories without conflicts of interest.
 - Must be able to collect and analyze certification samples according to the NGSP protocol, which includes screening for Hb variants and elevated HbF (>2%), and provide them to manufacturers and laboratories upon request.
 - Be able to send invoices to manufacturers and laboratories participating in the certification process following NGSP fee schedule and pay NGSP the data analysis portion upon receipt of NGSP (University of Missouri) invoice.
 - International (non-U.S.) laboratories must provide NGSP with documentation that they have the support of the professional clinical community in their country.
 - Depending upon shipping logistics/costs, international laboratories may need to provide some or all of the costs of shipping monthly monitoring specimens to their laboratory.

- Consideration for Network membership will be given to the laboratory's geographic location and the need for an additional network laboratory. **The NGSP Steering Committee reserves final authority in determining which laboratories are eligible to participate in the Network.**
 - SRL Method Certification (added to NGSP Protocol): A proposed SRL / method must perform the following as a Level I laboratory (or existing SRL):
 - 20 day precision evaluation following EP5. Total imprecision (CV) must not be statistically significantly >2%.
 - 40 previous quarterly monitoring samples using single results compared to the mean of SRL results.
 - 1) 38 of 40 results must be within $\pm 6\%$ (relative) of the SRL.
 - 2) For each quarterly monitoring comparison, candidate method results must also fall within a defined acceptance ellipse based on the slopes and intercepts of the differences between the individual SRLs results and the medians of all SRLs.

5) ASRL#1 2015 NGSP Certification Results: Good Performance of the POCT Methods—Violeta Raneva, Chief of ReCCS HbA1c Reference Laboratory. In Memoriam of Dr. Masao Umemoto (1951 – 2016)

- 2015 NGSP Certification at ASRL#1
 - 54 Methods and 10 Laboratories
 - POCT methods: 13 including 5 from China
- 2015 ASRL#1 Certified Methods with Good Performance (Bias $\leq \pm 0.25\%$ HbA1c, 95% Confidence Interval)
 - Methods from 17 different manufacturers
 - Five Level 1 laboratories, three Level 2 laboratories
 - Manufacturers and laboratories located in South Korea and China as well as Japan
- ASRL#1 Certified POCT Methods with Good Performance (Bias $\leq \pm 0.25\%$ HbA1c, 95% Confidence Interval)
 - 11 methods
 - Manufacturers from South Korea, China and Japan
- 4th 2015 HbA1c (NGSP) Japan (Asia) Proficiency Testing: POCT methods performed as well as laboratory methods.
- The NGSP web site states the ADA recommendation that POCT should not be used for diagnosis, the JDS Guideline for Treatment of Diabetes in Japan states the same.
- This is causing problems for POCT manufacturers as they are not able to sell to some customers due to the guideline.
- Since POCT methods perform comparably to laboratory methods, should they excluded from use in diagnosing diabetes?

6) NGSP Issues for Discussion—Randie Little , NGSP Network Coordinator

- Proposed SRL in China
 - Dept. Laboratory Medicine, Zhongshan Hospital, Fudan University. Dr. Pan Baishen, director
 - Level I Lab since March 2010 with good performance using Bio-Rad Variant II
 - Involved in HbA1c standardization activities and fresh WB proficiency testing in China
 - Have submitted letters to the NGSP Steering Committee from the director of the laboratory, the President of the University and the Chair of the Chinese Society for Laboratory Medicine
 - They have passed the new SRL criterion of 38/40 within $\pm 6\%$ of the mean of the SRLs for their last 40 quarterly monitoring samples (40/40).
 - They were within the SRL acceptance ellipses for these four exchanges.
 - Preliminary precision data (one run/day over 20 days) were excellent (total CVs of 0.8% and 1.1% at HbA1c levels of 5.43 and 9.95%, respectively), they are repeating EP5 with two runs/day as required.
 - Request provisional approval for Zhongshan Hospital now and final approval once precision data is confirmed to pass the standard EP5 precision evaluation.
- Is there a need to have every method type in the NGSP network?
 - E. Lenters has suggested adding the Abbott Enzymatic method as an SRL in the NGSP network
 - The method shows excellent performance

- Results show extremely tight correlations with existing ion-exchange HPLC SRLs, is there a need to add an enzymatic method?
- Manufacturer Certification Failures: Questions
 - When there are multiple platforms on one instrument series using the same reagents, is it reasonable for some to pass and some to fail?
 - When there are multiple certification failures and other indications of poor performance, should the manufacturer be allowed keep trying to re-certify?
 - Should the method that has repeatedly failed (e.g. twice or 3x) be required to notify their customers? How could this be enforced?
 - Should there be a limit on how many times they can fail and be allowed to try again? If so, what about fail, pass, fail, pass?
 - Are there any time limits? What if a manufacturer fails and then wants to re-certify a year later?

Discussion:

Hemoglobin variant interference study

S. Ruetten asked when the previous variant study was performed. R. Little and C. Rohlfing said many of the samples from the most recent study were actually analyzed in 2014 and 2015, the previous study was published in 2012. C. Terry noted that the interference with the Tosoh method shown in the current study mainly impacted results on the high end but you cannot really see this in the information presented on the web site. R. Little said it is difficult to present highly detailed information on each variant interference on the web site but acknowledged that details can be important, for example the presence of potentially interfering variants can generally be seen with ion-exchange methods but this is not the case for other method types.

CAP survey

S. Adams asked why the last CAP survey included a sample that was ~12% HbA1c, they normally do not include a sample that high. D. Sacks said this was an error on the part of the supplier, normally the high sample is supposed to be ~10%.

POCT methods in Japan

M. Schmid asked if the recommendation that POC methods should not be used for diabetes diagnosis will change given that technology is changing. D. Sacks said this is an ADA, not NGSP, recommendation, JDS likely followed ADA. R. Little noted that it is good to see that the POC method certified by ASRL#1 are performing well, and asked if physician offices doing POCT in Japan are required to participate in PT. V. Raneva responded that PT requirements are not as stringent in Japan as compared to the U.S., end-users are not required to perform PT; it is generally performed by the manufacturers. There are other requirements for labs such as ISO, but PT is not required, we would like to see this change in the future.

New SRLs in NGSP network

D. Sacks asked what burden would be added if the proposed SRL in China is added to the network. R. Little said extra sets of monitoring samples are already collected, and Zhongshan is already paying to have monitoring samples shipped quarterly. We will try to arrange to ship three months' worth of monitoring samples to the network quarterly in the future (as opposed to every month as we do now). Having a SRL in China should be useful for certifying manufacturers and laboratories in China as there are often issues with sending samples to China in terms of regulations, permits, etc. There are also often billing issues, labs have trouble with making payments, Zhongshan could directly bill labs in China and we would invoice Zhongshan for the data analysis part. Having a SRL in China has already been shown to be useful in terms of them working with manufacturers and labs in that country. C. Terry asked if the methods used in the NGSP network are listed on the NGSP web site. R. Little and C. Rohlfing said they are. D. Sacks made a motion to provisionally approve the addition of the SRL in China, the Committee passed the motion without objection. E. Lenters said that the Abbott enzymatic method shows excellent analytical performance, the CVs may be even better than HPLC methods. Also, no extra monitoring samples would be required, they can use the same samples already sent for ESRL#11 (Premier) and their new immunoassay (future ESRL#13). It also represents a new assay principle, there is currently no enzymatic method in the network. In any case it will be a secondary reference method in the IFCC network. D. Sacks asked if there is a downside to adding the enzymatic method to the network. C. Rohlfing said the report templates will need to be modified but this will need to be done anyway when the SRL in China is added. CVs are ~0.4%, data from 40 previous monitoring

samples have already been sent to C. Rohlfing along with data from the new c513 immunoassay, the EP5 precision will be completed soon. G. Miller asked how many reagent lots have been evaluated on the enzymatic method, E. Lenters said two so far, both are incorporated in the EP5 precision data along with three different calibrations and so far there have been no significant deviations. R. Little asked if the method is being calibrated offline with IFCC calibrators, E. Lenters said no, they normally do the offline calibration but for the current evaluation the raw data are being used. R. Little asked if we could obtain the offline calibrated data for the purposes of the SRL certification, E. Lenters agreed to send it. G. Miller asked how many calibrator lots have been used so far and if the calibrators and reagents come together as a kit. E. Lenters responded that two lots of calibrators have been used so far and they are separate from the reagent lots. G. Miller's only reservation was that there is no long-term performance data. R. Little agreed but noted that the network labs are monitored monthly, and the offline calibration protects against potential shifts in manufacturer-assigned calibrator values. D. Sacks asked how often Abbott releases new calibrator lots, Scott Ruetten said approximately two per month. The Committee approved adding the enzymatic method as an SRL providing it passes certification.

Manufacturer Certification Failures

R. Little said the current NGSP guideline is that if a manufacturer fails certification the manufacturer is supposed to investigate the cause, report what corrective actions were taken and how the resulting change will be communicated to customers if needed. This has happened in the past, sometimes the cause and corrective actions taken are clear but other times they are not. Sometimes there are multiple platforms using the same reagents, we sometimes see differences between them where some pass certification while others do not, is this reasonable? M. Schmid noted that sometimes there can be a technical issue or malfunction with an instrument that causes it to fail. There can be some performance differences between platforms since they are not identical, but usually if one fails and the others pass it is due to a technical problem with that specific instrument. G. Miller asked what the procedure is, if for example, one platform out of three submitted by a manufacturer fails, R. Little said it is treated the same as if it were an entirely separate method. The manufacturer is supposed to investigate to determine the cause, provide documentation of corrective action and explain how the changes made will be communicated to customers if needed prior to re-attempting certification. S. Ruetten said the manufacturer should have a process where the common reagents should be investigated to determine what systems may be affected, this is called "bracketing". It could just be a problem with the individual instrument but nonetheless this should be part of the investigation. Regarding multiple certification failures, R. Little asked if we should allow these methods to keep attempting certification over and over, even when there are other indications of poor method performance (e.g. CAP survey). If they keep trying there is a possibility they will eventually be able to pass. This issue has been discussed before and it was decided that they should be allowed to keep trying, does this need further consideration. G. Miller said the issue is that there is nothing in the NGSP guidelines to prevent them from re-attempting certification, do we need to add some language to the guidelines to state that there is a stopping point where they have to do something more prior to a further certification attempt. R. Little asked G. Miller if he could draft language to add to the protocol to address this issue, G. Miller agreed. C. Weykamp suggested allowing a second attempt after the first certification failure, but after a second failure there should be a waiting period, perhaps one year, before another attempt. D. Sacks asked what time frame would be reasonable. C. Weykamp a waiting period after the second failure would stimulate manufacturers to better address issues with their method. G. Miller asked to be sent the current text, he will draft a revision and send it to the rest of the committee. R. Little asked if a manufacturer should be required to notify their customers in the event of more than one certification failure, if so how would this be enforced? D. Sacks asked if FDA is supposed to be notified if a method fails certification, S. Ruetten and R. Little said only for the diagnostic claim, not for monitoring. R. Molinaro said that if a manufacturer claims that the method is certified in their labeling but then the method fails certification, it is considered non-conformance. Whether the manufacturer communicates this to the customer is within their own quality system, there must be clear communication from the committee as to what the expectations are. In the vendor's mind they are working with the NGSP to attain certification. If the expectation is once you fail the customer must be notified, that needs to be clearly stated by the committee. G. Miller asked if manufacturers generally state that the method is NGSP-certified in their labeling. R. Molinaro and S. Ruetten replied that at least some methods state this explicitly. G. Miller asked what would be required of manufacturers if this is stated in the labeling and then the method failed certification, S. Ruetten said that the manufacturer would perform an investigation and do a potential risk assessment which could result in communication with customers. G. Miller said the question is: what is the role of the NGSP? D. Sacks said the FDA only applies to the U.S., what about countries outside the U.S.? S. Ruetten said in many cases registrations outside the U.S. indicate NGSP certification, in which case the manufacturer would be out of compliance with these as well. C. Weykamp said that it would be difficult for the NGSP to force manufacturers to communicate with

customers but perhaps more additional information could be provided, for example showing which methods have been certified without interruption for a number of years. R. Little said customers can already look on the list to see which methods are certified if they are interested and they know about the web site. M. Shmid added that customers can, and often do, ask the manufacturer for a copy of their current certificate. G. Miller said his opinion is that the NGSP can provide information but it is not the role of the NGSP to make manufacturers inform their customers, this is a regulatory issue. D. Sacks agreed saying the NGSP is not a regulatory body. G. Miller noted that regulations are different in different countries.

7) **Clinical Advisory Committee Meeting Update—David Sacks**

- The CAC is composed of representatives from major clinical diabetes organizations. The purpose is to facilitate interchange between these organizations and the NGSP.
- The CAC met at the ADA in June 2016.
 - R. Little presented an update on NGSP progress.
 - Discussion of hemoglobin variants,
 - NIH is very concerned about hemoglobin variant interferences.
 - Some discussion of rare variants, discussion of possibly presenting information re. rare variant interference on the NGSP web site.
 - In the end there was no firm decision.
 - POC methods for diabetes diagnosis
 - Alere has applied for a diagnostic claim for the Afinion which is a POC HbA1c method.
 - Current ADA guideline is that POC methods are not to be used for diagnosis.
 - The method is NGSP certified and widely used for monitoring.
 - Since it is CLIA-waived there is no requirement to perform proficiency testing.
 - Plan is to submit to FDA for diagnostic claim as a moderate-complexity test, then later obtain waived status for the diagnostic claim.
 - There was no one from FDA at the CAC meeting.
 - The FDA held a meeting with an expert panel (Clinical Chemistry and Toxicology Device Panel) in Gaithersburg, MD July 22nd to discuss the Alere diagnostic claim application.
 - 1) Various speakers from ADA, Alere and others
 - 2) Panel was able to ask questions
 - 3) Panel advises FDA but their conclusions are not binding
 - 4) Conclusions were that they had no concerns about the moderate-complexity application, but there were more concerns about use of a waived test.
 - R. Little gave a presentation about fructosamine and glycated albumin.

Discussion:

Rare variants

R. Little said the group in the end was not really excited about putting the information on rare variants on the website. We published a study of 49 rare variants, Bio Rad actually has data that they have accumulated for their methods available on their web site. We did not want to clutter the website with too much information that could be confusing. C. Rohlfing added that in many cases we only have one or two data points for a given variant.

POC diagnostic claim

S. Ruetten asked if there is any advantage to having a diagnostic clearance for a POC test. M. Schmid noted that there is evidence that having the test available at the time of the visit can have a positive psychological impact, but this is for monitoring. Before there were claims for diagnosis a lot of labs were using it “off-label” for diagnosis. The lab receives an order for HbA1c but they do not know how the clinician is using the result. S. Ruetten asked if the diagnostic claim now forces the physician using POC in the office to confirm a POC HbA1c that indicates a diagnosis of diabetes with a laboratory test. D. Sacks said the ADA guideline currently states only that a HbA1c result indicating a diagnosis should be confirmed with a second HbA1c but it does not specify how, it could presumably be on the same instrument on the same day. S. Ruetten said this is a risk. M. Shmid asked if the FDA diagnostic claim criteria are the same for POC as with laboratory tests, D. Sacks said yes. What generated a lot of discussion at the FDA meeting was that in the U.S., you are not supposed to use POC glucose to screen for or diagnose diabetes. However, there are fairs, shopping malls, etc. where they have

screenings using these devices, the ADA is very concerned about this. S. Ruetten asked if they should be more concerned about the millions of people with undiagnosed diabetes. D. Sacks said they are concerned about that as well. R. San George said the benefit of having a waived test for diagnosis is that it would be more widely available and therefore could identify more people with previously undiagnosed diabetes. The risk is that if it were used in settings other than physician offices such as fairs where there is no medical oversight, there is some risk of people being told the wrong thing; that is the equation. S. Ruetten said the risk of a false negative, for example getting a 5 when the person actually has diabetes, is much higher than the risk associated with a false positive. D. Sacks agreed. R. San George agreed and said this is why as a manufacturer Alere has to demonstrate that the risk of this happening is extremely low. At the FDA meeting R. Kahn noted that the difference in terms of treatment for a value of 6.3 vs. 6.8 is minimal, although technically one is pre-diabetes while the other is diabetes the actual risk associated with this kind of difference is very low. However, the difference between a 5 and a 7% HbA1c is enormous, that is why it is our job to show that the risk of this kind of discrepancy occurring is insignificant as part of obtaining the CLIA waiver. S. Ruetten noted that results obtained in an R&D setting may be different than results obtained at a fair, for example. Validation studies should be conducted such that they apply to the user environment. A. Saenger agreed and added that this puts pressure on the manufacturer to prove that the method is “dummy proof” in the hands of inexperienced users. C. Weykamp mentioned that the discussion seems to be focused around diagnosis vs. monitoring, what about screening? R. Little said the FDA does not recognize screening as being separate from diagnosis; she has asked them about this but so far has not received any explanation. D. Sacks said it may be because the screening and diagnostic tests are currently the same; you just have to do it twice to diagnose. R. Little said that is the current guideline, if you detect diabetes with HbA1c you confirm with another HbA1c test, but many physicians screen with one test (e.g. glucose) and confirm with another (e.g. HbA1c) which may be a better way. D. Sacks said physicians often do FPG and HbA1c the same day, that way if both are positive you have your confirmation. M. Schmid noted that there are POC systems that can do both HbA1c and glucose. G. Miller said that from a practical point-of-view, whether a HbA1c method is waived or moderate complexity, or approved for diagnosis, is probably not that important because they will be used by physicians for diagnosis anyway. The conversation regarding these matters, while interesting and worth having, is really not relevant to the NGSP. R. Little said the big issue is that in a lab setting there is some oversight of how the method is performing in terms of requirement to run controls, PT, etc., whereas with a waived method used in a physician office there is virtually no oversight. G. Miller did not disagree but added that the job of the NGSP is to make sure that a method, when operated by the manufacturer, is able to meet a set of criteria. In terms of how the test is actually used, the NGSP might be able to offer an opinion but in the end this is not what the NGSP does. These conversations need to go on among physicians, regulatory bodies, etc., the NGSP just needs to make sure that POC devices are certified using the same criteria as laboratory methods. S. Ruetten asked if it would be appropriate for the NGSP to help improve the statement from ADA in terms of using two separate methods to diagnose diabetes. G. Miller said that is a separate question. The NGSP can inform the ADA about the performance of methods based upon our experience, but at the end of the day the ADA is going to make the decision. We could send them a letter. M. Schmid clarified that by the use of two different methods, we mean that screening could be done by a POC HbA1c method, but the confirmation would be done with a lab method. H. Vesper said the purpose of the NGSP is to assure accurate testing in patient care. With a waived POC device we assume that it maintains the same performance over time, the NGSP has a unique opportunity to monitor the performance over time thru annual re-certification. If the method loses its certification it is an indication that it is no longer performing to the same standard and it is no longer in compliance with the FDA. In that way we can help to ensure that the method performs as well as when it was cleared. You could have a situation where the manufacturer no longer certifies a method once it is cleared. R. Little and M. Schmid responded that maintaining NGSP certification is already a FDA requirement for the diagnostic claim, they want to know if a method loses its certification. A. Saenger asked if the manufacturer is required to maintain NGSP certification for a method that is waived. R. Little thought so, H. Vesper said there is no specific FDA requirement. M. Schmid said the wording is vague, but it does state that a method loses the diagnostic claim if it loses certification. G. Miller asked if a manufacturer fails a certification, does the NGSP have a responsibility to notify the FDA? Also, if NGSP has a responsibility for ensuring continued accuracy in HbA1c testing, should the NGSP have a PT requirement rolled into the certification process? This is something to consider in the future. R. Little said that PT is done by the labs, not the manufacturers. M. Schmid said there are implications to doing this, there are thousands of POC instruments in the U.S., CAP would need to provide much larger quantities of samples. D. Sacks said CAP can do this, G. Miller makes a good point, this is something to think about. R. Little said CAP used to have an alternative less-expensive

survey that used lyophilized samples, they did this because they could get more participation by smaller sites. D. Sacks noted that different countries have different laws regarding PT, C. Weykamp said in the Netherlands PT is not required for POC but almost all testing is done in laboratories. In Norway the population is much more spread out and therefore there are more small settings where POC is used, many of these participate in PT although it is not required.

Fructosamine and Glycated Albumin

P. Gillery asked if there was much interest expressed regarding the use of glycated albumin. R. Little said she was asked to write a mini-review on the topic and she thought it was interesting, so she wanted to get some input as to whether and how the test is being used. Some said they use fructosamine and that it might be useful to have GA, opinion seemed to be mixed. D. Sacks noted that the GA assay does not yet have FDA approval in the U.S., and asked about the situation in France. P. Gillery responded that fructosamine is used by some clinicians but GA is not yet being used in clinical settings. There is a lack of outcome studies. R. Little said there is some data that GA may be useful in some patients, for example, patients with renal disease. C. Weykamp noted that it may be useful in patients with altered erythrocyte lifespan.

8) AACC Update—IFCC HbA1c—Emma English

- IFCC Task Force on Implementation of HbA1c Standardization – objectives
 - 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, Leters-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.
- 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
- 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
- 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
- Nominated by National Societies
- 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 harmonization 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.
- Achievements to date
 - Scientific Advisory Committee for Satellite Symposium on diabetes at EuroMedLab, Athens, 2017
 - ESRC-IAA funding applied for to host a knowledge exchange workshop in Cape Town joint with Ethiopia
 - MRC GCRF outline submission Improving the understanding of the diagnosis and monitoring of diabetes in Ethiopia

Discussion:

R. Little said a lot of countries participate in regional meetings, can someone from the IFCC C-EUBD go to these meetings and present this information? E. English said yes, it is about getting the message out there and how to do it, the biggest issue right now is funding and to a lesser extent accessibility. One thing we found from the survey is that the problem is not a lack of will on the part of clinicians and laboratory scientists but a lack of will in governments to provide support. R. Little said that it should not be expensive to have one representative of the committee go to each of these meetings, E. English said they are willing to work with anyone who will sponsor workshops; these have been going on for some time. What they want to do now is get funding for research to take it a step further, the support can be in the form of material as well as monetary support to improve the situation in a given country. The use of the money depends upon what we can get funding for, for example if we can get support to develop a quality network inside of a country that is what we will do, we can fly people out to a country to train people.

D. Sacks thanked everyone for their attendance, the meeting was adjourned at 4:30PM.

Minutes prepared by C. Rohlfing 8/19/16, reviewed by R. Little 8/20/16.