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 ≥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

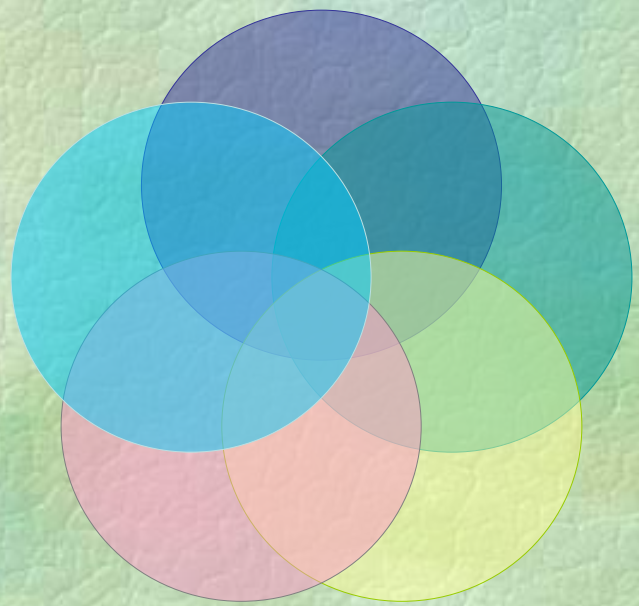
- Decision levels are independent of procedures used
- Today's patient may not even live in the same country when he is being monitored

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

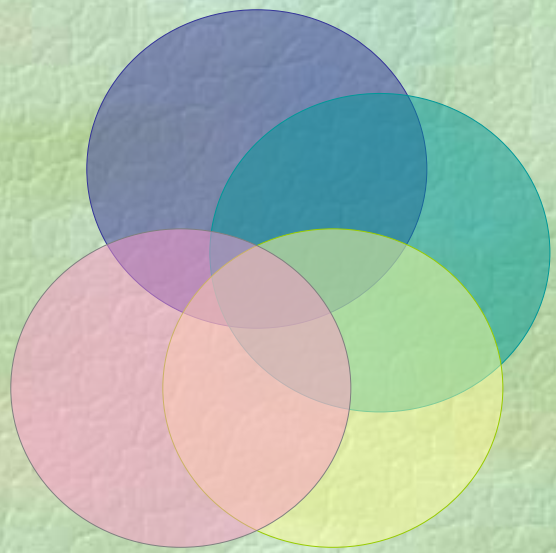
How Do We Make Results Consistent?

Each industry has a role!



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

Quality Attributes Compared to ISO 15194

Measurand defined , Intended use (5.10) ,Scope (5.4)	Y
Clear definition of units (5.8.6)	Y
Justification for choice (5.6), Commutability studies(5.8.7)	Y
Validation (5.9)	Y
Description of specific characteristics (5.8)	Y
Instructions for use: (5.11)	Y
Rugged Value Assignment process (Primary methods and not reliant on commercial assays) (5.9.5)	Y
Uncertainty of Measurement or Confidence Interval (5.8.10)	N
Warnings/ Safety Precautions (5.11.1)	Y

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