REFERENCE MATERIAL PRODUCER ADVISORY COMMITTEE MEETING

Friday, April 4, 2014
1:00 p.m. – 3:00 p.m.

SUMMARY

<table>
<thead>
<tr>
<th>AGENDA ITEM</th>
<th>DISCUSSION</th>
<th>MOTIONS &amp; ACTION ITEMS</th>
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<tr>
<td>Call to order</td>
<td>R. Querry and K. Black called the meeting to order at 1:00 PM.</td>
<td>None.</td>
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<tr>
<td>Introductions</td>
<td>K. Black conducted a brief introduction.</td>
<td>None.</td>
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<td>Review and approval of agenda</td>
<td>Agenda was reviewed and approved with no comments or objections.</td>
<td>D. Mettler Motioned to Approve</td>
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<td>M. Miller Seconded Motion Passed</td>
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<tr>
<td>Last Meeting minutes - Review/Approve</td>
<td>Previous meeting minutes were reviewed and approved with no comments or objections.</td>
<td>D. Mettler Motioned to Approve</td>
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<td>M. Miller Seconded Motion Passed</td>
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<td>Formation of Nominating Committee</td>
<td>Volunteers were solicited to form a nomination committee. Volunteer are: Dan Tholen, Gael Miller</td>
<td>Action Item 1: Nomination Committee to provide a list of candidates to R. Querry by April 30, 2014.</td>
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<td>Status of Open Action Items:</td>
<td>R. Querry discussed the status of the open action items. ISO Guide 34 Explanations: The current status of the action item was presented and the intent is to complete section 4 explanations working with the currently approved ISO/IEC 17025 requirements. Progress is being made and some explanations should be provided to the committee in the near future for their review and approval prior to sending to the Criteria Council for their votes to publish.</td>
<td>None.</td>
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<td>ILAC/APLAC/IAAC Activities Relating to ISO Guide 34 Accreditation (R. Querry)</td>
<td>R. Querry discussed the current status of the APLAC MRA and the developing MRAs for ILAC and IAAC. R. Querry provided the current MRA signatories to the APLAC MRA. Also, he explained that APLAC TC008 is still in the revision process and A2LA continues to provide comments.</td>
<td>None.</td>
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<td>R. Querry presented on the APLAC RMP workshop held in Japan in November 2013. The topics included accreditation criteria, contents of scopes of accreditation (how much detail, clarification on CRM vs. RM), discussion about listing characterization methods, etc.</td>
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<td>During the discussion an A2LA assessor brought up the concern that laboratories are confused when it comes to purchasing a CRM and/or RM. Also, it was felt that they need guidance as to when a CRM is needed and when an RM is sufficient. It was felt that many RMPs’ websites do not clearly indicate what products are or are not CRM vs. RM.</td>
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<td>It was pointed out that this is also a common problem when ordering calibration services as calibration service providers frequently offer different levels of services. There is often a gap of knowledge between the purchaser and the RMP and that needs to be addressed. R. Querry pointed out that A2LA is attempting to generate some guidance to help users of their RMs to ensure that they know what a G34 certificate should include and when a G34 CRM is needed.</td>
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<td>The comment was made that RMPs should confirm that each customer really intended to purchase a RM and/or CRM. Essentially, the RMP should confirm in all instances that, when a customer orders a product, they</td>
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<td>did not intend/need to order another product. Providers in attendance did not agree that it was their responsibility to do this level of review for customers purchasing their product but stated they could see the benefit of further clarity in the purchasing process for their customers. It was stressed by the group that there needed to be more clarity on the behalf of the providers that the materials they offer are either CRMs (accredited) or RMs (accredited or otherwise). Confusion is causing a lot of issues with their customers, especially those that are accredited laboratories.</td>
<td>None.</td>
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<td>A2LA Peer Evaluation</td>
<td>R. Querry discussed the outcome of the recent peer evaluation. He explained that there were really no changes to the program based on that evaluation other than some minor internal SOPs that A2LA needed to revise.</td>
<td>None.</td>
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<td>Revisions to ISO Guide 35 – Anticipated Changes (D. Tholen)</td>
<td>D. Tholen led a discussion regarding the current status of the G35 revision. There was a concern about randomly sampling for homogeneity. The discussion was over purely random, systematic, stratified, etc. There was a concern that purely random sampling would not catch areas that are commonly known as “problem” areas in production. It appeared that G35 would address this and allow for strategic sampling if purely random sampling was also</td>
<td>None.</td>
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</table>
## DISCUSSION

- performed and there were reasons to perform strategic sampling.

D. Tholen offered a presentation. (Attachment 1)

### ISO Guide 31 Revision (R. Querry)

- R. Querry explained that the document is still in the current REMCO stage of revision and presented a current draft and highlighted some areas of interest. He clarified that the document would eventually be available to the committee for comment.

- **None.**

### New Business

- K. Black initiated a discussion regarding A2LA providing an example certificate of a CRM that meets the requirements of ISO Guide 31. It was raised that there should be multiple templates so that they cover a variety of reference materials. It was felt that a general template guidance would be the best approach and that it would not be considered as a requirements document to be assessed against.

  **Action Item 2:**

  - R. Querry to develop an example template and/or guidance regarding ISO Guide 31 requirements for certificates to be published on the A2LA website for CABs. Due July 31, 2014

- K. Black initiated a discussion regarding the distinction between distributors and resellers of the reference material producers’ products. ISO Guide 34 clarifies that distributors are considered subcontractors and must meet the requirements of the standard; resellers are not considered subcontractors. The key distinction is that the reseller does not have to meet the requirements of the standard through contract with the RMP.

  - The definition of reseller/distributor was considered

- **None.**
AGENDA ITEM

DISCUSSION

along the lines of ownership but there were also other considerations. The issue is that RMPs have many different relationships with their distributors and some purchase the products and some don’t actually own the product they just sell the RMP products and charge a fee for that distribution.

It was stated that, in practice, this may not normally be a problem as RMPs want to protect the integrity of their product and the integrity of their brand name.

MOTIONS & ACTION ITEMS

Attendees: John Adams, Sue Styles, Susan Audino, Barry Arnold, Christine Atkinson, Doreen Rumery, Steve Lerman, Pat Royal, Brian Lane, Charlie Pixley, Karen Stephani, Kristen Durie, Alex Klein, Hetal Patel, Heather Williams, Debbie Chilson, Chuck Goudreau, Tom Ouimet, Brad Rauch, Lauren Pittenger, Brian Scott, Kathryn Gumpper, Marwa Adly, John Gumpper, Lonna Potter, Lauryl Smith, Tina Buffington, Denise Archer, Richard Sheibley, Nile Luedtke, Dan Tholen, Heidi Phillips, Dawn Mettler, Arlene Fox, Bill Watson, Ray Schiltz, Huifan Lang, Gael Miller, Julian Burton, Lauren Smith, Saeed Almeer, Abdul Hanan, Robert Audette, Steve Crupi, John Kinsella, Jeffry Smith, Bob Olevson

Staff Attendees: Robert Knake, Randy Querry, Lauren Smith

GENERAL NOTE: Any proposed revisions to A2LA documents or processes are not considered final and enforceable until reviewed and approved by A2LA management and/or the A2LA Criteria Council (CC) and until the revised document has been placed under document control and formally issued.

Summary prepared by Robert L. Knake, A2LA Program Manager.
ISO Guide 35: Proposed revision

A2LA Technical Forum
April 4, 2014
Dan Tholen, M.S.
ISO Guide 35 Update

Guide 34 requirements in Guide 35
- Traceability, Characterization,
- Homogeneity, Stability (short term, long term)
- Uncertainty

Guide 34 requirements not in Guide 35
- Replacement batches
- Qualitative properties
- Non-certified Reference Materials
- Uncertainty in the presence of degradation
  - Except when there’s a kinetic model (isotopes)
ISO Guides for Reference Materials

ISO Guides developed out of step

Each revised document slightly changes others, especially Guides 34 and 35
Revisions to ISO Guides 30 and 31 – 2014

New Guidance documents:
  – Internal production of RMs for QC (Guide 80)
  – RMs for Nominal properties (TR 79)
  – Guidance for use of RMs (Guide 33)

ISO 17034

Next meeting of REMCO in July, USA
Current Approach in Guide 35

- Intended for REMCO members who are responsible for transferring traceability
- Assumes high level technical competence by RMP, including statistical techniques
  - Competence and integrity of accreditation body
- Requirements are not clearly stated
  - Not an assessment document
Current Approach in Guide 35

- Not designed for situation of commercial Reference Material Producers
  - Cost considerations
  - Time to market
  - Uncertainty

- Difficult for many Accreditation Bodies
  - Statistics, traceability, uncertainty
Issues not addressed in Guide 35

- Non-certified RMs (RMs for use other than calibration) – e.g. QC and PT
- Demonstrating equivalence of replacement batches
  - Use of information from similar batches
- Uncertainty in the presence of degradation
- Qualitative RMs
- Stability under usage conditions
  - Might not be addressed in revision
Confusing topics in Guide 35

- Minimum uncertainty for homogeneity?
  - Must be > 0
- Minimum uncertainty for stability?
  - Must be > 0
- Short term stability vs. transportation
- Characterization in one laboratory using a single (primary) method
Current status of revision

Four sections discussed
- 7 conference calls

Draft CD distributed for comment, February,
Comments discussed in July, 2014

Approval time?
Proposed changes from latest circulated drafts

General changes
- Considerations for commercial RMPs
- Use of information from previous batches
- Restructure for process of production
  - Design
  - Homogeneity
  - Stability
  - Characterization
  - Uncertainty
  - Statistical Annex
  - Examples
Draft Scope

This Guide gives general guidance and explains concepts to assist with the understanding and development of valid methods to assign values to properties of a reference material, including the evaluation of their associated measurement uncertainty, and the establishment of their metrological traceability.
This Guide complements ISO Guide 34 by providing detailed descriptions of acceptable approaches for the production of reference materials with reference to the assessment of homogeneity and stability, the characterisation of reference materials, estimating uncertainties of the assigned values and by giving information on how to achieve and demonstrate the metrological traceability of assigned values.
Homogeneity –
General considerations

Homogeneity testing is usually necessary
- New Reference materials
- Inherently inhomogeneous materials (e.g., food matrix, soils, gases)

Can use estimates of uncertainty from previous batches of similar material
- With confirmation check
Homogeneity – Uncertainty

Uncertainty due to homogeneity \( u_{bb} = s_{bb} \)

\[ u_{bb}^2 = s_{bb}^2 = \max\{ (\text{MS}_b - \text{MS}_w) / n_0, 0 \} \]

Can allow \( u_{bb} = s_{bb} = 0 \)

- When \( s_r < 0.3u_{\text{target}} \)

- Else \( u_{bb} = \sqrt{s_{bb}^2 + s_r^2 / n_0} \)
Homogeneity – Minimum Number of Units to Test

When $N_{\text{prod}} \geq 50$

$$N_{\text{min}} = \max\{10, \sqrt[3]{N_{\text{prod}}}\}$$

When $N_{\text{prod}} < 50$ units

$$N_{\text{min}} = \max\{3, 0.10 \times N_{\text{prod}}\}$$
Homogeneity – Other considerations (in current G35)

- Check within-unit homogeneity
- Check for trend in testing order
- Check for trend in production order
- Check for outlier difference between replicates
- Can use interlaboratory nested design
- Report minimum sample amount (uptake)
- Do not need to test all properties
Stability –
General considerations

- Can use information from previous batches of similar material
  - Need technical justification
- Can allow $u_{lts} = 0$
  - Need evidence from previous batches
- Should test all properties
Stability – Post-release monitoring

- Frequent monitoring can be used when there is little classical or accelerated stability testing.
- No monitoring needed if shelf life is short.
- Possible change between monitoring points less than 1/3 claimed uncertainty.
- If there are replacement batches, there should always be testing of retained samples at time of expiration.
Stability –
Short term Stability

- Short term Stability includes 2 factors
  - Transportation
  - Storage by user under alternative conditions
- If no alternative storage conditions, use ‘uncertainty due to transport’ ($u_{tran}$) instead of $u_{sts}$
- Should generally test all properties
Stability – Types of Long-term Studies

- Classical, or real-time studies
  - Analyses as time elapses
  - Includes reproducibility variance

- Isochronous studies
  - All analyses at same time (no reproducibility)
  - Requires conditions under which no degradation occurs

- Accelerated studies
  - Requires model for degradation
  - Requires inclusion of uncertainty of model
Stability – Uncertainty when there is degradation

When predicted change exceeds 30% of $u_{target}$

Need to report change and uncertainty of change (from Guide 34)

Report time-dependent property value

Report time-dependent uncertainty

Could report as equations or as property value and uncertainty at point of sale.
Stability – Usage conditions

- Applies when unit of RM can be repeatedly subsampled within claimed shelf life
- Mentioned as a consideration, no procedures
Characterization - General

Four types of studies (as discussed in G34)

a. Single (primary) method in single laboratory
b. Two or more methods in one or more laboratories
c. One or more methods in a network of laboratories
d. Method-specific, operationally defined property values, using network of laboratories
Characterization - proposed

Three types of studies (combine b&c)

a. Primary method in single laboratory
   - Advisable to have independent confirmation method

b. Two or more methods in one or more laboratories
   - Need 5 or more independent data-sets

c. Method-specific, operationally defined property values, using network of laboratories
Characterization – unresolved issues

What is a primary method?
- “…a method having the highest metrological properties, whose operation can be completely described and understood, for which a complete uncertainty statement can be written down in terms of S.I. units” (CCQM)

Combining approaches b & c

Use of robust statistical procedures

Use of same study to characterize RM and to demonstrate competence of laboratory
Characterization – special issues: Purity CRMs

Current Guide 35:
- Determined by subtracting impurities from 100%
- ???

Add option:
- Determined directly (freezing point depression)
- Requires evidence of identity
Characterization – special issues: Secondary CRMs

A material whose values are assigned by directly comparing candidate CRM with an already characterized CRM

– Reference and candidate must be comparable
– Reference must have a link to a primary CRM
  Therefore tertiary CRMs can be linked to secondary
– Method for validation meets traceability criteria

Then CRM can be characterized in a single laboratory, using a non-primary method
Identity CRMs

Identity is usually not a measurement result, but is a conclusion drawn on measurement results from one or several methods – e.g., DNA sequence

Useful only if error probability is negligible

Slight inhomogeneity and instability should not change the conclusion

Requires information on the source of the material and processing steps
Characterization – special issues: Presence/Absence CRMs

- A quantitative measurement is evaluated in a qualitative manner
  - e.g., value above or below a limit of detection
- Advisable to test with all relevant methods
- Uncertainty should state the confidence level of the limit of detection
Characterization – special issues: Ordinal properties

Quantities where the outcome of measurement puts the result in a certain ordered class

CRMs will be useful only if measurement places the value unequivocally

– All technically accepted measurements by all participating labs place material in same class
Characterization – special issues: Qualitative properties

- Properties such as color, order, shape, etc.
  - In some cases these properties have quantitative forms
- Usually a method-defined measurand
Uncertainty

There are some clarifications to current requirements, but no substantive changes.
Thank you