Meeting of the National Glycohemoglobin Standardization Program Steering Committee Minutes
Sunday July 24, 2011 3:00 PM – 5:30 PM
Marriott Marquis, Atlanta. GA

Participants:

*David Sacks —NIH, Chair, NGSP Steering Committee
*Randie Little—Univ. of MO, NGSP Network Coordinator
*Phillip Gillery—American Memorial Hospital (FR), IFCC Scientific Division
*Garry John—Norfolk and Norwich University Hospital (UK), Chair, IFCC Integrated Project on HbA1c
*W. Greg Miller—Virginia Commonweath University
*Curtis Parvin—Bio Rad Laboratories
*Scott Reutten—Abbott Diagnostics
*David Simmons—Bayer Diabetes Care
*Michael Steffes—University of Minnesota
*Hubert Vesper—CDC
*Cas Weykamp—Queen Beatrix Hospital (NL), IFCC Network Coordinator

***Member of the NGSP Steering Committee**

Jim Albarella—Siemens Healthcare
David Armbruster—Abbott Laboratories
Carol Benson—FDA
Denise Furtado—Axis Shield
Jon Gilcrist—Nova One Diagnostics
Mark Herlan—Roche Diagnostics
Erna Lenters— Isala klinieken (NL), ESRL
Guy Marseille—Abbott Diagnostics
Gary Myers—AACC
K. Ramadrishnan—ProdConcepts/AACC Ind. Div.
Curt Rohlfing—Univ. of MO, NGSP
Alexander Stoyanov—University of Missouri
Charles Xie—Bayer

Steering Committee members not present:

David Nathan—Massachusetts General Hospital
William Roberts—ARUP Laboratories

1) **Welcome and Introduction—David Sacks, Chair, NGSP Steering Committee**
D. Sacks welcomed those in attendance, introduced new Steering Committee member Scott Reutten of Abbott Diagnostics, and thanked outgoing member Jack Zakowski of Beckman Coulter for his service to the NGSP. Those present introduced themselves.

2) **The 2010 Steering Committee minutes were approved by the members present.**

3) **NGSP Progress Report—Randie Little , NGSP Network Coordinator**
- NGSP Network Monitoring
  - The PRLs and SRLs continue to demonstrate excellent comparability,
  - Monthly between-lab CVs for the NGSP network were all under 2.5% over the past year.
- Certification
  - The number of certified methods and laboratories has continued to increase.
  - The number of certified laboratories now exceeds the number of certified methods.
  - We are currently still able to provide sufficient samples but we may be reaching our limit.
  - The increase in Level 1 Labs is a reflection of large clinical trial labs increasing the number of sites around the world, especially in places like India and China.
  - Asia now has the most Level 1 Labs.
  - Shipping to some regions can be expensive and difficult.
- CAP Data
  - The CAP data show much improvement in the comparability of HbA1c results in the field between 1993 and 2010.
  - 2011A Survey
    - The method-specific means were all within 0.35 at all levels. Only one method showed a bias >0.3% HbA1c.
    - Method-specific, between-laboratory CV's ranged from 1.4% to 7.2%. All but 3 methods had CVs below 5% for all 3 HbA1c levels.

- Approximately 97% of laboratories were using methods that had between-lab CVs<5%.
- Between-laboratory CVs
  1) CVs for the ion-exchange HPLC methods were all below 3%.
  2) Some of the immunoassay methods also showed CVs<3%.
  3) CVs for the POC methods were not necessarily worse than those of lab methods.
  4) Very few labs are using the methods that showed the highest CVs
- Pass Rates
  1) Pass rates for the IE HPLC methods were all >95%
  2) Some immunoassay methods also showed pass rates >95%
  3) The POC methods showed high pass rates, the A1cNow could not be evaluated due to known EDTA interference from the CAP samples.
  4) Pass rates:

Specimen	NGSP Target (% HbA1c)	Acceptable Range (±7%)	Pass Rate % (Low/High)	Cumulative Pass Rate %
GH2-01	8.5	7.9-9.1	85.7/100	95.2
GH2-02	5.4	5.0-5.8	78.6/100	92.8
GH2-03	6.4	5.9-6.9	64.3/100	95.2

- Decrease in all-method CVs over time
  1) All-method CVs were ~5% in 2000
  2) On the 2011A survey the all-method CVs were ≤3.5%

Discussion:

Increase in Labs/Methods

D. Sacks noted that the increase in laboratories and methods has been dramatic, if the trend continues we will eventually exceed our capacity, what should we do? Also, what is the limiting factor, sample availability or the number of samples that can be analyzed? RL responded that if it keeps going up it will need to be discussed at the next meeting; we should not monitor L1 labs less frequently than we already do (quarterly). The limiting factor is the number of samples, cutting the range has helped. We are fine for now, and the number may level off. D. Simmons noted that huge population centers are just now coming online in clinical trials, waiting until you get to capacity may result in a gap. MH noted that the diagnostic claims may result in increased demand for NGSP samples as well. RL said we are currently certifying the large labs like ICON which have one primary lab in each region (China, Europe, etc.). D. Sacks said that if the limiting factor is the number of samples one possibility is to obtain samples from a commercial company as is done with the CAP samples. RL responded that we prefer to obtain samples in-house if possible since we know they are fresh. We will monitor the situation, if there continues to be an increase in labs/methods we may have to look at a different way of obtaining specimens.

CAP performance

SR asked what the tightened CVs can be attributed to. RL responded that the tightening of the certification and CAP criteria have encouraged manufacturers to improve performance, also new technologies tend to perform better and the older methods are being phased out. MH added that labs have tended to change to methods with better CVs. G. Miller noted that manufacturers should be congratulated for the improvements in methods, D. Sacks agreed. D. Armbruster added that having an accuracy-based survey has been important, CAP has few of these. JA said that among end-users more understanding of pre-analytical factors, e.g. sample handling, may have played a role in improving results. RL noted that overall stability for HbA1c assay methods has improved.

4) Proposal to Tighten NGSP Manufacturer Certification Criteria—Randie Little

- Current manufacturer certification criteria: 95%CI of the differences (between method and NGSP) must be within ±0.75% HbA1c.
- Current CAP criteria
  - Each result must be within ±7% of NGSP assigned target value
  - At 7% HbA1c, limit is 0.49% HbA1c

- Propose changing the NGSP certification to 95%CI of the differences (between method and NGSP) must be within ±7% of the NGSP HbA1c (to match CAP)

5) New rules for re-certification of POC instruments after failing certification

- In the past most methods that fail certification were lab methods where they would make changes, such as a new calibration value assignment, that would be passed down to end-users in the field.
- With a POC method that is already out in the field, the manufacturer can just pick a different lot of reagents for the next attempt at certification, but this would not have an effect on how the method is used in the field.
- This was discussed with the committee, and it was agreed that when a POC method is re-certified after failing they need to certify at least three lots of reagents.

6) New candidate SRL

- A laboratory in Japan run by Dr. Umemoto, ReCCS, is interested in becoming a NGSP SRL.
- The laboratory uses the KO-500 reference method.
- They have been a Level 1 laboratory for some time and have consistently shown excellent performance.
- There are quite a few certified laboratories and some manufacturers in Asia that they could potentially certify.
- They have agreed to cover the shipping costs for the monitoring samples.
- They are currently in the process of completing network certification.

Discussion:

Changing the NGSP Criteria

CP said that the question at hand is how to set criteria for 40 samples run in duplicate (NGSP certification) such that we can detect the same differences as CAP (single sample run one time). CP asked if the 40 certification specimens have a specified range, RL responded that they span the range from 4 to 10% HbA1c. D. Sacks said that CAP monitors the performance of individual laboratories while the NGSP criteria are used to monitor the relationship between the NGSP and manufacturers. The issue is that the CAP criteria are now tighter than the NGSP (manufacturer) criteria. CP said that this may not necessarily be correct, the CAP criteria are clearly tighter than NGSP at certain concentrations of HbA1c but that does not necessarily make it tougher to pass CAP vs. NGSP, depending upon the underlying assumptions. D. Sacks noted that CAP sends out samples at different HbA1c concentrations per survey. RL added that the 3 levels are pools while the 40 NGSP certification samples are individual specimens, typically we see less variability among methods with pools. CW noted that CAP sample values are assigned by all of the NGSP SRLs while the NGSP certification samples are assigned values by a single SRL. CP said that in either scenario bias will modify the probability of passing at a given imprecision. Looking at CAP, assume that a given lab has a bias/imprecision combination such that it has a 95% probability of passing the CAP criteria of ±7%. Next consider a lab that will test 40 times with the same 95% probability of passing at ±7%. The question is: how many out of 40 specimen results would you expect to be within ±7% in order to have the same chance of failing as for a single specimen? You would need to decide on one probability in order to "match" CAP and NGSP, it could be 95%, or 90%, or 99%. For example, if 95% probability is used, a lab that actually has a 90% probability of passing CAP will find it much harder to pass NGSP vs. CAP. Going the other way, if the lab has a 99% probability of passing CAP they will have a much greater chance of passing NGSP vs. CAP. One issue with the 40 NGSP specimens is that they are run in duplicate, this complicates matters because you cannot treat the 80 results as independent observations. The duplicate data may be useful for looking at other things like outliers, etc., but for the purposes of defining criteria that will match CAP it is problematic. For the moment we will assume random selection of one of each duplicate for each specimen (n=40). Based on initial calculations, if you require a lab to have at least 36 of 40 results within ±7%, there is about a 5% chance of them failing to do so if they truly have a 95% probability of passing CAP, which is about the same failure rate as for n=1. If they have >95% probability of passing CAP they would have an even greater chance of passing NGSP vs. CAP, conversely if their probability is <95% they would have less chance of passing NGSP vs. CAP. You could define error limits for the specimens that fall outside the ±7% as

well. D. Simmons noted that this scheme is similar to ISO requirements where a given proportion of results are required to fall within a certain range. RL said that when this first came up she looked at all of the methods over the previous years and calculated the percentage of certification results that fell within the CAP criteria for each method, we may need to do this again. CP said if there is more inherent imprecision in the NGSP specimens vs. CAP this would make it less likely to pass NGSP. Also, the range of concentrations may be an issue; if the NGSP includes concentrations that are well outside of where decisions are made, which is what CAP tends to focus on, this could have an impact. In all of these cases it would tend to be harder to pass NGSP vs. CAP. RL said that this may be what we want eventually but probably not yet. D. Sacks asked RL how many methods fail each year on average, at least among the standard, widely used methods. RL said most pass every year. D. Sacks then asked whether there would be an increased failure rate of these methods if we tightened the manufacturer criteria. RL said we could look. CP said that he does not know how the criteria he suggested earlier would compare to the current NGSP criteria. It is easier to talk about it being in alignment with the CAP criteria. DA said that when CAP announced it would go to ±7% instead of ±6% as originally planned the rationale was that too many labs would fail at ±6%; this begs the question of whether we should match the CAP criteria or be better than CAP when certifying methods. D. Sacks asked if manufacturers feel that changing the criteria would be prohibitive. MH asked if the proposed criteria would require a CV of 2% or less with no bias, CP responded that a method that met these criteria would easily pass the ±7% criterion at a probability level of >99%. DA said that the NGSP and CAP have been good about providing manufacturers with data on how their methods would perform if future tighter criteria were applied, could this be done again? RL said we probably do not want to wait a full year to change the criteria but we can let manufacturers know if their previous certification data would meet the new criteria, we need to do this anyway so that we know if the new criteria are reasonable. CP noted that manufacturers with at least a 95% chance of passing CAP should have at least that much chance of passing the new NGSP criteria. JA asked what the uncertainty of the NGSP certification samples and whether it changes with the range of HbA1c values. SR asked whether the accuracy criteria are being tightened for the sake of it or is it based on clinical needs? RL said that is why we are looking at the CAP criteria, most people feel that the current CAP criteria is relevant, at least in the critical range. We could see if loosening the criteria at the high end makes a difference in terms of whether methods pass or fail. D. Sacks asked if manufacturers focus on the clinically relevant range or the entire range, the response was that they tend to focus more on the clinically relevant range. GJ said that in analytical terms, if you allow drift and imprecision at the extremities you will impact the middle of the range as well. The response from manufacturers was that this is not necessarily true, calibration in the middle of the range can minimize middle-range deviation even if there is more deviation at the extremes. D. Simmons said that manufacturers do care about deviations at the high end but less so than in the clinical range. KR supported the idea of percent criteria, noting that the current criteria of ±0.75% HbA1c allow a deviation of 18% at a HbA1c level of 4. D. Simmons said that if we use a criteria as described by CP we could re-evaluate the entire certification process including sample size, the percentage that need to fall within the criteria, etc., and start de-novo to come up with a process that will achieve the goal of equivalency between CAP and NGP criteria. RL said the new criteria will be decided upon by the committee, then we can share past data with manufacturers as to how their data look with the new criteria.

Critical Decision Limits and Cutpoints

D. Simmons said the other question is whether CAP should be the only way of looking at manufacturers in a world where there are more POC methods in use. CP has laid out the issue we struggle with when it comes to monitoring glucose. With billions of results generated each year, 99% of results being within ±10% is an entirely different issue than 95% of results being within ±20%. The statistical problems become more and more challenging, we have come up with different ways of looking at manufacturer requirements for glucose methodologies done in the field vs. devices that will be monitored and calibrated in a lab. The CAP survey really doesn't serve the POC world in the same way as for the laboratory world. RL said that the patient decisions made based on POC results are basically the same as for results from a laboratory method, therefore the requirements should be the same. D. Simmons said that in the glucose world the decisions made for patient POC are critical. We do not need to have the tightest error bars, we just need to make assays accurate enough to meet the needs of the decision-maker and the determination of the needs should be science-driven. RL said that

is why we look at 0.5% HbA1c, because guidelines say this is significant. D. Simmons said that at a HbA1c of 5% the current CAP criteria correspond to ±0.35% HbA1c, at this level one could argue that the criteria should be wider since this is not a critical decision level. RL said the criteria could possibly be different for different HbA1c levels. D. Simmons said that we need to ask the experts who use the test what they are expecting from test results. They should know the basis on which they are making the decision, many of them think in terms of 0.5% HbA1c units, not a percentage of the value. At some point we may have to put some teeth behind this to protect the regulatory authorities, manufacturers, etc. so that we can serve the public in a broader sense than everyone having to have testing done by the tightest HPLC methodology available. RL said this is why we are trying to figure out what our criteria should be based on, maybe we should look at making acceptance limits wider at the ends (at 5 and 10% HbA1c). HbA1c levels of 7-8% are critical, and 6% is as well because of the diagnosis recommendation. D. Sacks added that 5.7% is going to become an important cutpoint and even lower levels may be as well when we talk about pre-diabetes. We need to look forward, at 4% HbA1c it is not critical, but 5.5-8% needs to be tight, 9 or 10% is not as critical. JA asked whether a patient is treated differently at 5.7% vs. 7%. D. Sacks said they do. D. Simmons said the great majority of decisions are made at a few cutpoints. Pre-ADA diagnosis, 7 and 8% were the critical cutpoints. JA asked if 5.7% vs. 6.5% results in different treatment. D. Sacks said yes, 5.7% means the patient will be asked to come back in 6 months or a year, 6.5% means a diagnosis of diabetes and resulting therapy. DA said that the recommendation for diagnosis is if one result indicates diabetes it should be repeated to confirm the diagnosis. D. Sacks said being labeled as having diabetes has huge implications in terms of causing stress to the patient, insurance, etc. A label of pre-diabetes does not have the same impact. D. Simmons said that context plays into this, if a patient comes into the ER with a blood sugar of 240 the doctor needs to know if you have diabetes or are pre-diabetic with an elevated sugar due to stress. If the result is 6.5% the follow-up will be different than for a result of 5.7%. D. Sacks said the simple answer to what the critical clinical range is would be ~5.2-8%. Higher levels are not as critical. There aren't too many CAP samples that have been below 5.2%, we do need to try to get a bit higher for the high sample. CP said we could define the criteria such that the ±7% applies to HbA1c levels of 5.2-7, then wider limits would be applied to higher levels.

Re-certification of POC

D. Sacks asked when a POC method is certified, is the lot already being used out in the field? RL said it is supposed to be but we have no way of knowing, the certification protocol says the method should be used as it is by an end-user when performing the certification. D. Sacks said that if a lot fails should the lot continue to be used in patient care or should the manufacturer have to pull the lot? D. Simmons said this is a regulatory not an NGSP question. D. Sacks responded that the NGSP has said the device is certified which gives the end-user a certain degree of confidence, if a given lot then fails certification this is a problem because there is still the implication that the device is NGSP-certified. RL said that we do not have a say over what the manufacturer releases, there are still a few methods being used that are not certified. JA said that if a manufacturer's method is not performing well out in the field, the manufacturer would get reports from customers and would then check and see if the lot meets specs. If not they would pull that lot. D. Sacks said this does not happen with POC methods because they are waived. JA said this is not necessarily true, if a manufacturer gets reports from customers they would be treated the same way whether they came from a laboratory or POC site or whatever. RL asked how the end-user would know there was a problem if the results are not being compared to anything else. JA responded that the physician's office would get suspicious if results looked unusual compared to previous results, they would look at the total picture with that patient. They would probably have the result confirmed by a central laboratory. RL said this might be true of a large practice but not necessarily in a small practice. GJ said that if a lot fails the accreditation process there should be a mechanism in place where the manufacturer must withdraw the lot from use. RL said we do not have the authority to tell manufacturers to do this. CW said that ideally if one lot does not pass certification all lots should be tested, but this cannot be done. JA said he does not believe that the system is broken. If there is a customer complaint it would start a complete evaluation process by the manufacturer. D. Sacks asked if a manufacturer would withhold a lot if it failed manufacturer certification, or would this depend upon the manufacturer. D. Simmons responded that releasing of a lot does not depend upon NGSP certification but rather internal quality assurance. Those internal QA characteristics are driven by what you are promising in the field, NGSP

does not get to tell you whether you get to sell, the FDA or other regulatory agencies do this. There is a statistical issue with passing NGSP certification, it is not an absolute certainty issue, there is a statistical possibility of a lot not passing with 40 samples even though it might pass if a larger number, like 5000, samples were used. RL said the issue of lot-to-lot variation generally does not come up for methods that have low imprecision and bias, they will almost always pass certification, but for methods with more scatter a slight shift can cause them to fail. DF asked what is done for non POC methods that fail certification. RL said we have to look at what the problems are, usually there is a long time lag, or the application is never re-sent or the method is not certified for another year, etc. unless they simply messed up the certification process which happened once. We make sure they do not just come back and try another lot or tweak it in-house, they must make changes that will translate to the field. CW asked if there is a limit to how often a manufacturer can attempt to re-certify. RL said they do not just keep trying over and over again, there is some expectation that they have an explanation and plan, sometimes they do not attempt again for a long time. GJ asked if there are many POC devices in use that are not NGSP-certified, RL responded that there are a few, the most-used POC methods are certified unless they failed recently and have therefore come off the list.

Certification issues

EL noted that there are often problems with certification samples when the manufacturer supplies certification samples instead of the SRL. Samples can show evidence of deterioration due to improper storage conditions and the range of HbA1c values can also be incorrect, this leads to additional analyses and work. Also, if we run samples by the immunoassay SRL method we may not be able to tell if there is a problem with aging, who is responsible for the values assigned in these cases? We try to encourage manufacturers to use samples supplied by the SRLs. RL agreed that this can cause problems. An additional issue is that sometimes samples with variant hemoglobins are inadvertently included. However, a few manufacturers with many methods require large volumes of blood and it would be difficult for the SRL to provide this. Because of this we probably should not require manufacturers to use specimens supplied by the SRL but we can encourage it. If additional analyses are required in terms of replacement samples or checking for degradation using the ion-exchange method you can charge the manufacturer for the additional analyses. In terms of degradation affecting results, if a manufacturer supplies samples that are not good it is likely to cause them to fail, so it is in their interest to provide good specimens if they choose not to use samples provided by the SRL.

Candidate SRL in Japan

DF asked what the criteria is for certifying a network laboratory. RL responded that it is the same criteria the NGSP has had all along for network labs. It involves 100 samples for the bias comparison which follows CLSI EP-9. There is also EP-5 precision and outlier criteria. GJ mentioned that the situation is fluid in Japan right now, they have discussed reporting HbA1c results as NGSP and JDS which are both percents and are only 0.4 units different. RL said that regardless of what numbers are reported in Japan, having a SRL there could be another way of insuring stability of their HbA1c results.

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 2011.
  - R. Little presented an update on NGSP progress.
  - I informed them that the CAP decided to tighten the criteria to ±7% for 2011 and 2012, this might be tightened in the future.
  - HbA1c reporting outside the U.S.:
    - The Czech Republic appears to be reporting IFCC numbers in %.
    - Many countries in Europe have switched to IFCC numbers in mmol/mol or are planning to do so, some are reporting dual units before switching.
    - There is some uncertainty about Japan, also the situations in India and China are not clear.
  - HbA1c for diagnosis

- The WHO endorsed HbA1c for diagnosis with the 6.5% cutoff (same as ADA) in January.
- The UK is talking about recommending HbA1c for diagnosis.
- Not all of the clinical organizations within the U.S. have the same diagnostic criteria.
  1) Veteran's Administration guidelines call for ≥7.0% HbA1c on two occasions or ≥6.5% plus fasting glucose indicating diabetes.
  2) AACE calls for diabetic glucose along with HbA1c.

- David Aron gave a presentation on VA guidelines
  - Some individuals with the VA want to report HbA1c as a range to clinicians and have drafted a white paper on the topic.
  - One issue that has not been addressed is how they will calculate the bias and variability within each lab.
- Ian deBoer gave a presentation on the use of HbA1c in patients with renal failure
  - Discussed how ESRD affects the relationship between HbA1c and glucose, particularly patients treated with erythropoietin.
  - There are inadequate careful studies to really evaluate whether HbA1c can be used on patients in dialysis as opposed to the use of other glycemic indicators such as fructosamine or glycated albumin.

Discussion:

HbA1c for diagnosis

GJ said that the WHO recommendation has sparked much debate by just endorsing the one cutoff for diabetes and nothing else relating to "pre-diabetes". D. Sacks asked if other countries will recommend use of HbA1c for diagnosis. PJ said there has been discussion in France but no decision has been made. CW said it has been discussed in the Netherlands; many physicians are already effectively using it for diagnosis. In Germany they have established a "grey zone" where 6.5% HbA1c is indicative of diabetes and 5.7-6.5% diagnosis should be supported by other parameters, it is generally clinically accepted. CW said Japan is moving toward HbA1c combined with fasting glucose to diagnose diabetes, GJ added that they are collecting a huge dataset on the people being diagnosed with HbA1c and glucose. D. Simmons said that in China they have data from a large study showing that the western cutpoints may not be appropriate for their population and there is much concern regarding this. CW asked if we know how well the HbA1c assay is traceable, D. Simmons said he did not know. GJ said that in India they are seeing evidence to suggest that the cutpoints would need to be slightly different in their population. RL asked if this means the discrepancies are the result of HbA1c or glucose, GJ agreed saying that it is a kind of catch-22. D. Simmons added that looking at HbA1c vs. fasting glucose vs. post-prandial glucose for diagnosis, there is large overlap between the three but there is a significant amount of discrepancy between them. This does not mean one test is "better" than another; in any case we layer technologies. A lot of physicians are looking to move to a continuum of risk kind of hypothesis, across blood pressure, lipids, etc. D. Simmons said that the VA rationale for diagnosis is based on the decisions that are being made. Their formulary is very restrictive, their criteria are reasonable and rationale even though their formulary may not be.

Reporting of results and calculation of uncertainties

D. Sacks and RL said that the VA has not indicated how the bias and imprecision for each lab will be calculated in order to report results as a range. They are doing a pilot study but we still do not know where the numbers will come from. CW said that laboratories are struggling with calculating uncertainties for their assays, GJ said that in the UK labs are required to state uncertainties in their SOPs but these numbers are not actually given out on lab reports. CW and D. Sacks said that it has been shown that clinicians do not want the uncertainties on the lab reports, and noted that labs participating in the IFCC EQA program could easily calculate uncertainty from the EQA results. RL said her concern is that every lab may calculate the uncertainty differently. DA said that there is not only analytical uncertainty but also pre and post-analytical uncertainty. D. Simmons asked if there should be some obligation on the part of the physician to understand that there is inherent variability in the test result they are using to make a critical decision. CW responded that most physicians are aware that there can be some uncertainty with laboratory results, it is only one part of making the

decision, in their mind there is a possibility that a result might not be correct. GJ said the senior staff generally understand this, it is often the junior staff that do not always understand. D. Simmons said we see this in clinical practice where house staff use the delta in management of ketoacidosis. The anion gap is a surrogate marker for ketones. They don't take into account that all of the values used to calculate this have inherent error, so the end delta has more error than value. This gets tracked along so they have a delta of a delta which adds more error. D. Sacks said a result is taken in context with the entire clinical picture; it is not the sole arbiter in decision-making.

Renal disease

GJ said the majority of people with ESRD are on EPO in the UK. D. Sacks said this is true in the U.S. as well. RL said that we need to look more closely at clinical situations where the use of HbA1c may not be appropriate. D. Sacks said this is very true of kidney disease since diabetes is the main cause of people being on dialysis.

8) Manufacturer Claims for Diagnosis—David Sacks, Randie Little

- Carol Benson from the FDA is here; she will not speak on this topic today but will tomorrow at the manufacturer forum.
- This topic will also be discussed at a symposium on July 27.
- Initially the FDA sent out a letter to the manufacturers inviting applications for a diagnostic claim.

Discussion:

RL said that it is not clear how critical this is as far as actually using the test for diagnosis, will it increase the use of it for diagnosis or affect reimbursement if manufacturers are able to make a diagnostic claim? It is something that should happen since it is being used for diagnosis. CB agreed, the FDA is trying to accelerate the process too. The FDA sent out the letter last year, we've been dealing with manufacturers on an individual basis thru the pre-ide process because for us to do a guidance is a very long process that needs to be vented in public. RL asked what manufacturers need to do in order to be cleared for diagnosis, and can it be applied to everyone using the same criteria up front? CB replied that the FDA does not have any firm criteria right now, we want to be sure to get it right. When we get more people presenting us with data, we have the option of presenting it in public panel meetings. Once it is decided that we have particular criteria that are acceptable the expectation is that this will be the criteria used for everyone seeking a claim. RL asked what is meant by "public", CB responded that in panel meetings there are government employees and experts in the field, the issues are presented and manufacturers discuss their issues. We present data, there is much discussion, and it must be open to the public. All manufacturers would be invited as well as representatives of the major clinical organizations. RL asked if this is something that will have to happen, if so what can we do to accelerate the process? CB responded that we are not certain it will have to happen; we also need manufacturers to present their data to us. DA noted that physicians currently use the test for diagnosis, manufacturers just can't promote this use. D. Sacks added that it is basically the same situation as off-label use of medicines. CB said that the FDA does not regulate the practice of medicine; we regulate the manufacturers that distribute the devices and make claims regarding them. D. Simmons said that there is a further issue for manufacturers; they could be accused of marketing off-label if physicians widely adopt the use of the devices for diagnosis even in the absence of a diagnostic claim on the label. GJ said in the UK they have gone around about this issue of using HbA1c for diagnosis before it has been officially accepted for that use, where do you stand legally if challenged? This could be an issue in the UK. D. Sacks said that in the US it is different since the ADA has officially endorsed HbA1c for diagnosis, it is now considered a standard of practice which gives it legal standing. GJ said that there are differences in the criteria recommended in the US (e.g. VA vs. ADA criteria). D. Sacks and RL said they all agree you can use it; there are just slight differences in the criteria. RL asked if all of the manufacturers want to make the diagnostic claim. CB was asked how many manufacturers had contacted her office; she said she could not discuss this. RL said that some may be waiting for someone else to get the claim first so that the process is easier the next time around while others may be trying to be the first. D. Simmons said this is driven by the expense, whether it has an impact on your marketing, perceived probability of success, what you think the criteria might be, etc. CB said that the FDA cannot say in a public meeting what the criteria are, we have to fair to all people, when

we put out something that is considered guidance we must invite public comment. To put out a guidance requires much effort and time, there are a number of channels it has to go through. We had discussed having a workshop, we do not have the funds for this but a sponsored workshop might be a possibility. Also, guidance is guidance, not the law, it simply tells how you can meet statutory requirements but does not say you have to follow the exact steps as there could be other approaches. RL asked how we could facilitate a workshop, CB said there could be a meeting but it would have to be open to all interested parties and it would require more than a few hours. The FDA encourages manufacturers to come and talk to us. RL said it seems like everyone is waiting for someone else to clarify things. SR agreed and said that there needs to be a concerted effort to get stakeholders together to move things forward. CB said that manufacturers need to be proactive in this process. D. Sacks said that representatives from all of the manufacturers will be at the forum and we can discuss this with them.

D. Sacks thanked everyone for their attendance; the meeting was adjourned at 5:10 PM.

Minutes prepared by CR 8/11/2011, reviewed by RRL 8/19/11.