Implementing Traceability for Heterogeneous Analytes – An Industry View

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Agenda

- “Recent” trends in laboratory practice and the impact on the IVD Industry
- Who brings what to the standardization table
- One partial biological standardization success story (PSA)
Will Not Be Discussing

- Biological activity measurements – not often the subject of IVD products
- Coagulation – similar to enzyme measurements, principles are in place
- Limit discussion to chemical measurement of heterogeneous analytes
The Goal – Proper Diagnosis

- Laboratory practice today often utilizes specific guidelines for a measurand.
- Few clinicians ask what method or kit is used to obtain the values they just expect them to be accurate.
- Decisions are based on the result compared with a guideline!
Fixed Decision Points, Examples

- If LDL-C is $\geq 100$ mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.\(^{(1)}\)
- The ACE Diabetes Mellitus Consensus Conference in August 2001 established the following goals:
  - HbA1C level of 6.5% or less
  - Pre-prandial Glucose of 140 mg/dL or less \(^{(2)}\)

\(^{(1)}\) Third report of the National Cholesterol Education Program (NCEP).
\(^{(2)}\) AACE Diabetes Guidelines. Endocr Pract. 2002;8 (Suppl 1)
Fixed Decision Points, Examples (cont)

The National Comprehensive Cancer Network endorses lowering the guideline cutoff value for PSA – Clinicians should consider biopsy at 2.5 ng/mL. (Previous guideline 4.0 ng/mL)

www.nccn.org/professionals/physician_ls/PDF/prostate_detection.pdf
Fixed Decision Point Guidelines are:

- Evidence based
- Based on large studies, often international
- Many times one procedure or similar procedures are used
- Naively assume that all methods obtain the same results.
- Can only be effective if methods are traceable
Consistent Decisions Require Internationally Comparable Results

- Today’s population is more mobile
- 1/3 of United States Companies transfer personnel to other countries during their career
- It is now common for Europeans to live in multiple countries during their lifetime.
Consistent Decisions Require Internationally Comparable Results

- Decision levels are independent of procedures used
- Today’s patient may not even live in the same country when he is being monitored
To Improve Effectiveness of Laboratory Medicine:

- The procedures used must
  - agree with each other with a high level of comparability
  - Be consistent over space and time
How Do We Make Results Consistent?

Each industry has a role!

- Laboratory
- EQAS Provider
- Manufacturer
- Reference Laboratory
- Reference Material Provider
If Any One is Not Involved, The Result Will Be Incomplete

Each industry has a role!
All Five Services Must

- Have an **ongoing** commitment to consistent results across time and space
- Be stakeholders in developing the processes
- Be open in the approach to standardization
- Be willing to share issues and reach a common resolution
Manufacturer responsibilities

Provide “Kits” that are sufficiently free of bias and precise (fit for purpose)

- Commutable calibrators for their systems
  - Across reagents and systems
  - Across value assignment processes
- Acceptable uncertainty
- Adequate imprecision
- Acceptable specificity, sensitivity, etc.
- Performance parameters are properly relayed to the user

Quality System and validations will include:

- Product and Working Calibrator commutability
- Rugged Manufacturing Processes (including Value assignment)
- Document realistic estimates of uncertainty
- Fit for purpose method design
- Fit for purpose method design and validation
- Accurate and clear instructions and Labeling that reflects typical performance
Reference Material Provider Must

Have an ongoing commitment to provide the material in question

- Each lot will be consistent or better in performance

- Provide a clear description of the intended use of a material.

- Provide understandable and thorough instructions for the material use

- Provide materials that are commutable considering their intended use

- Provide an understanding of the lot to lot variability of the material(s) they provide

Quality System and validations will include:

- Manufacturing and value assignment instructions that ensure consistency

- Provide a certificate with intended use and limitations and clear instructions for use

- Validation must include evidence of commutability

- Include in their certificates uncertainty estimates
Reference Laboratory Provides

Traceable results for reference materials, calibrators for kits and patient samples

- Valid recognized procedures reference procedures
- Performance and claims that are consistent or better than customer needs
- Reliable services that meet the customer’s needs

Quality System and validations will include:

- Validations demonstrating fit for purpose results
- Ongoing evidence that results are consistent with claims
- Reliable Quality Systems and timely service throughput
EQAS Laboratory

Committed to accurate assessment of the laboratory's performance

- Samples that are commutable
- Traceable target values
- Rapid feedback on performance

Quality System and validations will include:

- Consistently prepared reference materials validated as commutable
- Target Values based on reference procedures
- Timely and understandable reports reflecting performance of laboratory and peers
The Clinical Laboratory:

- Provide guidance regarding fitness for purpose needs for measurands
- Demand standardized results as a customer requirement to manufacturers and reference providers
- Provide feedback to manufacturers and reference providers as to needs for higher levels of standardization
- Establish and express the risk of not standardizing specific measurands (prioritization)
PSA: a Partial Success Story

1986 - First commercial immunoassay was approved by the FDA

1991 – 1993 recognition that different PSA procedures obtained different results based on relative sensitivities to PSA-ACT bound and F-PSA

1995 – Epitope mapping and inter-laboratory comparisons indicate that 90:10 mixtures of PSA-ACT and F-PSA improve test results obtained on patient samples
PSA Continued

1995 – Commutability studies using 90:10 Mixture demonstrates improved harmonization of patient results

1997 – NCCLS I/LA19-A (Primary Reference Preparations Used to Standardize Calibration of Immunoassays for Serum Prostate Specific Antigen Published
PSA Continued

1999 – Wadsworth Center reports on preparation and qualification of commutable survey samples

2000 – WHO 96/670 and 96/668, Reference Reagents for PSA and First IS for Free PSA and PSA (90:10) announced. Additional commutability data also published
<table>
<thead>
<tr>
<th>Requirement</th>
<th>Compliance</th>
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<tbody>
<tr>
<td>Measurand defined, Intended use (5.10), Scope (5.4)</td>
<td>Y</td>
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<tr>
<td>Clear definition of units (5.8.6)</td>
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<tr>
<td>Justification for choice (5.6), Commutability studies (5.8.7)</td>
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<tr>
<td>Validation (5.9)</td>
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<td>Description of specific characteristics (5.8)</td>
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<tr>
<td>Instructions for use: (5.11)</td>
<td>Y</td>
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<tr>
<td>Rugged Value Assignment process (Primary methods and not reliant on</td>
<td>Y</td>
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<td>commercial assays) (5.9.5)</td>
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<tr>
<td>Uncertainty of Measurement or Confidence Interval (5.8.10)</td>
<td>N</td>
</tr>
<tr>
<td>Warnings/ Safety Precautions (5.11.1)</td>
<td>Y</td>
</tr>
</tbody>
</table>
RESULTS

Manufacturers are now able to harmonize the results obtained by their kits.

These reference materials have facilitated the development of “equimolar” PSA test procedures.

Laboratories can obtain more consistent results over time and between locations.

Progress must continue - There is still no reference procedure for PSA.
Thank You For Your Attention

Rick