Meeting of the NGSP Steering Committee
Minutes
Sunday July 28, 2024 2:00 PM – 4:30 PM
Hyatt Regency McCormick Place, Chicago, IL

Participants:

*David Sacks —NIH, Chair, NGSP Steering Committee
*Carla Siebelder—IFCC HbA1c Network Coordinator
*Randie Little—Univ. of MO, NGSP Network Coordinator
*Garry John—IFCC Scientific Division
*Erna Lenters—ERL, IFCC, NGSP
*Michael Steffes—Univ. of Minnesota
*Monica Swenson—Abbott Diagnostics
*Hubert Vesper—CDC
*Mathew Wagner—Sebia
Shawn Connolly—Univ. of MO, NGSP
Emma English—Chair, IFCC C-EUBD
Kuanysh Kabytaev—Univ. of MO
Curt Rohlfing—Univ. of MO, NGSP
Salvatore Secchi—NIDDK/NIH

Virtual:

*John Higgins—Massachusetts Gen. Hosp.

Steering Committee members not present:

*Robert Cohen—Univ. of Cincinnati
*Philippe Gillery—IFCC Scientific Division
*David Nathan—Massachusetts General Hospital
*Elizabeth Selvin—Johns Hopkins University

***Member of the NGSP Steering Committee**

1) **Welcome and Introduction—David Sacks, Chair, NGSP Steering Committee**
D. Sacks welcomed those in attendance and introduced E. Lenters as the newest member of the Steering Committee. Those present introduced themselves and the 2023 minutes were approved.

2) **NGSP Progress Report—Randie Little , NGSP Network Coordinator**
- NGSP Network Monitoring
  - The PRLs and SRLs continue to demonstrate excellent comparability (June between-lab CVs were 1.56% and 1.10% for the PRLs and SRLs, respectively).
  - Currently there are two PRLs the CPRL and the EPRL in Europe.
  - The SRLs include all major method types.
  - Monthly between-lab CVs for the NGSP network were all <1.5% over the past year.
  - The SRLs are also monitored 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.
- Long Term Quality Controls (LTQC)
  - Provides another estimate of long-term consistency of NGSP results
  - Three levels of frozen whole blood aliquots
  - Analyzed monthly by the Missouri SRLs and quarterly by all SRLs
  - The original LTQC samples were analyzed from 2010 to 2019
  - New LTQC samples were prepared and have been analyzed from 2018 to the present
  - In all cases the mean CVs for the LTQC samples were all ≤1.5%
- NGSP Certification
  - The number of certified methods continues to increase, while the number of laboratories has leveled off.
  - There are ~330 methods and ~140 laboratories currently certified.
  - Approximately 30% of certified methods are from China, these are generally certified by the SRL in China.
  - Most certified labs are Level I and are outside of the U.S.
- Variability of Level 1 Labs May 2024
  - Level 1 labs are monitored quarterly, so each month approximately 1/3 of the total number of L1 labs participate in monitoring.
  - In May, the between-lab CV for the L1 labs was 1.47% (n=26)

- Status of HbA1c Measurement (CAP data)
  - Current CAP limits (2013-2024): Each result must be within ±6% of NGSP assigned target value (mean of 8 SRLs, multiple results from each).
  - There has been much improvement in within and between-lab variability since 1993 as the CAP and NGSP certification criteria have been tightened over the years.
  - Variability among methods improved dramatically from 1993 to 2014 but the improvement has been more subtle in recent years.
  - Summary reports containing the details of the performance of individual methods and overall performance among methods on the CAP survey are available on the NGSP web site.
  - CAP 2024A survey
    - Pass Rates (±6%)

Specimen	NGSP Target (% HbA1c)	Acceptable Range (±6%)	Pass rate % (Low/High)	Cumulative Pass Rate % ±6%
GH-01	5.32	5.0 – 5.7	87.3/100	96.9
GH-02	7.24	6.8 – 7.7	89.1/100	97.0
GH-03	8.92	8.3 – 9.5	88.9/100	97.2
GH-04	6.47	6.0 – 6.9	90.5/100	98.0
GH-05	9.95	9.3 – 10.6	86.2/100	97.5

    - Cumulative pass rates were all >96%.
    - For individual methods, pass rates ranged from 86.2% to 100%.
    - All-method CVs have dropped over time since 2000.
    - All-method CVs for the 2024A survey were all ≤3%. This has been the case for the last several surveys.
    - CAP data Summary (2024A)
      1) Method-specific, between-laboratory CVs ranged from 0.6% to 4.3%.
      2) Overall, only 80% of laboratories are using methods with CVs < 3% at all five HbA1c levels.
      3) All-method CVs for the most recent survey ranged from 2.6-3.0%.
      4) Overall Pass rates are between 96.9 and 98.0% for the current 6% limits
- Raw data from Manufacturers
  - We began requesting raw data from manufacturers submitting certification data for POC methods after our 2021 meeting.
  - This data is still being requested.
  - All raw data have matched data sent for certification.
  - Should we continue to ask for raw data?
- A new paper on issues and considerations for using POC in clinical practice has just been published (Sacks, Kirkman and Little, Diabetes Care 2024;47(7): 1104-1110.).
- Conclusions
  - The NGSP network is still doing well with very low CVs.
  - CAP survey results show that the all method CVs (including all laboratory & methods' results) have been <3% for the last 4 surveys. We hope to see this continue.
  - Measurement of HbA1c continues to improve but there are still a few methods with between lab CVs >3%.

Discussion:

NGSP Network

E. Lenters noted that a commercial laboratory she visited in Korea was analyzing thousands of samples on an immunoassay method, but analyze CAP samples on an ion-exchange method and submit those results to CAP. The results are submitted under the correct ion-exchange method, but their routine patient samples are analyzed on the immunoassay. This shows that results obtained on the survey may not always reflect what is actually happening in the laboratory. D. Sacks noted that this is not allowed in the U.S., it is against the law, CAP samples are required to be treated the same as patient samples. E. Lenters was very concerned about POC methods that do not perform well but are obtaining NGSP and IFCC certificates (data presented later in the meeting). C. Siebelder noted that she also requests raw data from the POC methods and it always matches,

the same as for NGSP. R. Little said they probably deliberately select good reagent lots for their certifications. E. Lenters suggested that some of the manufacturers have a well-performing laboratory method in their facility that they can compare to. R. Little said that when the raw data matches the submitted results it is difficult to know what to do about this problem. They are not falsifying data but they clearly have ways of optimizing their methods to produce results that are better than what end-users obtain. R. Little noted that there are only two POC methods that appear on the CAP surveys and they generally show good performance, although one of them has had some recent issues with certain lots. E. Lenters said that many of the POC methods she evaluates are from Asia, especially China. D. Sacks asked if end-users of POC methods in Europe are required to test new lots against old lots prior to using them for patient samples, and reject lots that do not perform well. E. Lenters said in her lab every lot is tested, but everyone does things their own way, there are no protocols. G. John said new lots are required to be checked in laboratories, but they set their own criteria. R. Little noted that most POC testing is not done in laboratory settings, where they just follow manufacturer instructions. E. Lenters said in their institution there are POC HbA1c instruments in clinics, but the lab checks them and makes sure internal and external QC is performed. They have a POC coordinator to watch over this process. R. Little said their institution also has a POC coordinator and the lab monitors their POC methods, although they do not participate in the CAP surveys. However, this type of monitoring does not occur in most POC settings. Proficiency testing is the best way to monitor method performance but most POC users do not participate.

3) CAP Proficiency Testing Update—David Sacks

- Proficiency Testing (PT)
  - In USA all labs that measure patient samples are required by law to perform PT
  - Regulated by CMS (Centers for Medicare & Medicaid Services) through CLIA
  - CAP (College of American Pathologists) is largest provider of PT material in the world
- CAP Grading
  - Initially, CAP used peer group grading for PT for HbA1c
  - 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% of laboratories passed
- PT Criteria Tightened
  - In 2008 acceptability reduced to 12%
  - 2009 - 10%
  - 2010 - 8%
  - 2011 - 7%
  - 2014 - 6%
- Proposed CAP PT Criterion 2020: ±5%
- CLIA Proposed PT Rule 2019 (CLIA 88 update)
  - Hemoglobin HbA1c would become a regulated analyte
  - Criterion for acceptable performance: Target ±10%
- Implications of New CLIA Proposal
  - HbA1c would become, for the first time, a regulated analyte
  - 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 elected NOT to reduce criteria from ±6% to ±5% in 2020
- Response to CMS 2019 Proposal
  - Multiple organizations (clinical and lab) and individuals sent comments to CMS
  - Almost all the 107 comments received by CMS protested loosening HbA1c criteria
  - Delegation from ADA went to speak to CMS
  - An editorial was published in 2019 in a clinical diabetes journal criticizing the proposal (Klonoff et. al, J Diabetes Sci Technol 2019 May;13(3):424-427).
- Pass Rates for CAP 2020 GH5-C: ±6% vs. ±5%

Sample ID	Target (%)	±6%	±5%
GH-11	5.5	97.9	95.2
GH-12	8.3	97.7	95.4
GH-13	5.1	97.6	97.6
GH-14	10.1	96.9	95.1
GH-15	6.0	97.6	96.6

- CMS Response
  - Not persuaded by comments
  - Acknowledge improvement in accuracy
  - Concerned that "…tighter criteria will limit access to testing…"
- Final CLIA Rule
  - Acceptance limits for HbA1c are 8%
  - Effective January 1, 2025
- CAP Conundrum
  - CAP has 2 separate programs
    - PT
    - Accreditation
  - Grading of regulated analytes by PT providers must follow rules in Federal Register
  - Accrediting agency can require better accuracy for lab to remain accredited, but PT provider must grade HbA1c at 8%
  - Formal grading will have to change to 8%
- CAP Plans for HbA1c—2 sets of criteria
  - Labs not using accuracy-based PT OR not accredited by CAP have to be graded by +/- 8%
  - Labs using accuracy-based PT and accredited by CAP graded by +/- 6%
  - Evaluation reports sent to the participating labs will show if lab passed at both 6% and 8%
  - The CAP inspection checklist will add a new item for HbA1c where the lab will be required to show evidence of passing ±6% or show documentation of corrective action if they fail
- Summary
  - Acceptable performance for HbA1c PT in USA will change to 8%
  - Change effective January 1st, 2025
  - Labs accredited by CAP that use accuracy-based PT will have to meet 6% criterion

Discussion:

D. Sacks noted that not all U.S. labs use the CAP survey for PT, there are other options. Also not all labs are accredited by CAP, there are labs that are accredited by other organizations such as the Joint Commission on Hospital Accreditation. R. Little asked if CAP could eventually change the 6% to 5%, and if CAP still has a non-whole blood survey. D. Sacks said CAP could eventually change the accreditation criterion to 5% although it will likely remain at 6% for some time. CAP still provides a non-whole blood survey to some labs outside of the U.S. as some of these labs are unable to receive the specimens in a timely manner. These labs can choose either whole blood or processed materials. The processed materials survey is called GH5-I (for international). C. Siebelder asked if there are assigned target values for this survey, D. Sacks said no, it uses peer group grading because the materials are not whole blood. It is a completely separate survey from GH-5. E. English asked if there are CAP-accredited labs that use PT surveys other than CAP that are not accuracy-based, D. Sacks said yes although he wasn't sure how many. Those labs will have to be graded at ±8%. The CAP survey is the only whole blood survey in the U.S. It was generally agreed that the scheme CAP has developed is likely the best way to address the issue. S. Connolly asked what percentage of U.S. labs are not accredited by CAP, D. Sacks did not know but probably very few. JCHAO is a large organization that accredits hospitals in the U.S., and they also accredit some hospital labs although they do not provide a PT survey. S. Connolly asked what CMS requires, D. Sacks said CMS does not care as long as the lab is

accredited by an approved agency. R. Little said she used to follow the other PT surveys but stopped doing so, D. Sacks said there are a few besides CAP. C. Rohlfing noted that API still provides PT for a lot of analytes.

4) 2024 Clinical Advisory Committee Meeting Update—Randie Little

- The 2024 CAC meeting took place at the ADA annual meeting in Orlando, FL in June.
- CAC: To facilitate communication between the NGSP and the clinical community
- There was a large group (~40 people in person, 6 on zoom)
- The meeting was chaired by Dr. Christopher Holiday, Director of Diabetes Translation at the CDC
- Summary
  - R. Little presented a NGSP/CAP update
  - There was a debate regarding the use of Glycemic Management Indicator (GMI--HbA1c estimated from CGM)
    - GMI-Pro: Using GMI can improve diabetes management (Irl Hirch, Univ. of Washington)
    - GMI-Con: Time to rethink the use of GMI in diabetes management (Elizabeth Selvin, Johns Hopkins)

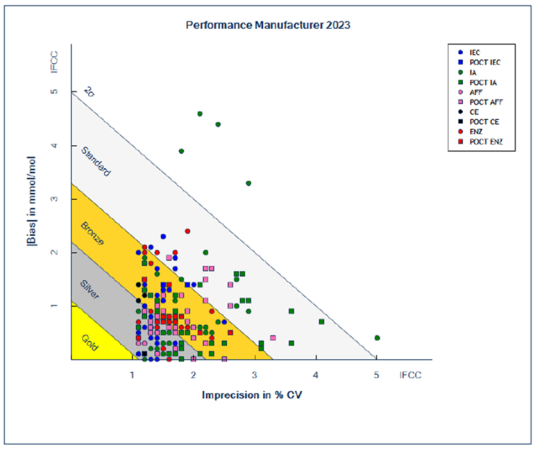
Discussion:

R. Little said there has been some confusion re. GMI, it is not a HbA1c but rather an estimated HbA1c based on CGM glucose readings. However, some people think it is a HbA1c. D. Sacks explained that GMI was previously named estimated A1c but the FDA would not allow the use of that term. R. Little said both speakers spoke about the pros and cons of estimating HbA1c from CGM. I. Hirsch focused more on interferences with HbA1c, including hemoglobin variants, kidney disease, altered red cell lifespan, etc. E. Selvin discussed data showing the variability among CGM devices and sensors. In the end both speakers agreed that CGM is useful, and that CGM and HbA1c are best used together for clinical management. Where there are discrepancies there should be further investigation as to the cause of this. The problem is that there are a lot of physicians that are under the impression that they do not need HbA1c for patients using CGM, they can just use GMI. CGM is not standardized, there is a lot of variability between different CGM sensors and devices. Readings can also vary depending upon where the sensor is placed on the body, and they do not measure blood glucose but rather interstitial fluid glucose. HbA1c is not just a mean of glucose over the previous 3-4 months, it is a weighted mean. Also for CGM they typically are not looking at the previous 3-4 months, but a shorter timeframe. The two do not measure the same thing, so some discordance can be expected. D. Sacks noted that there are lots of examples where analytes that do not measure the same thing are used together, G. John agreed. C. Rohlfing mentioned that E. Selvin mentioned creatinine and Cystatin C as an example of this. E. Lenters mentioned that her group is working on a manuscript that addresses the issue of discordances between GMI and HbA1c, it will provide a "checklist" of steps to follow when investigating these discrepancies. R. Little said that would be helpful, it would also be useful to have a good way to measure red cell lifespan, which we currently do not have. Robert Cohen, who has done research in this area and has been trying to find better ways to measure red cell lifespan, was at the CAC meeting. J. Higgins has been working in this area as well. M. Wagner asked how GMI is calculated. R. Little and D. Sacks said they likely do not all use the same equation to calculate it, the information is proprietary so we do not know how they do it. This is part of what will make standardizing CGM difficult. R. Little and G. John mentioned that there are differences among the CGMs in terms of the frequency of the measurements and the studies used to develop the equations. D. Sacks said no one knows what the time lag is between interstitial fluid and blood glucose, or how much this can vary within or between individuals. R. Little said CGM metrics are very useful in terms of showing the patterns where the highs and lows are, physicians find this useful and they do not care about the details of how the calculations are done. They think the GMI number they get is absolute, since glucose is being measured. E. English thought that in the clinical community there is a lot of resistance to the notion of GMI limitations, since they find the technology useful.

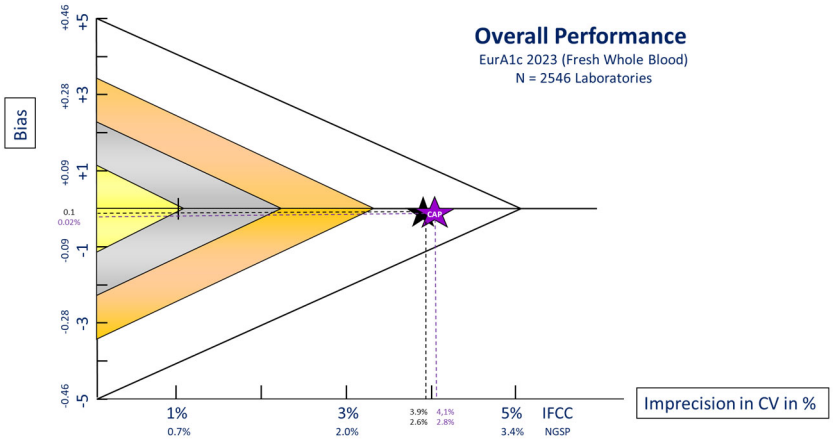
5) Update IFCC Network—Carla Siebelder

- There are currently 16 approved laboratories and 1 candidate laboratory in the IFCC laboratory network. Two laboratories, one each in Italy and Japan, that dropped out over the past year. The laboratories are spread around the globe and include labs in the U.S., Europe, South America and Asia.

- The IFCC/NGSP master equation is still being monitored via sample comparisons between the two networks performed twice a year. The equation remains very stable, after 20 years.
- Performance Manufacturers: IFCC Certification 2023
  - 0 Gold
  - 99 Silver
  - 112 Bronze
  - 31 Standard
  - 5 IFCC criteria not met



- IFCC Quality Targets Modification
  - A new graph design will be implemented in 2025 showing the direction of bias as well as the magnitudes of bias and imprecision
  - Criteria: Due to the impact of bias on risk of misinterpretation it is suggested that the IFCC MQT is revised and more weight given to bias (Weycamp et. al, Clin Chim Acta 548 (2023) 117495). This is being considered by the IFCC C-EUBD
- EurA1c 2023 Preliminary Data
  - A project of the IFCC C-EUBD and EQA/PT organisers
  - Once a year EQA Organisers use the same 2 samples
  - 2023: 22 countries - 26 EQA - 4082 laboratories



6) POC Study Data—Erna Lenters

E. Lenters evaluated a number of POCT methods for HbA1c. Most of the methods tested were documented as having met the IFCC and NGSP criteria. The aim of this study was to verify the manufacturer's performance characteristic claims, with respect to precision, bias and interferences from common Hb-variants. Methods were also compared to IFCC/NGSP reference methods and evaluated based on the current NGSP criteria. Her findings indicated that some methods met manufacturer claims for precision but others did not, and several showed vastly higher imprecision compared to the claims. There were also several methods that met manufacturer precision claims but the manufacturer claims were unacceptably high. Also, many methods that that previously met the NGSP criteria did not meet these criteria in her study. The studies were performed in her laboratory where there is far more experience and expertise with POC HbA1c methods than is typical for most POC settings.

Discussion:

POC HbA1c Methods

E. Lenters expressed much concern over the fact that so many POC methods that have NGSP and IFCC certificates perform poorly. The poor methods tend to be lower in cost, so many end-users will be drawn to them thinking they perform well since they have certificates. R. Little noted that for NGSP certification methods are compared to one SRL, and the manufacturer can choose which SRL/method type to compare to. Usually the method is compared to an SRL that is the same method type, which tends to result in less scatter. This mainly applies to boronate affinity vs. other methods. D. Sacks asked about the number of POC method lots, do we know how many a manufacturer releases in a year? M. Swenson replied at least one a week. E. Lenters said she only evaluated one lot, D. Sacks noted that NGSP also only tests one lot in each year. R. Little mentioned a recent case where there were issues with some lots for one POC instrument and this was reflected in performance on PT. There is a letter to the editor coming out regarding this. E. Lenters acknowledged that a few methods in her studies performed well, but most did not. She wondered if NGSP certificates for POC methods is doing more harm than good. D. Sacks said that the fact they obtain NGSP and/or IFCC certificates showing acceptable performance means that either the manufacturer's method can perform adequately but they choose not to translate that performance to the field, or they are manipulating the system in order to pass. R. Little thought they might be selecting the lots that perform the best for their certifications. E. English noted that for the several methods that performed extremely poorly there would have to be large discrepancies between the lots used for certification and the lots evaluated by E. Lenters. R. Little asked whether the lots used in E. Lenters' study were pre-selected by the manufacturer. E. Lenters did not know for sure but noted that the study sponsor purchased the methods off the market without going thru the manufacturer. She expressed disappointment with WHO as they initially wanted the lab to do independent pre-qualification of POC HbA1c tests and glucose meters, but after she spent a lot of time doing the necessary paperwork they later decided not to. E. English felt that this recent data may change their minds, saying that once these data are ready the discussion needs to be reopened in light of the potential risks. E. Lenters asked whether, if WHO decides not to do these independent evaluations, we (NGSP/IFCC) should do it. R. Little said that if the POC testing is done by the SRLs it will be much more expensive, especially if the NGSP has to buy the instruments and reagents. If the manufacturers provided these they could still pick the lots. G. John asked if we know what lots they provide for certification, R. Little responded that they are required to provide the lots to NGSP when they submit their data. However, NGSP certification is only performed annually. R. Little noted that if a POC method fails and they attempt another certification they are required to submit data from three separate lots. The NGSP could require this for the initial certification as well, but we would need to charge more. D. Sacks did not see this as an issue, they will pay more in order to obtain or maintain their certification because it would cost them much more not to do so. R. Little suggested they could just select three good lots, D. Sacks agreed but noted that it is more difficult to select three as opposed to one. G. John wondered about what else the manufacturer might be doing to pass the certification. Although R. Little noted that the raw data submitted to her is in sequential order and there is nothing to indicate any manipulation, he wondered what might be happening prior to that point. E. Lenters pointed out that there are POC manufacturers with well-performing HPLC methods in their laboratories that they can compare the POC results to. She followed manufacturer instructions when using these methods, and when the manufacturer's

controls were analyzed the results were always in even when patient results were clearly unacceptable. R. Little said that most end-users rarely run controls. There was general agreement that this issue is of great concern, especially because of potential harm to patients, the question is what to do about it. E. Lenters said it would be best to not offer certificates to these methods unless the evaluations are independent. D. Sacks said that if the certification process is eliminated it will not stop them from selling these methods, E. Lenters agreed but noted that the manufacturers would then have to take it upon themselves to show that the performance of their method is adequate. E. English said that with no external body regulating them they would be free to claim and present whatever they want. Maybe the criteria need to be more stringent, e.g. incorporate more SRLs, more lots, etc.? C. Siebelder noted that a big problem is that POC methods generally don't participate in EQA and PT schemes. M. Wagner asked whether that is going to ever change, can POC users be required to participate in PT? D. Sacks said the FDA has approved these tests to be CLIA-waived which is why they are not required to participate in PT. Several years ago he looked into whether it is possible to "un-waived" a waived test, the answer was no, it would require a change in the law. R. Little noted that in their institution the surrounding clinics use POCT and the hospital provides oversight over this testing, but they are still not required to perform PT. D. Sacks said the hospital can simply require this if they want to. It was noted that there is a formal process for a method to receive initial approval and a waived designation from the FDA that includes an independent evaluation, and there are currently only a few approved CLIA-waived POC HbA1c methods in the U.S. E. English noted that the CLIA-waiver only applies to the U.S., the methods that were evaluated can still be sold in countries that do not have these kinds of approval processes. D. Sacks asked R. Little if it would be possible for the NGSP to require POC methods to submit data from multiple lots and to shorten the length of their certification, e.g. three lots every six months. M. Swenson, referring to discussions from last year's meeting, noted the time lag between data submission and certification confirmation can already be burdensome for manufacturers and a shorter certification duration could make this worse. There are consequences to manufacturers if they fail a certification and are not able to investigate, document corrections and re-attempt certification before their current certification expires. E. Lenters said this would also be a lot of work for the SRLs. For example, with Abbott POC it takes them two weeks just to send the certification samples since they have to be fresh. R. Little said this is also the case for the Missouri SRL when they have to send fresh samples for POC certifications. E. English asked how many POC methods require fresh samples. E. Lenters said four, C. Siebelder said that for IFCC there are 10. G. John said the problem is now highlighted and we know we are granting certificates to methods that do not perform well, now the issue is how to address the problem. R. Little thought the SRL in China, where a number of the newer POC methods are coming from, could probably handle additional lots and a shorter certification interval. E. Lenters and C. Siebelder said it would be a lot of additional work for them. E. English suggested starting with three lots, then once that is worked out the 6 month certification interval could be considered. D. Sacks asked M. Swenson if a six month interval would be feasible for their company. M. Swenson replied that the concern is the time required in the event of a certification failure, it takes time to investigate and correct problems then try to re-certify before expiration of the current certification. R. Little said they can submit their data several months in advance in order to allow more time. E. Lenters asked about the possibility of randomly having POC methods sent to the SRL for repeat certification testing. D. Sacks and E. English noted that if they fail the independent evaluation they would already have their certificate, and they could say they are already done with that particular lot and are on a new one. It was generally agreed that requiring three lots is a good idea and is feasible, M. Swenson said the only issue is they may require more volume or additional sample aliquots. It was agreed that the SRLs could provide this. It was also agreed that since the raw data submitted for POC always matches the submitted results, it can probably be done less frequently. R. Little said we can consider the change to requiring three lots for POC methods, the committee can vote on this later via e-mail.

Interferences on the NGSP Web Site

M. Wagner asked what the process is for getting the interferences section of the web site updated when there is an improvement to a method that results in less interference. R. Little said the change has to be based on published data, not just data supplied by the manufacturer. D. Sacks noted that the published data can be in the form of a letter to the editor as long as it is peer-reviewed, it does not need to be a full paper.

D. Sacks noted that the Manufacturer Forum would be taking place the following day, and thanked everyone for their attendance. The meeting was adjourned at 4:10 PM.

Minutes prepared by C. Rohlfing 9/5/2024.