Minutes of the NGSP/IFCC Manufacturer Forum

Monday July 29, 2024 2:30—4:00 PM
Hyatt Regency McCormick Place, Chicago, IL

Presenters:
Randie Little—NGSP Network Coordinator (virtual)
David Sacks —Chair, NGSP Steering Committee
Carla Siebelder—IFCC HbA1c Network Coordinator
Emma English—Chair, IFCC C-EUBD

Present were members of the NGSP Steering Committee and representatives from various manufacturers and laboratories.

1. **Welcome and Introduction— David Sacks, Chair, NGSP Steering Committee**
   D. Sacks welcomed those in attendance on behalf of the NGSP and IFCC.

2. **NGSP Update—Randie Little, NGSP Network Coordinator**
   - The NGSP Steering Committee oversees the administrative core and laboratory network; it includes two manufacturer representatives. The laboratory network consists of the Central Primary Reference Lab (CPRL), which runs the original DCCT HbA1c method, 2 backup PRLs and 10 Secondary Reference Laboratories (SRLs) located in the U.S., the Netherlands, Japan and China.
   - The NGSP network is linked to the IFCC network via a master equation that is monitored by sample comparisons performed twice a year.
   - The network is monitored monthly via comparisons between the SRLs and CPRL using 10 fresh-frozen pooled samples.
   - The NGSP has three processes
     - Calibration: Informal process where samples are exchanged to assist manufacturers/labs with calibration of their methods.
     - Certification: Formal process where manufacturer or lab certifies against a SRL via a 40-sample comparison and must pass specific criteria.
     - Proficiency testing: CAP whole blood survey, which is accuracy-based with target values assigned by the NGSP network, shows how well routine laboratories are performing.
   - NGSP network mean between-lab CVs by month were all <1.5% from May 2023 to May 2024.
   - Number of certified methods and laboratories
     - The numbers of certified methods and laboratories have increased over the years; currently there are over 330 certified methods and ~130 certified laboratories.
     - The number of certified methods continues to increase while the number of certified labs has leveled off.
     - Certified laboratories are mostly Level I and outside of the U.S., and are distributed throughout the world.
   - Current Limits for NGSP and CAP
     - Beginning January 2019: NGSP Manufacturer and Level II Lab Certification Criteria: 36/40 results must be within ±5% (37/40 for Level I labs)
     - CAP Survey Grading for HbA1c remains at ±6%
   - There has been much improvement in the comparability of HbA1c results since 1993 when the results of the DCCT were reported.
     - In 1993 results were reported as HbA1, total GHB or HbA1c.
     - By 2004 all results were reported as HbA1c

- The CAP HbA1c PT survey changed from peer-group to accuracy-based grading in 2007.
- Both the CAP and NGSP criteria have been tightened over time.
- Improvement in between-method variability has been subtle over the past several years.
- The target values for the CAP GH-5 survey are assigned by the U.S. and European NGSP SRLs.

- Latest CAP survey (2024 GH5A)
  - 2024A CAP 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

  - The all-method CVs have shown an overall downward trend since 2000.
  - All-method CVs for the most recent survey ranged from 2.6-3.0%.
  - Method-specific between-laboratory CVs ranged from 0.6% to 4.3%.
  - Overall, only 80% of laboratories are using methods with CVs ≤3% at all five HbA1c levels.
  - Overall Pass rates are between 96.9 and 98.0% for the current 6% limits
- A new review of POC HbA1c use in clinical practice has 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 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:
R. Little noted that about 30% of NGSP-certified methods come from Japan, and that only a small number of these methods are FDA-approved in the U.S. and appear on the CAP survey. The new NACB recommendation is that HbA1c methods show between-lab CVs≤2.5%, many methods meet this criterion but there are still some methods that do not.

3. CAP PT Update—David Sacks, Chair, NGSP Steering Committee

- Proficiency Testing (PT)
  - In US all labs that measure patient samples are required by law to perform PT
  - Regulated by CMS (Centers for Medicare & Medicaid Services) through CLIA
  - CAP is largest provider of PT material 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%
- 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 (dual grading)
  - 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%
  - Reports sent to participating labs will show pass/fail for both criteria
  - The CAP inspection checklist will now include an item indicating that CAP-accredited labs using accuracy-based PT are required to evaluate their results using +/- 6% and show evidence of corrective action for results outside of these limits.
- 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 most failures on the CAP survey are due to transcription rather than analytical errors. He also noted that the vast majority of laboratories in the U.S. are accredited by CAP, but there are some that are accredited by other agencies such as Joint Commission (formerly JCHAO). He felt that the CAP did a very good job in finding a way to keep the CAP criterion at 6%.

If a lab passes CAP PT at 8% but fails 6%, can the lab simply switch PT providers?
D. Sacks said they can, U.S. law simply specifies that they must use a CLIA-approved PT provider but it does not have to be CAP.

So a laboratory can remain CAP accredited as long as they follow the proper PT survey schedule, even if they use a PT survey other than CAP?
D. Sacks said yes.

The FDA requires manufacturer methods to pass NGSP which is +/-5%, in that context 8% would not seem to make sense.
D. Sacks agreed and noted that the NGSP is not changing their criteria. R. Little said that what manufacturers do with their method is different than what is out in the field. NGSP certification is performed by the manufacturer, generally with one lot of reagents. That is why the NGSP recommends that labs look at PT data as well as certification status when choosing a method.

An important reason for tightening the criteria was that HbA1c is now recommended for the diagnosis of diabetes as well as monitoring, so it would seem important to maintain strict PT criteria.
D. Sacks agreed, noting that a major reason HbA1c was recommended for diagnosis in the original 2009 Expert Committee report was that HbA1c was well-standardized. There is evidence suggesting that HbA1c is being used for diagnosis more than glucose in the U.S. He also noted that CAP will officially announce the new CAP PT rules in October.

4. Update: IFCC HbA1c Network—Carla Siebelder

- IFCC Roadmap: Optimum Performance HbA1c
  - IFCC Working Group
  - Reference Method
  - Global Network
  - Services Manufacturers
  - Model Quality Targets
  - Monitoring Quality
- Reference Method
  - To come to worldwide standardisation and worldwide comparability of HbA1c results. the IFCC WG developed a scientific sound Reference Measurement System within the concept of Metrological Traceability
  - Approved in 2001(published 2002), progress report was published in Clin Chem in 2008.
- Global network of reference laboratories remains in place and continues to perform well. Currently there are 16 approved laboratories and one candidate laboratory.
- Services to Manufacturers
  - Calibrators to achieve Traceability
  - Controls to check Traceability
  - Certification Programme to prove Traceability
  - Variant Samples (FDA Approval)
  - Value Assignment Specimens
  - Monitoring Master Equation IFCC – NGSP
  - Calibrators: Specifications
    - Eight level frozen whole blood panel
    - Units provided: HbA1c: IFCC (mmol/mol) and NGSP (%) Units, mmol/L, g/dL
    - Total Hb: mmol/L, g/dL
  - Controls: Specifications
    - Low, medium and high levels
    - Medium provided with low, medium and high hemoglobin concentrations

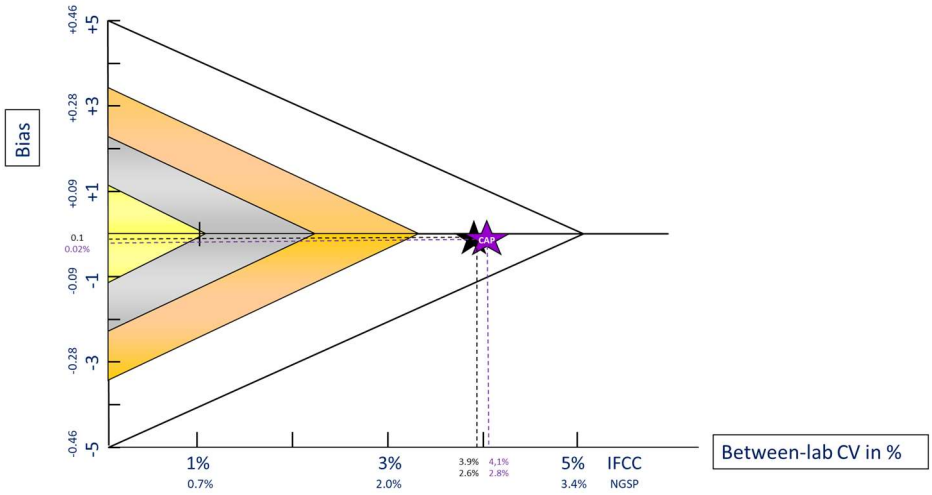
- Certification Programme
  - 24 samples
  - Certificate is provided showing how the method performed compared to quality targets.
  - There are 4 levels of acceptable method performance: Gold, silver, bronze, standard (minimum).
  - TAE of 5 mmol/mol
  - In 2023, the number of manufacturer methods that fell into each category were:
    a. Gold: 0
    b. Silver: 99
    c. Bronze: 112
    d. Standard: 31
    e. IFCC criteria not met: 5
    f. Information can be found at www.ifcchba1c.org (login required)
    g. Decimal
      i. For the certification programme reporting with 1 decimal is important for quality reasons as it may impact the calculations
      ii. Clinically not relevant: routine reporting should be no decimal places (consensus statement)
- Variant samples: Collection of AS, AE, AC, AD samples in stock along with limited quantities of A2, elevated HbF and rare variants.
- Monitoring Master Equation IFCC – NGSP
  - Master Equation: NGSP = 0.0915 x IFCC + 2.15
  - Sample comparisons between the networks are performed twice a year.
  - The ME is monitored over time and has been shown to be stable over time since 2004

- IFCC Model Quality Targets
  - A small error has high impact on interpretation
  - Quality test is important
  - How good is good enough?
  - IFCC Task Force, published in 2015 (Clin Chem. 2015 May;61(5):752-9).
  - Concept of TE
    - 2 sources: Bias & Imprecision
    - Criterion: TEa 5 mmol/mol Risk 2 σ
  - Model is applicable for multiple use.
    - Performance of a single lab (within lab CV),
    - Group of labs/ manufacturer (between-lab CV)
    - Country (between-lab CV)
  - A new certificate design which shows the direction as well as the degree of bias will be implemented in 2025
  - Impact of bias (Clinica Chimica Acta 548 (2023), 117495 https://doi.org/10.1016/j.cca.2023.117495)
    - 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.
    - Being considered by the IFCC C-EUBD
- Monitoring Quality— EurA1c: A Project of the IFCC C-EUBD and EQA/PT organisers
  - International Cooperation: Once a year EQA Organisers use the same 2 samples
  - Data combined to get a global overview of the performance of HbA1c
  - EurA1c samples
    - Fresh Whole Blood
      a. Advantage: commutable and suitable all methods
      b. Disadvantage: limited stability
    - Lyophilised Hemolysate
      a. Advantage: stable
      b. Disadvantage: not commutable for all methods; note suitable for some POC instruments
    - Choice: National EQA organisers: logistics in the country
  - First survey was in 2016 (published 2018)

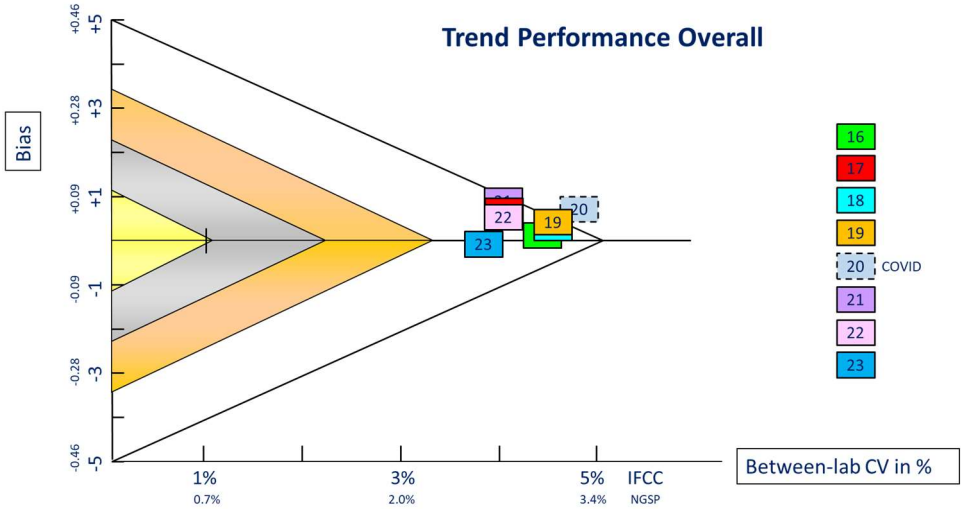
- Number of Laboratories

Year	Total	Fresh Whole Blood	Lyophilised Hemolysate
2016	2166	1517	649
2017	2647	1809	838
2018	3980	2875	1105
2019	4575	3038	1537
2020	5120	3286	1834
2021	4077	2524	1553
2022	4325	2788	1537
2023	4082	2546	1536

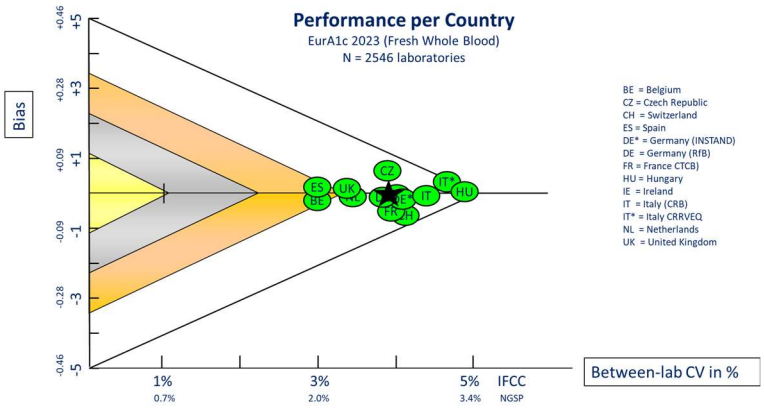
- EurA1c 2023: 22 countries - 26 EQA - 4325 laboratories (5 of the countries from outside of Europe: Mexico, South Africa, South Korea, Vietnam, Thailand)
- EurA1c 2023 (preliminary) results
  - Overall Performance EurA1c 2023 (fresh whole blood) N = 2546 Laboratories



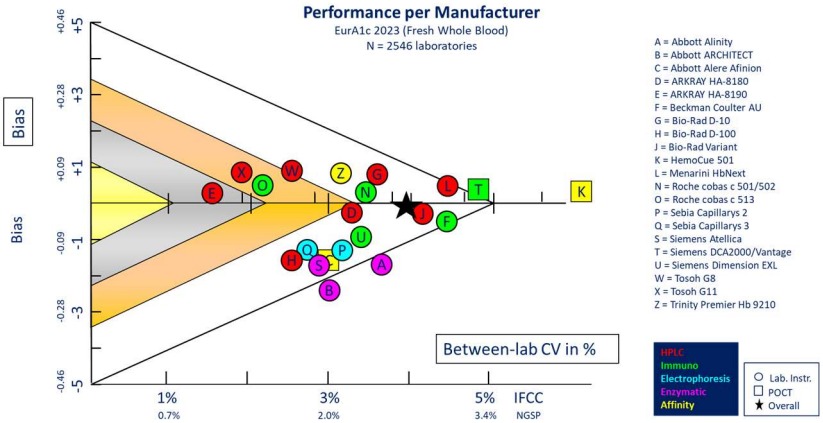
  - Trend performance overall



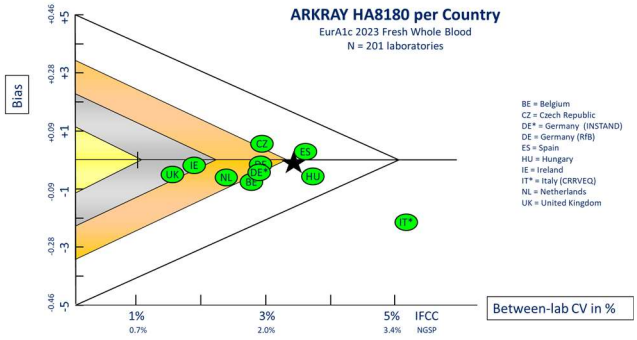
  - Performance Per Country

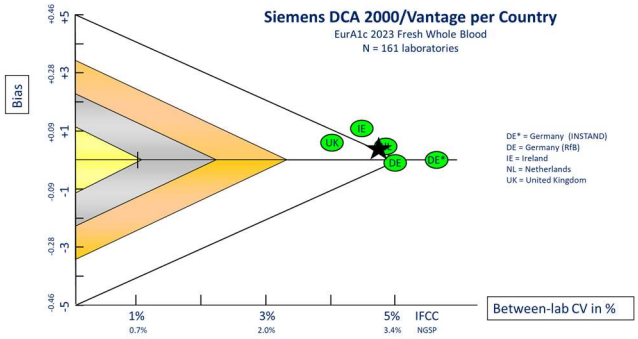


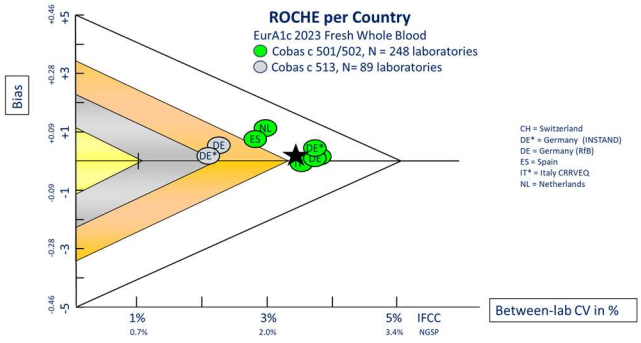
- Performance per Manufacturer

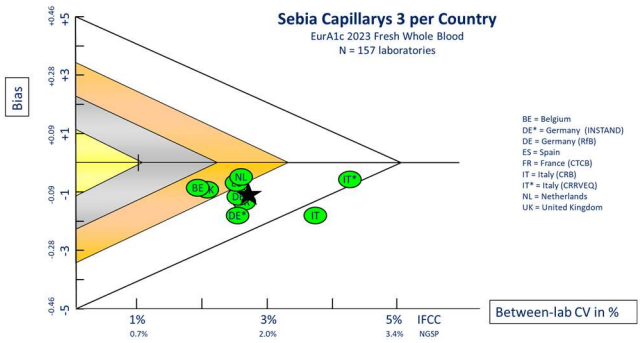


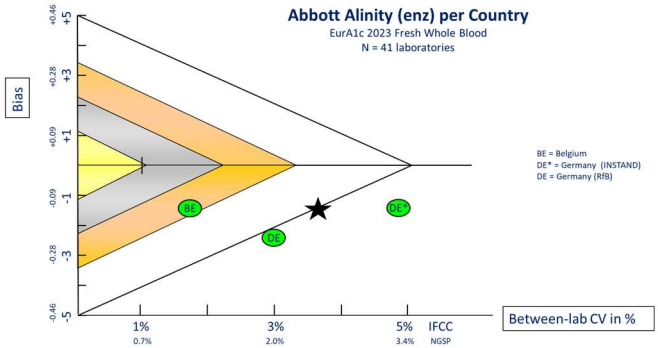
- Performance per Manufacturer per Country

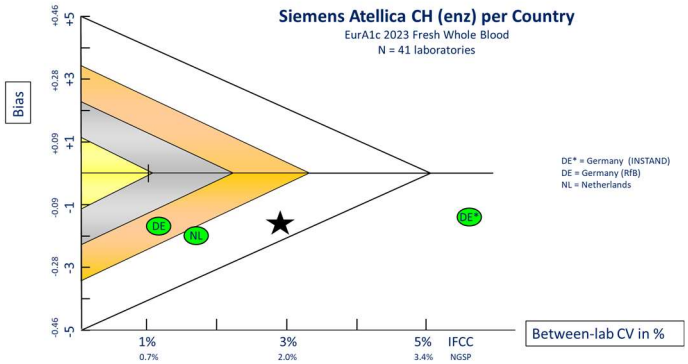


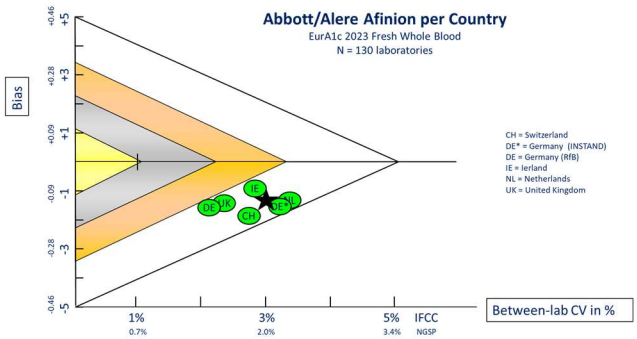


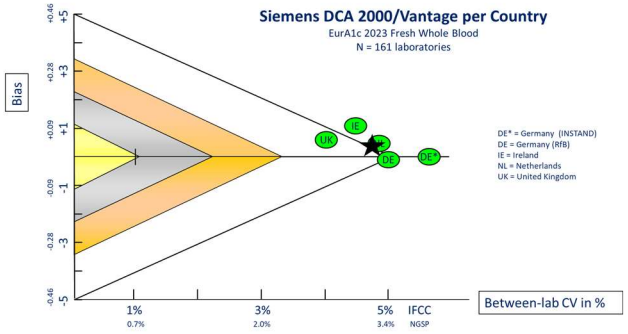

ROCHE per Country
EurA1c 2023 Fresh Whole Blood
Cobas c 501/502, N = 248 laboratories
Cobas c 513, N= 89 laboratories
Bias
+0.46 +5
+0.28 +3
+0.09 +1
-0.09 -1
-0.28 -3
-0.46 -5
NL
ES
DE
DE*
CH*
CH
CH = Switzerland
DE* = Germany (INSTAND)
DE = Germany (RfB)
ES = Spain
IT* = Italy CRRVEQ
NL = Netherlands
1% 0.7%
3% 2.0%
5% IFCC 3.4% NGSP
Between-lab CV in %


Sebia Capillarys 3 per Country
EurA1c 2023 Fresh Whole Blood
N = 157 laboratories
Bias
+0.46 +5
+0.28 +3
+0.09 +1
-0.09 -1
-0.28 -3
-0.46 -5
BE
NL
ES
IT*
IT
DE*
BE = Belgium
DE* = Germany (INSTAND)
DE = Germany (RfB)
ES = Spain
FR = France (CTCB)
IT = Italy (CRB)
IT* = Italy (CRRVEQ)
NL = Netherlands
UK = United Kingdom
1% 0.7%
3% 2.0%
5% IFCC 3.4% NGSP
Between-lab CV in %


Abbott Alinity (enz) per Country
EurA1c 2023 Fresh Whole Blood
N = 41 laboratories
Bias
+0.46 +5
+0.28 +3
+0.09 +1
-0.09 -1
-0.28 -3
-0.46 -5
BE
DE*
DE
BE = Belgium
DE* = Germany (INSTAND)
DE = Germany (RfB)
1% 0.7%
3% 2.0%
5% IFCC 3.4% NGSP
Between-lab CV in %


Siemens Atellica CH (enz) per Country
EurA1c 2023 Fresh Whole Blood
N = 41 laboratories
Bias
+0.46 +5
+0.28 +3
+0.09 +1
-0.09 -1
-0.28 -3
-0.46 -5
DE
NL
DE*
DE* = Germany (INSTAND)
DE = Germany (RfB)
NL = Netherlands
1% 0.7%
3% 2.0%
5% IFCC 3.4% NGSP
Between-lab CV in %





- EurA1c: Lot of information about the performance of many HbA1c tests
  - Pressure to improve the quality
  - Optimum Performance of HbA1c
  - Contribute to Optimum Patient Care

5. IFCC EUBD Update—Emma English

- Continue to have oversight of IFCC HbA1c Standardisation Network--This is facilitated through the partnerships between the C-EUBD, C-TLM and the network meetings.
- Working with global NGOs
  - Development of guidelines for the World Health Organization (WHO) prequalification of BGM and POCT HbA1c devices
  - Opportunity to influence global policy on what is needed for high quality diabetes testing
  - In 2023 the HbA1c pre-qualification documents, TSS 18, went through external peer review and public consultation for final approval
  - TSS19 blood glucose recently completed the final stages of approval for 2024
- WHO Pre-qualification of Medical Products
  - The aim of WHO prequalification of in vitro diagnostics (IVDs) is to promote and facilitate access to safe, appropriate and affordable in vitro diagnostics of good quality in an equitable manner. The focus is on IVDs for priority diseases that are appropriate for use in resource-limited settings.
  - Steps to achieve pre-qualification: WHO IVD prequalification incorporates comprehensive assessment of individual IVDs through a standardized procedure, to determine whether the product meets WHO prequalification requirements. Assessment has three components:
    - Review of a product dossier
    - Laboratory evaluation of performance and operational characteristics
    - Manufacturing site(s) inspection
    - Following prequalification post-market surveillance is undertaken
  - Review of the product dossier
    - The TSS documents are the guide for manufacturers as to what is needed to compile a product dossier for submission
    - TSS-18: Haemoglobin A1c point of care analyzers for professional use

        - TSS-19: In-vitro diagnostic medical devices for monitoring of blood glucose in capillary blood
    - The independent evaluation
        - The aim of the performance evaluation is to independently verify the manufacturer's claim regarding product performance. In addition, if UN procurement criteria have been established, performance evaluation enables it to be determined whether these criteria have been met.
        - Manufacturers can choose between organization of performance evaluation coordinated and financed by WHO (option 1), or performance evaluation coordinated and paid for by themselves (option 2). But whichever option is chosen, the evaluation must be performed by a WHO prequalification laboratory according to the appropriate standardized evaluation protocol for the corresponding type of assay.
    - However
        - The need to undertake a prequalification independent evaluation also follows risk-based principles.
        - In this context and as part of a broader effort to streamline assessment processes **WHO has taken the executive decision to waive prequalification performance evaluations for in vitro diagnostic medical devices for monitoring of blood glucose in capillary blood and HbA1c point-of-care assays.**
        - For such products the prequalification assessment will include the review of a product dossier, a site inspection and labelling review.
- Previous forum meeting: Two key topics you suggested we work on
    - Glycated albumin
        - Standardisation and analytical performance
        - As a clinical tool
        - Recent publication: Lenters-Westra et al. Limitations of glycated albumin standardization when applied to the assessment of diabetes patients. Clin Chem Lab Med 2024 Jun 17. doi: 10.1515/cclm-2024-0591. Online ahead of print.
    - Hb Variants
        - Protocol for determining interference from Hb Variants
        - Includes steps for dealing with fresh versus frozen samples
        - Of particular importance for POCT devices
        - We aim to publish this in the autumn
- GMI and HbA1c – guide to assessing discordant results: This is ongoing and we are still aiming to publish this in autumn this year
- What we would like to know from you
    - What topics would you like us to continue to work on?
    - Which aspects of those topics are most important to you?
    - How can we support your educational endeavours?
    - Webinars do serve a purpose but what more can we be doing (we want to diversify our educational outputs!)
- Contact: emma.english@ice.cam.ac.uk

Discussion:

E. English noted that the TSS-18 and TSS-19 documents were the first non-infectious disease pre-qualification documents approved and published by WHO. She expressed disappointment that WHO has waived prequalification performance evaluations for capillary glucose and POC HbA1c. Experience from prior studies and a current study has demonstrated that independent evaluations are probably the only way to identify some of the poorly performing devices. The C-EUBD will be pushing back on this by providing data to WHO and strongly suggesting that they reinstate some form of independent evaluations.

D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 4:10 PM.

Minutes prepared by C. Rohlfing 09/30/2024.