Minutes of the NGSP/IFCC Manufacturer Forum

Wednesday July 31, 2013 2:00PM-4:00PM
Hyatt Regency Houston, Houston, TX

Presenters:
David Sacks —Chair, NGSP Steering Committee
Randie Little—NGSP Network Coordinator
Ruth Chesler—FDA
Cas Weykamp—IFCC HbA1c Network Coordinator

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

1. **Welcome and Introduction— David Sacks, Chair, NGSP Steering Committee**
   - D. Sacks welcomed those in attendance on behalf of the NGSP and IFCC.
2. **NGSP Progress Report—Randie Little, NGSP Network Coordinator**
   - The NGSP is overseen by a Steering Committee and includes a administrative core and a laboratory network consisting of Primary and Secondary Reference Laboratories (PRLs and SRLs) in the U.S., Europe and Japan.
   - The Central Primary Reference Laboratory has shown consistency over time since the early 1980s.
   - The network is linked to the IFCC network via sample comparisons performed 2X/year.
   - The NGSP assists manufacturers with calibrating their assays, has a formal certification process and monitors performance of HbA1c testing in the field via the CAP survey which uses fresh whole blood.
   - The lists of certified methods and laboratories are posted on the NGSP web site.
   - Status of HbA1c measurement
     - The numbers of certified methods and laboratories continues to increase; currently there are over 130 of each.
     - Some methods are actually variations of the same method.
     - There are a number of new certified methods from Japan.
     - A number of certified methods are not used in the U.S.
     - Certified laboratories are distributed throughout the world, most are outside of the U.S.
     - Level 1 laboratories are generally laboratories performing clinical trials where sponsors require them to be certified. In addition to certification, L1 labs are monitored quarterly to insure consistency of their results over time.
     - There has been much improvement in the comparability of HbA1c results since 1993 when the results of the DCCT were reported.
     - All-method CVs on the CAP surveys have dropped from ~7% to 3.5% in the normal range (4-6% HbA1c) since 2000. The CVs have also declined, albeit to a lesser extent, in the middle and high range as well.
     - Our goal is all-method CVs<3.5% at all levels; we are getting close to that goal.
     - CAP GH2 survey 2013A:
       - The method-specific means were all within 0.38 at all levels. Except for 2 methods, bias was within 0.3% HbA1c.
       - Method-specific, between-laboratory CV's ranged from 1.2% to 8.2%! All but 2 methods (<30 participants) had CVs below 5% for all 3 HbA1c levels.
       - Over 98% of laboratories were using methods that had between-lab CVs<5%. About 50% of labs use methods with between-lab CVs <3% at all three levels.
       - There appears to be room for improvement but it is getting better!
       - The CAP acceptance criterion was tightened to ±6% for the 2013A survey.

        - Cumulative overall pass rates for the CAP 2013A survey were 93.4%, 95.3% and 94.3% at the low, middle and high levels, respectively.
        - Between-lab CVs by method type
            1. Ion-exchange HPLC methods consistently show low CVs (<3.0%), some boronate affinity and immunoassay methods have low CVs as well.
            2. Some immunoassay methods have high CVs (>3.5%).
            3. POC methods do not necessarily perform worse than laboratory methods, however only a few POC methods show up on the survey.
            4. Most methods had pass rates >90% but some immunoassay methods had lower pass rates.
- Tightening the NGSP criteria
    - Current criteria (effective Sept. 2012): 37/40 individual results must be within 7% of the SRL (one SRL) mean.
    - At the time the current NGSP criteria went into effect the CAP limit was ±7% of the NGSP target.
    - Current CAP limits: Each result must be within ±6% of NGSP assigned target value (mean of 7 SRLs, multiple results from each).
    - New NGSP certification criteria
        - The Committee is considering tightening the NGSP certification criteria, probably to 37/40 individual results within 6%.
        - Analyses indicate that NGSP 37/40 within ±6% would be roughly comparable to CAP ±6% in terms of probabilities of passing.
        - We do not have enough data to make a decision yet.
- Summary
    - HbA1c measurements continue to improve.
    - In an effort to further decrease the variability in HbA1c measurement, the NGSP will likely tighten manufacturer certification criteria.
    - If the criteria change to ±6%, this would be at least comparable to CAP 3/3 passing at ±6%.

Discussion:

Has there been any discussion of using the mean of all of the SRLs for certification as opposed to a single SRL?
R. Little said this has been discussed; it would be very laborious to do this. We have strict monitoring criteria for the SRLs and they are monitored every month, if there are any problems with a SRL it is not used to certify methods/labs until the problem is resolved. The SRLs represent different method types (ion-exchange, boronate affinity, immunoassay), we try to match the method type being certified with the appropriate SRL but good methods will generally pass regardless.

3. CAP Grading: Future Plans—David Sacks

- In the past peer group grading was used for HbA1c
- In 2007 CAP switched to accuracy grading using the DCCT target
    - Initial limits were ±15%
    - 99% pass rate
- The limits were tightened to ±12% in 2008, ±10% in 2009, and ±8% in2010.
- Plan was to reduce to ±6% in 2011 but ±7% was selected and this was kept for 2012.
- CAP 2010 GH2A Pass Rates at ±8% and ±6% (projected) HbA1c cutoff:

	At ±8%	At ±6%
GH2-01 (5.1%)	95.5	91.0
GH2-03 (6.0%)	95.4	91.6
GH2-02 (8.4%)	95.2	88.6

- CAP 2012 GH2A Pass Rates at ±7% and ±6% (projected) HbA1c cutoff:

	At ±7%	At ±6%
Low (5.6%)	95.6	95.6
Medium (7.2%)	96.2	92.9
High (9.4%)	94.9	92.5

- CAP 2010 & 2012 GH2A Pass Rates at ±6% (projected) HbA1c Cutoff

		2010	2012
Low	(5.1/5.6%)	91.0	95.8
Medium	(6.0/7.2%)	91.6	92.9
High	(8.4/9.4%)	88.6	92.5

- CAP 2010, 2012 & 2013 GH2A Pass Rates at ±6% HbA1c Cutoff

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

- Summary
  - CAP progressively tightened PT grading
    - 2007 -- 15%
    - 2013 – 6%
  - Lab performance on CAP surveys improving

Discussion:

D. Sacks noted that the HbA1c CAP survey pass rates for 2013 are very comparable to those seen with other analytes.

Will CAP be including hemoglobin variants in future surveys?
D. Sacks said they included one heterozygous HbS (HbAS) sample in one survey 7-8 years ago and again in 2012. The idea is to have a sample with the same HbA1c level as one of the non-variant survey samples. Last year CAP also offered a voluntary "high level" challenge that included either a HbAD or HbAE sample, but very few labs participated. One of the difficulties is obtaining a sufficient quantity of variant sample. For the HbAS sample included last year, two methods showed significant bias with this sample and both were known to show interference from this variant. CAP will keep trying to periodically include variant samples in the surveys. R. Little noted that CAP included a questionnaire in the original survey that included HbAS to determine if the laboratory noted the presence of this variant and if the result would normally be reported; it would be useful to obtain this information in the future. D. Sacks said this was an inadvertent omission; CAP will try to include a questionnaire in the future.

4. FDA Approval for HbA1c Diagnosis Claim—Ruth Chesler

- De novo petition approval granted May 23, 2013 (21 CFR 862.1373, product code PDJ) for:
  - Roche COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 assay- k121291
  - Can be used as predicate device for future 510(k)s
  - All information in this presentation is available publicly on FDA 510(k) Database
  - Decision Summary and Approval Letter with Special Controls listed can be located at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
- New Special Control Regulation for Hemoglobin A1c Devices With A Diagnostic Claim
  - Performance testing of device precision must, at a minimum, use blood samples with concentrations near 5.0%, 6.5%, 8.0% and 12% hemoglobin A1c. This testing must evaluate precision over a minimum of 20 days using at least 3 lots of the device and 3 instruments, as applicable.
  - Performance testing of device accuracy must include a minimum of 120 blood samples that span the measuring interval of the new device and compare results of the new device to results of the standardized test method. Results must demonstrate little or no bias versus the standardized method.
  - Total error of the new device must be evaluated using single measurements by the new device compared to results of the standardized test method, and this evaluation must demonstrate a total error less than or equal to 6%.
  - Performance testing must demonstrate that there is little to no interference from common hemoglobin variants, including Hemoglobin C, Hemoglobin D, Hemoglobin E, Hemoglobin A2 and Hemoglobin S.

- When assay interference from Hemoglobin F or interference with other hemoglobin variants with low frequency in the population is observed, a warning statement must be placed in a black box and must appear in all labeling material for these devices describing the interference and any affected populations.

- Instructions for Use (IFU) for HbA1c Test Systems That Are to Be Used to Diagnose Diabetes: A Hemoglobin A1c Test system is a device used to measure the percent concentration of hemoglobin A1c in blood. Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of patients at risk for development of diabetes mellitus.
- Traceability
  - Previously cleared for monitoring and seeking a diagnosis claim:
  - Device must have and maintain yearly certification
- Hemoglobin Variants
  - Evaluate the potential interference with your assay from common hemoglobin variants.
  - Variants and Concentrations to be tested:

Hemoglobin Variant	Concentration (%)
A2	6
S	40
C	40
E	30
HbD (Punjab or Los Angeles)	35
F	30

  - Boxed Warning for Hb Variant Interference: When assay interference from Hemoglobin F or interference with other hemoglobin variants with low frequency in the population is observed, a warning statement must be placed in a black box and must appear in all labeling material for these devices describing the interference and any affected populations.
- Method Comparison
  - Evaluate accuracy of your device by comparing results of samples run on your new test system to results of the same samples run by the NGSP standardization program (NGSP Secondary Reference Laboratory).
  - Analyze a minimum of 120 samples, of which fifty percent fall within a range between 6% and 7% HbA1c. Distribute the remainder of the samples across the measuring interval of the assay.
  - 141 samples were evaluated using the candidate COBAS INTEGRA 800 Tina-quant HbA1cDx Gen. 2 method. Samples were tested in singlicate over a 3 day period. The results were compared to testing performed at a NGSP secondary reference laboratory.
  - Provide results of the regression analysis for this evaluation. Select a regression method that accounts for the random measurements errors associated with your new method and the reference method (i.e., the method used by the standardization program), such as weighted Deming regression or Passing-Bablok regression.
  - Total error of the new device must be evaluated using single measurements by the new device compared to results of the standardized test method, and this evaluation must demonstrate a total error less than or equal to 6%.
- Thank you! Ruth.Chesler@fda.hhs.gov
- Contacts:
  - Katherine.Serrano@fda.hhs.gov
  - Meshaun.Payne@fda.hhs.gov

Discussion:

If a method is affected by a variant hemoglobin but also indicates that the variant is present (and therefore the inaccurate result will not be reported) is the method still eligible for a diagnostic claim?
R. Chesler said that with this kind of special circumstance a pre-submission is recommended for review. R. Little noted that there are some very good methods that fall into this category.

Regarding the 6% total error criterion, do the results for every individual sample have to fall within the 6% limit?

R. Chesler said the total error analysis (based on % bias and %CV) and is performed at several levels (the Decision Summary for the Integra 800 indicates that TE analysis was performed for HbA1c levels of 5.0%, 6.5% and 8.0%).

Will POC methods be considered?
R. Chesler said the FDA is open to it. The manufacturer would have the burden of proof in demonstrating that the method can meet these criteria in the hands of end-users.

Is the Integra 800 assay that was approved for diagnosis the same assay as the one approved for monitoring and was it Gen. 2 or Gen. 3?
R. Chesler said it is the Gen. 2 and is the same assay previously approved for monitoring.

The Decision Summary shows that the evaluation included testing for a long list of potential drug interferences, will this be required of all methods submitted for a diagnostic claim?
R. Chesler said manufacturers may not need to test for all of these interferences, manufacturers can include a shorter list as part of a pre-submission at which time the FDA evaluate it and determine if additional tests are needed. The maximum levels for the drugs tested were not specified by the Special Control regulation, these levels are what the manufacturer chose to submit.

Were the drugs listed suggested by Roche or the FDA?
R. Chesler was not sure.

If a new method is submitted does it have to be approved for monitoring first then submitted for a diagnostic claim?
R. Chesler said no, for new methods the submissions can be done at the same time.

When submitting for a diagnostic claim does the predicate device have to be an immunoassay?
R. Chesler said the Integra 800 would have to be named as the predicate device since it is the only method currently approved for diagnosis. However, it is different from the typical 510K predicate device in the sense that it will not be the actual method comparison method. The submitted method will actually be compared to the standardized NGSP method.

Is there any intention to go back and potentially re-evaluate monitoring claims?
R. Chesler did not think so, the FDA has no mechanism for this. There may be assays going back many years that were subjected to less rigid criteria and they may still be on the market, as long as they haven't changed they can still be on the market.

If a common assay is used across multiple instruments would a separate 510K have to be submitted for each instrument?
R. Chesler said yes, there may be some differences between instruments and they may not all be able to meet the criteria.

5. IFCC Network and Integrated Project—Cas Weykamp

- Oversight of the IFCC Network is performed by the IFCC Committee on Traceability in Laboratory Medicine (metrological aspects) and the IFCC Task Force on Implementation of HbA1c Standardization (educational/clinical aspects, formerly the Integrated Project).
- IFCC Task Force on HbA1c
  - Aim: "To establish an interface between IFCC…and its National/Corporate Members…and the clinical users of HbA1c to enable: The implementation of a scientifically sound reporting structure for HbA1c standardised to the IFCC Reference Measurement Procedure"
  - Activities
    - Changed Name: "Integrated Project" to "Task Force HbA1c"
    - Education: Lectures China, Korea, Brazil
    - Quality Targets: Advise on use of HbA1c monitoring/diagnosis
    - WHO
      1. Advise on potential use of HbA1c in lower and middle-income countries

2. Revise 2002 manual regarding laboratory monitoring/diagnosis

- IFCC Reference System for HbA1c
  - Mission of the IFCC Network is to warrant continuity of the IFCC reference measurement procedure and make HbA1c assays worldwide traceable to it.
  - Internal checks
    - Old Primary Calibrators
    - New Primary Calibrators
    - Controls previous years
    - Approval Network Labs (2x/year)
  - Network Laboratories
    - There are approved network laboratories in the US, Europe and Asia
    - Three new labs (India, Korea and China) were approved last year
    - There are three current candidate labs (Brazil, Europe, China)
    - Future plans
      1. Tighten criteria for approval of laboratories
      2. Make IFCC interlaboratory comparison/approval data available on a web site with listing of individual participating laboratories.
- Traceability: The IFCC reference system has been established as the only valid anchor for worldwide HbA1c standardization to which manufacturers should show tracebility.
- Services for Manufacturers
  - Calibrators to achieve traceabililty
    - Provided with HbA1c results in IFCC (mmol/mol Hb) and DCCT (%) units, also mmol/L and g/dL.
    - Provided with total hemoglobin in mmol/L and g/dL.
    - All are provided with expanded uncertainties.
  - Controls to check traceability
    - Low, middle and high levels
    - Middle level is provided with low, normal and elevated total hemoglobin
    - Units provided
      1. HbA1c and Total Hb
      2. IFCC- NGSP Units
      3. mmol/mol, %, mmol/L, g/dL HbA1c
      4. mmol and g/dL Total Hb
    - All are provided with expanded uncertainties
  - Monitoring to prove traceability
    - 24 frozen whole blood samples per year (12 blind duplicates) to be analyzed throughout the year
    - Once a year mean deviations from the targets, imprecision and linearity are calculated
    - Certificates of traceability are provided
    - Many manufacturers participate
- Questions from Manufacturers.
  - Sustainability of Calibrators: How do we know that they are stable for years, there are no batch-to-batch differences, and they are commutable?
    - CBS (commutability, batch-to-batch, stability) test: Test every batch of calibrators
      1. Fresh whole blood samples (n=10)
      2. Assay with 4 different methods using different principles (Menarini HA8160, Tosoh G8, Trinity Ultra^2, Roche Tina Quant)
      3. Calibrated with 4 different batches of calibrators (2009-2012)
      4. Results: All within-method and between-method means for all batches were 62 or 63 mmol/mol indicating commutability, batch-to batch consistency and stability.
  - Different CVs for IFCC and NGSP
    - Hypothesis: “The variation in the Temperature of the Human Body is much lower in Scientists than in Others”
    - Body temperature is 311^{o}K or ~100^{o}F with corresponding equivalent SDs of 1^{o}K and 1.8^{o}F

- However, when these numbers are used to calculate CVs, results are (1/311)=0.3%CV for Kelvin, (1.8/100)=1.8%CV for Fahrenheit.
- The same applies to HbA1c: At a HbA1c level of 6.5% NGSP or 48 mmol/mol IFCC, corresponding SDs of 0.4% or 4 mmol/mol correspond to CVs of 6.2% and 8.3%, respectively.
- When specifying CVs one must refer to the units, CVs can be converted between units:

Conversion Table CVs IFCC/NGSP

Clin Chem 2011;57:1204-6

HbA1c		Conversion Factor*	
IFCC	NGSP	From NGSP to IFCC $CV_{IFCC} = f_1 \times CV_{NGSP}$	From IFCC to NGSP $CV_{NGSP} = f_2 \times CV_{IFCC}$
30	4.9	1.79	0.56
40	5.8	1.58	0.63
50	6.7	1.46	0.68
60	7.6	1.39	0.72
70	8.6	1.34	0.75
80	9.5	1.29	0.77
90	10.4	1.26	0.80

** Applies to Precision (CVs), Desirable Specifications and Biological Variation*

$$f2 = \frac{HbA1c_{IFCC}}{HbA1c_{IFCC} + 23.5} \qquad f1 = \frac{HbA1c_{NGSP}}{HbA1c_{NGSP} - 2.15}$$

- Where do CVs apply?

		CV_{IFCC}	CV_{NGSP}
1.	Instrument Evaluation	0.9%	0.6%
2.	Desirable Specifications Intralab	<3%	<2%
3.	PT/EQA Desirable Interlab CV	<5.2%	<3.5%
4.	Biological Variation	7.3%	4.1%

- Important for Manufacturers
  1. In Instrument Evaluation, the precision (CV) in IFCC units will be higher than in NGSP units.
  2. Desirable Specifications and PT/EQA Requirements for CVs will be proportionally higher in IFCC units.
  3. Thus, Performance Evaluation will be the same, irrespective in which units the evaluation is done.
- More information: The analytical Goals for Hemoglobin A1c Measurement in IFCC Units and NGSP Units are Different. Weykamp C, Mosca A, Gillery P, Panteghini M. Clin Chem 2011;57:1204-6.

Discussion:

There were no further questions, D. Sacks thanked everyone present for their attendance; the meeting was adjourned at 3:30PM.

Minutes prepared by C. Rohlfing 8/23/13. Modified by R. Little 08/27/13 and D. Sacks 08/30/13.