

# Assigning Traceable Values to Commercial IVD Calibrators

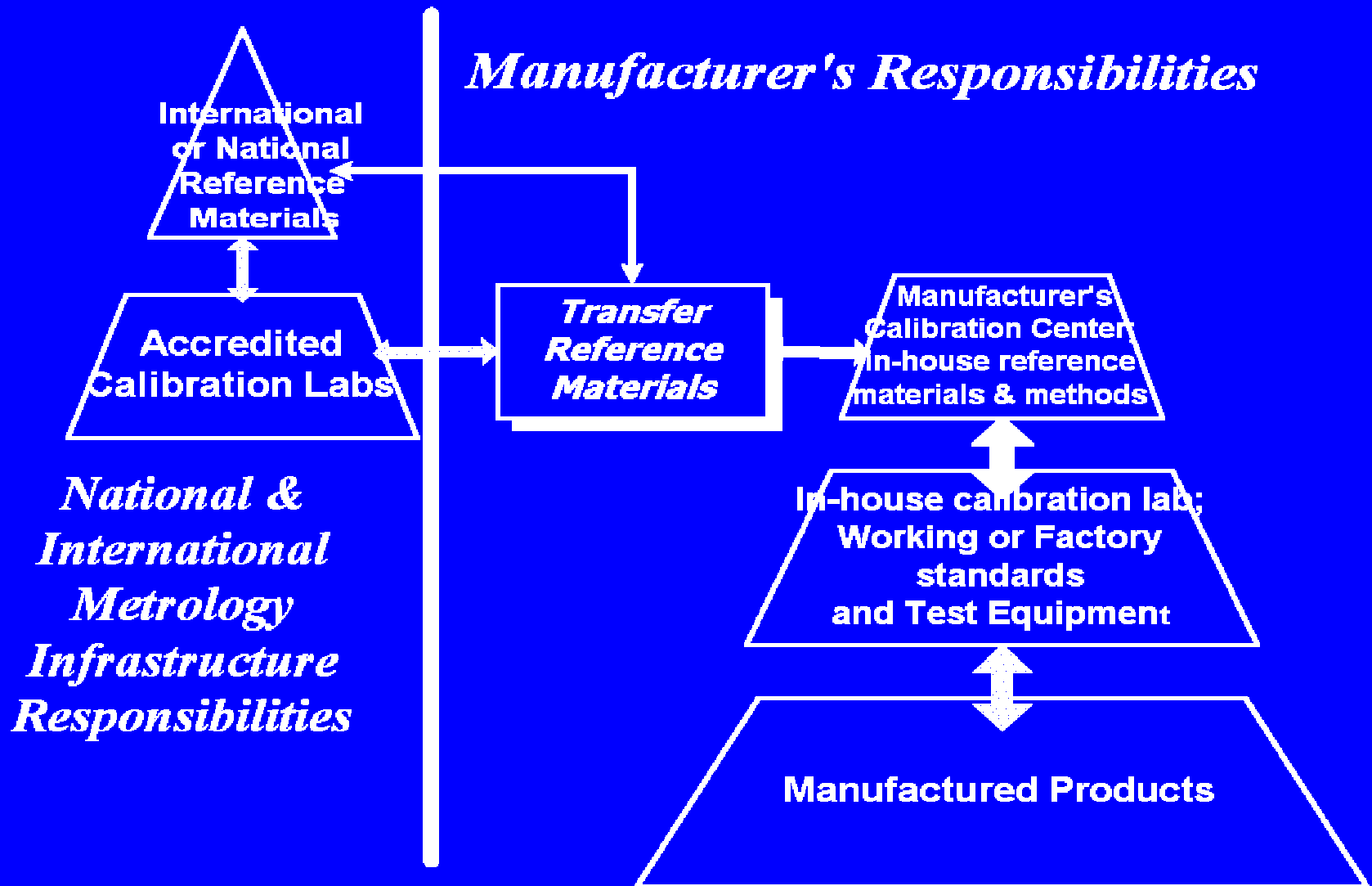
**Neil Greenberg, PhD, DABCC**

Ortho-Clinical Diagnostics, Rochester, NY

*US Delegate to ISO TC212 WG2*

*ADVAMED Delegate to JCTLM*

# Calibration Traceability ...*Basic Concepts*



## **Calibration Traceability... *ISO Standards***

- ISO/DIS 17511 Metrological traceability of values assigned to calibrators and control materials
- ISO/DIS 18153 Metrological traceability ... for catalytic concentration of enzymes in calibrators ...
- ISO 15193 Presentation of reference measurement procedures
- ISO 15194 Description of reference materials
- ISO/DIS 15195 Requirements for reference measurement laboratories in laboratory medicine

# **Calibration Traceability - *ISO/DIS 17511 Overview***

- Main Objective: Ensure TRUENESS of test results based on AVAILABLE internationally recognized reference materials or procedures, when using a routine (lower metrological order) commercial method
- Specifies process documentation needed when establishing traceable assigned values for analytes in a product calibrator
- Requires definition of an UNBROKEN series of linked steps, starting at higher order (available) reference methods or materials, moving stepwise downward to assigned values for product calibrators

# Calibration Traceability - *ISO/DIS 17511 Overview*

## Calibration Traceability is...

- A tool to ensure accurate results
- A process that relates measurement values to a reference standard
- A property of the test result
- Maintained through monitoring and correction over time

# Calibration Traceability - *ISO/DIS 17511 Overview*

## Calibration Traceability Requires...

- Definition of the measurand
  - ⇒ (Analyte)+(type of quantity)+(sample)+(units)
- Higher order Reference Systems

# Calibration Traceability - *Scope of ISO17511*

- Specifies how to assure metrological traceability of values assigned to calibrators and control materials intended to establish or verify trueness of a method.
- Applies to calibrators and some control materials sold by manufacturers
- 4.1.7 “The responsibility of the manufacturer for describing the traceability chain ...start(s) at the value of the manufacturer's product calibrator and end(s) at the metrologically highest reference used by the manufacturer.”

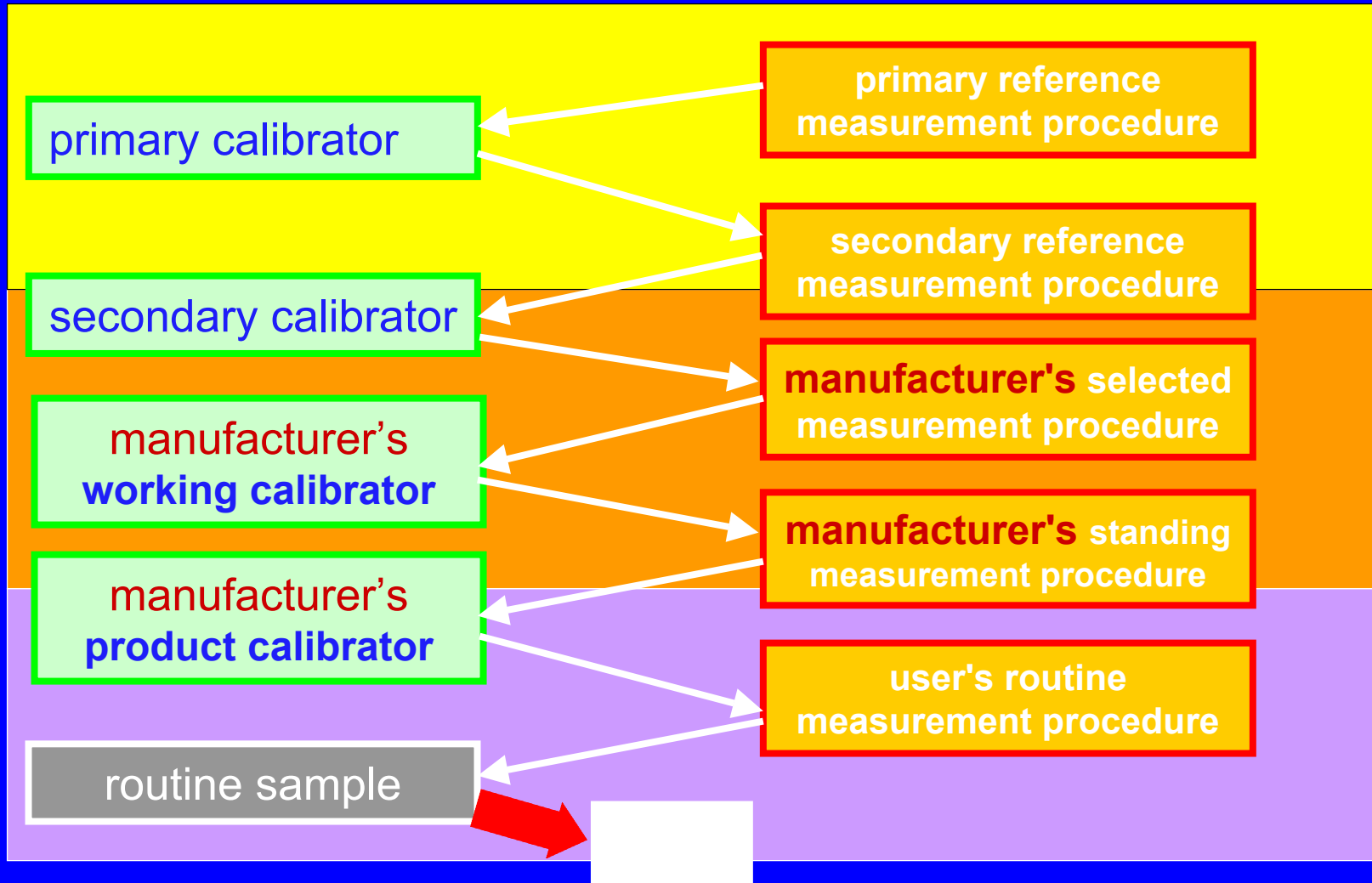
## ***ISO/CD 17511 - Specific Requirements***

- The traceability chain for a product calibrator must be described, from the highest metrological level down to the assigned value for the calibrator
- Each subsequent/lower level in a traceability hierarchy alternates between a measurement procedure and a measurement standard (i.e., a reference material)...
- A given measurement standard (*material*) with its assigned value at one level calibrates the measurement standard (*material*) at the next lower level, by applying a measurement procedure ...specified in a transfer protocol.



# Calibration Traceability

*Complete Hierarchy - Tracing to SI* [Courtesy - E. Voelkert, Roche Diagnostics, GmbH; modified from ISO/CD 17511, Figure 1]



# Calibration Traceability...Key Definitions

## *Primary Measurement Standard*

- Standard (material) that is ... widely acknowledged as having the highest metrological qualities and whose value is accepted without reference to other standards  
*(ISO 15194, 3.1)*
- Value is assigned either directly with a primary reference method, or indirectly by analysis of composition and impurities

# Calibration Traceability...Key Definitions

## *Secondary Measurement Standard*

- Standard (material) whose value is assigned by comparison to a primary standard

*(ISO 15194, 3.2)*

# Calibration Traceability...Key Definitions

## *Reference Measurement Procedure*

- Thoroughly investigated measurement procedure shown to yield values having an uncertainty...commensurate with the intended use, especially in assessing the trueness of other ... procedures ... and in characterizing reference materials.

*(ISO 15193, 3.7)*

# Calibration Traceability...Key Definitions

## *Primary Reference Measurement Procedure*

- Has the highest metrological qualities
- Detailed procedure and performance is completely described and understood
- Proved to be analytically specific
- Low uncertainty, with complete uncertainty statement available (in terms of SI units)
- Results accepted without reference to a measurement standard for the same quantity.

*(adapted from ISO 17511, 3.25)*

# Calibration Traceability...Key Definitions

## *Secondary Reference Measurement Procedure*

- Any Reference Measurement Procedures that are NOT primary, e.g.
  - Abell Kendall Cholesterol Method
  - GC or HPLC for many therapeutic drugs
  - CDC Hexokinase Glucose Method
  - CDC Urease Method for UREA
  - Atomic Absorption Spectrometry for various metals (Na, K, Ca, Mg, Mn, Fe)

# Calibration Traceability...Key Definitions

## *Selected Measurement Procedure*

- A measurement procedure that is calibrated by one or more primary or secondary calibrators (*ISO 17511, 4.2.2*)
- Can be a secondary reference method

# Calibration Traceability...Key Definitions

## *Manufacturer's Working Calibrator*

- A reference material that has its value assigned via measurement with a selected measurement procedure (*ISO 17511, 4.2.2*)
- Commonly known as “Master Calibrator Lot”



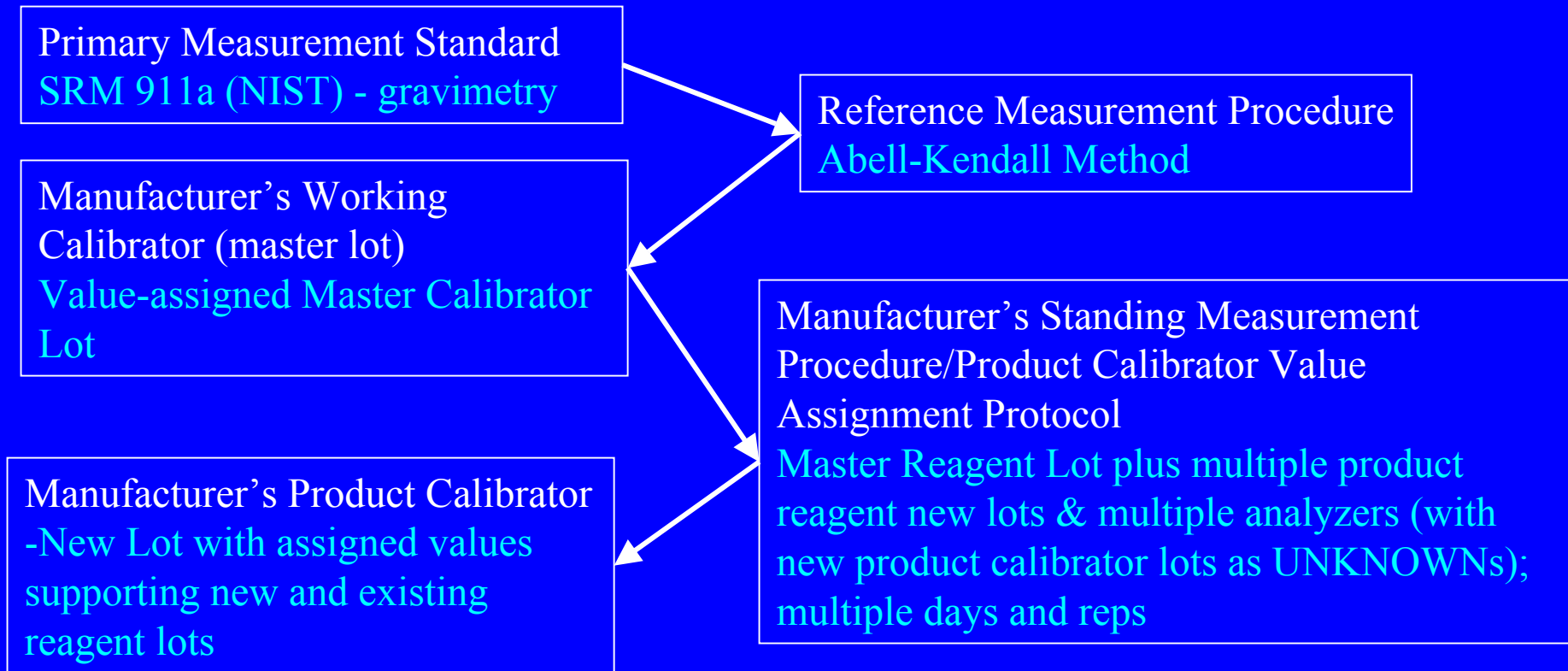
# Calibration Traceability...Key Definitions

## *Manufacturer's Standing Measurement Procedure*

- Is calibrated by Manufacturer's Working Calibrator (Master Lot)
- Can be based on same principle/method as the routine commercial method, but with lower uncertainty due to robust implementation (ie., replications; strict quality control measures)  
*(ISO 17511, 4.2.2)*

# Assigning Traceable Calibrator Values...

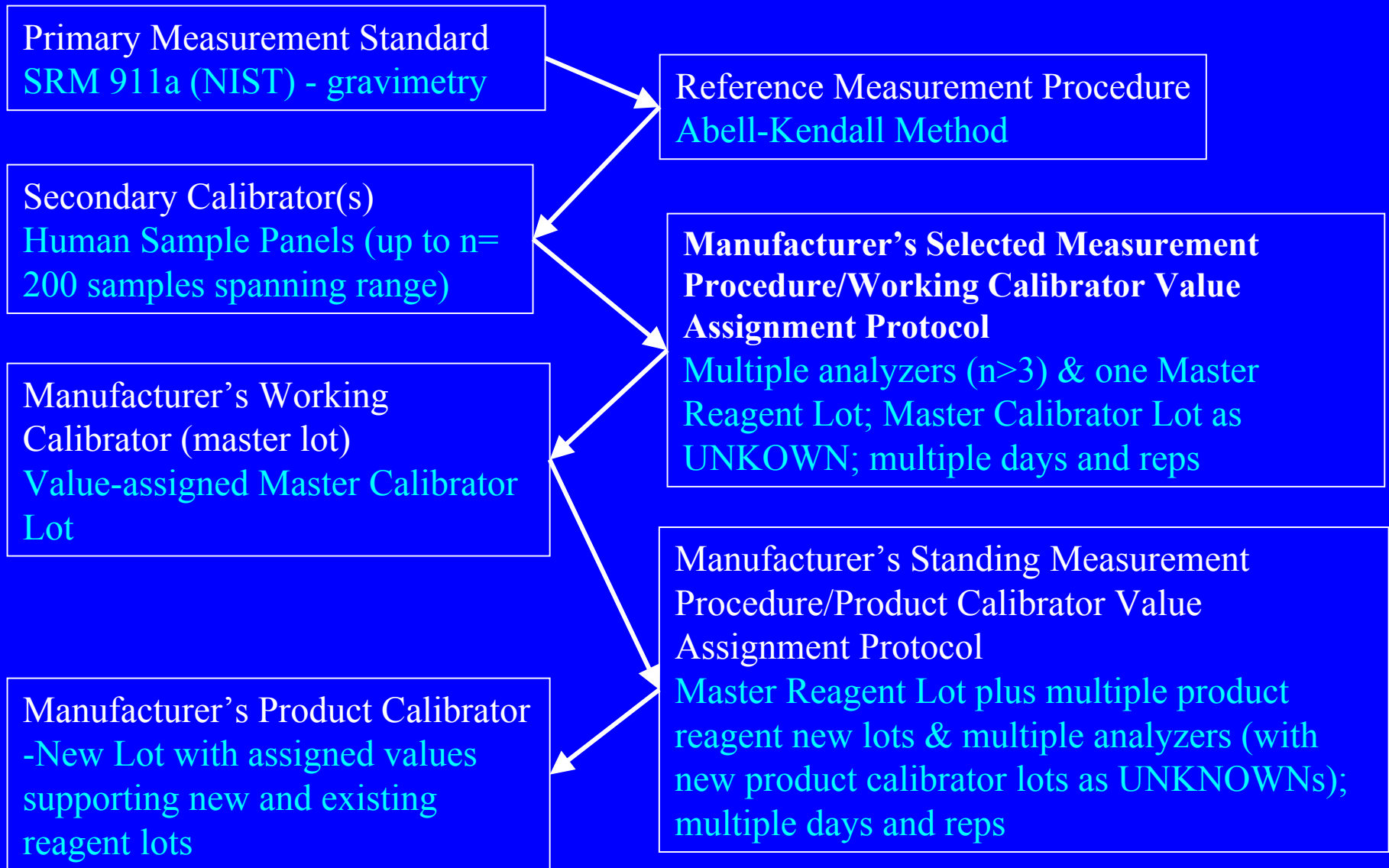
## Field Serum Cholesterol Method with no Matrix Effects



**Suitable for systems without calibrator matrix effects,  
and demonstrated commutability of Product Calibrator vs. Patients.**

# Assigning Traceable Calibrator Values...

## Example 1: *Commercial Cholesterol Method (with matrix effects)*

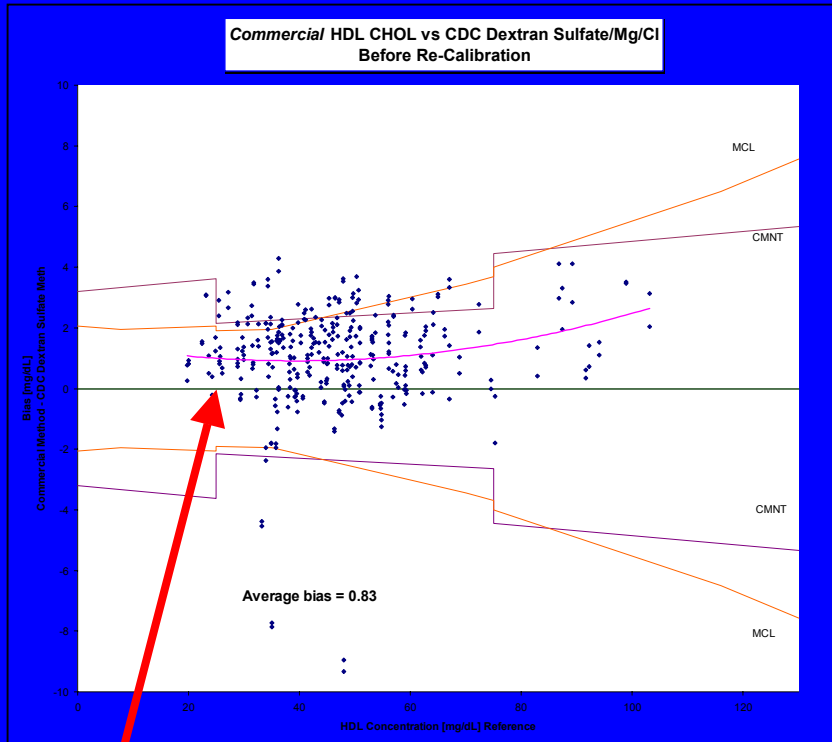


## **Assigning Traceable Calibrator Values...**

Calibration Traceability is...

- Maintained through monitoring and correction over time

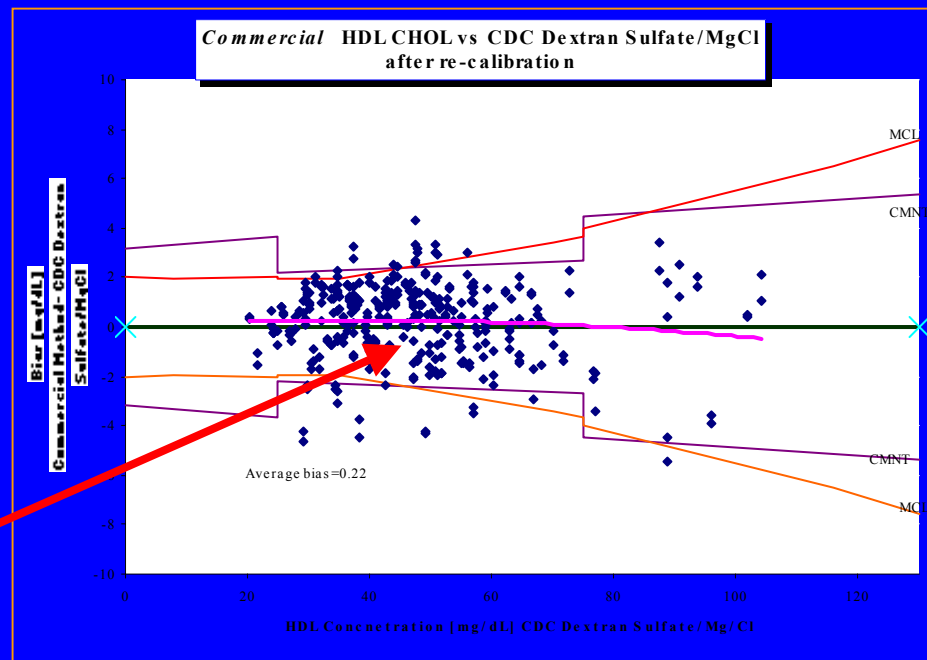
# Maintaining Traceability Over Time



Accuracy Not "zero"-bias

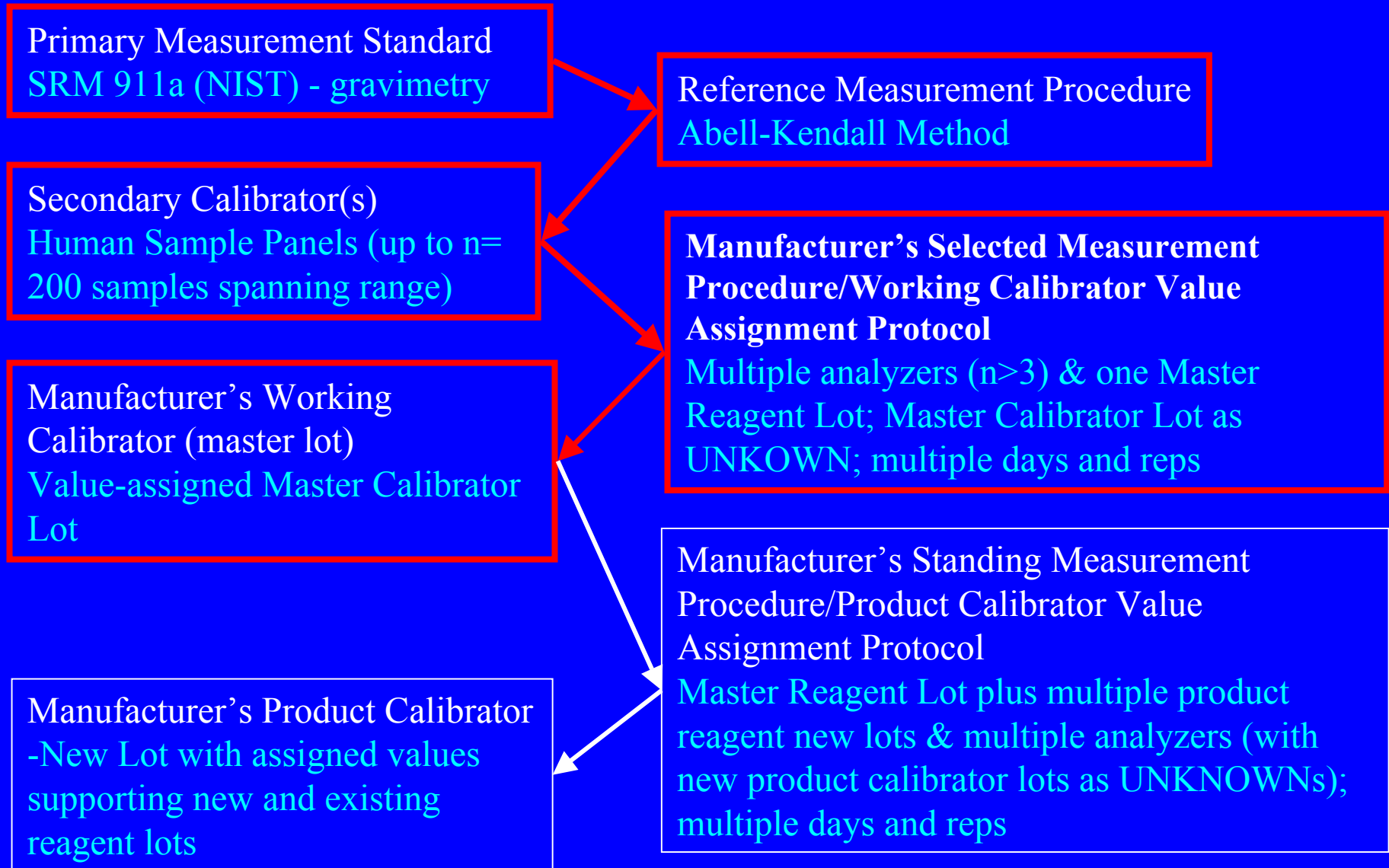
Accuracy "zero"-bias after  
calibration adjustment

- ◆ To verify assigned-value stability, \ Calibrator Master Lot values are re-checked periodically with human sample panels assayed with Reference Method.
- ◆ Master Calibrator Lot Assigned-values are adjusted as needed.



# Assigning Traceable Calibrator Values...

## Maintaining Traceability Over Time



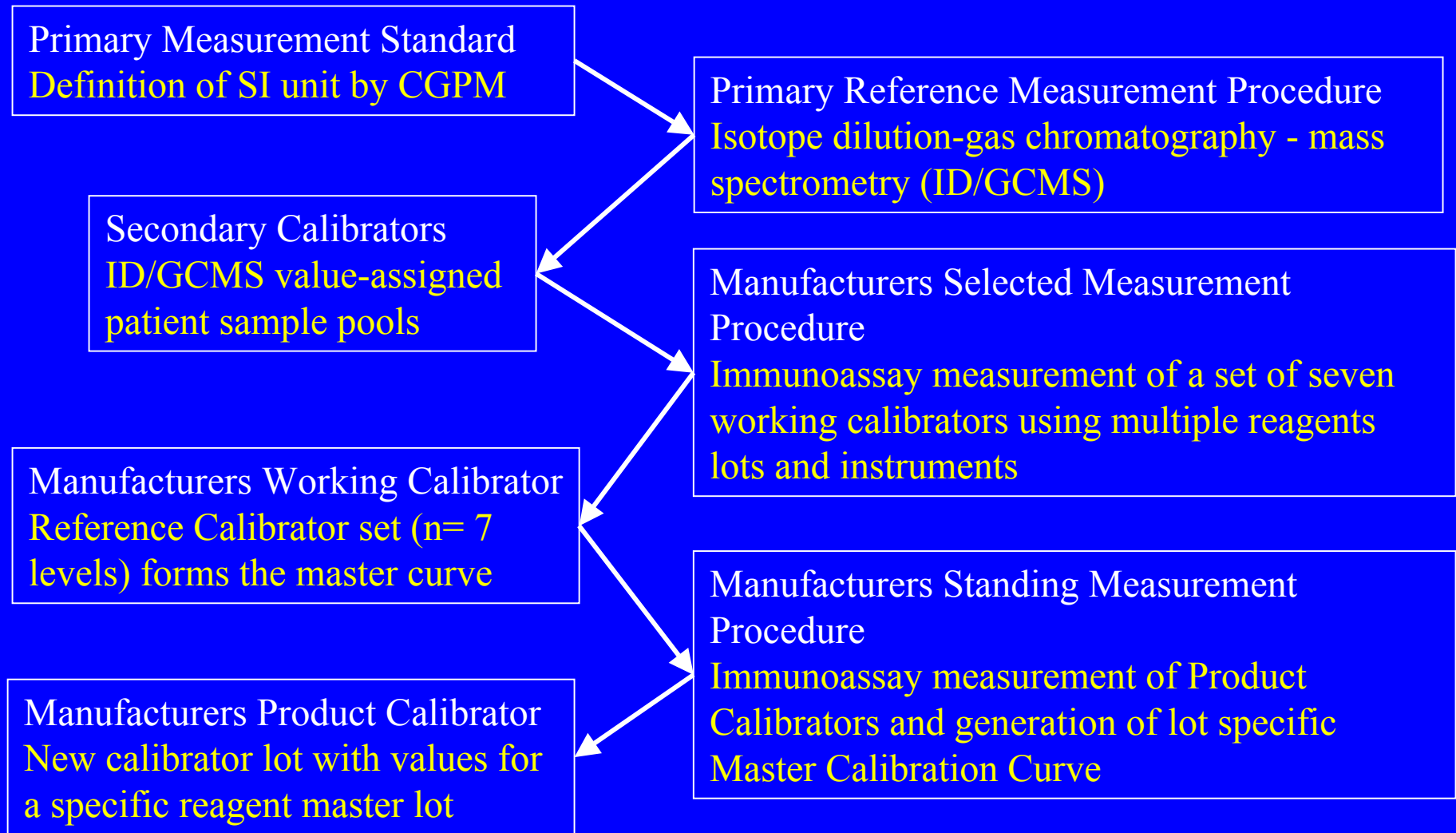
# Calibration Traceability

## *ISO/CD 17511 - Specific Requirements*

- The value assigned to a standard (*material*) at a given level ... (*has an*) uncertainty ...
  - includes inherited contributions from measurement standards and procedures at all higher levels of the calibration hierarchy.
  - additive and cumulative
  - Includes all measurement factors (e.g. pipetting, weighing)
  - Should be estimated (preferably) according to the GUM (*International Guide to Uncertainty in Measurement*)
  - Uncertainty information must be available, if requested

# Assigning Traceable Calibrator Values...

## Example 2: Commercial Cortisol Method





# Calibration Traceability

## - *Is Traceability to SI Required?*

- ISO 17511 Distinguishes between SI-traceable and non-SI-traceable quantities or measurands (analytes)
  - SI-traceable: physico-chemically well-defined substances - Type 'A' Quantities
    - Applies to ~25 analytes which are well defined, e.g. some electrolytes, metabolites, and hormones.
  - Non-SI-traceable: complex mixtures of different molecular entities, measured together because of a clinically relevant characteristic (e.g. lipoproteins, tumor markers) - Type 'B' Quantities
    - Applies to 100's of quantities/analytes

# **Calibration Traceability...Key Definitions**

## *International Conventional Calibrator*

- Calibrator with a value not metrologically traceable to SI;
- Assigned value is based on international agreement

## *International Conventional Reference*

### *Measurement Procedure*

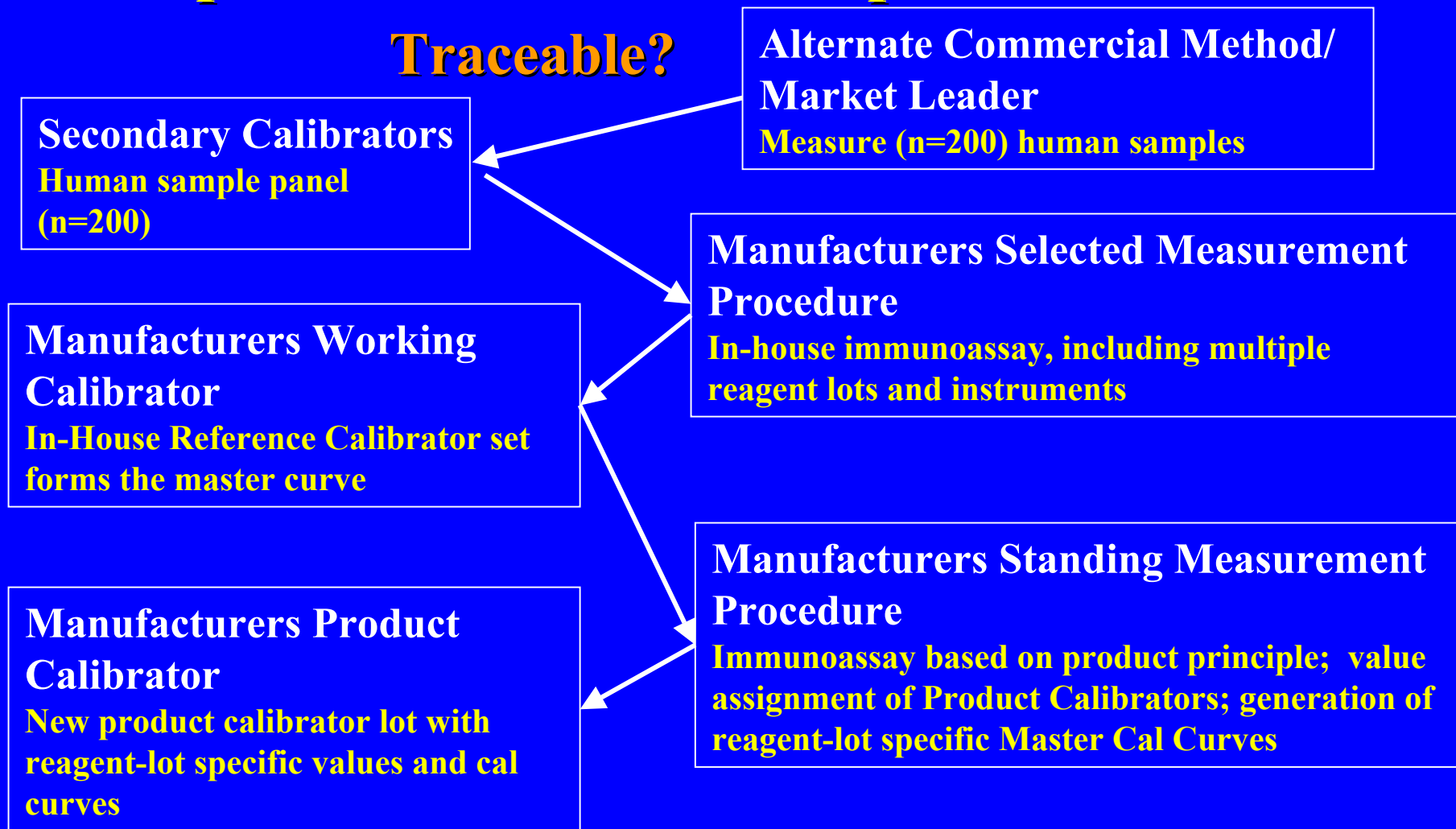
- Yields values not metrologically traceable to SI, but the values obtained are agreed as reference values by international agreement

## **Calibration Traceability - *Some Limitations***

- For a large number of analytes, there may not be traceability above the level of manufacturer's “selected measurement procedure” or a manufacturer's “working calibrator,” absent universally agreed reference methods and materials.  
- **The Standard recognizes this.**
- In such cases, TRUENESS might be defined only in terms of a given manufacturer’s in-house calibration hierarchy (working methods and/or materials) until a universally agreed reference measurement procedure and/or calibrator becomes available.

# Assigning Traceable Calibrator Values...

## Example 3: *Commercial Troponin I Method*



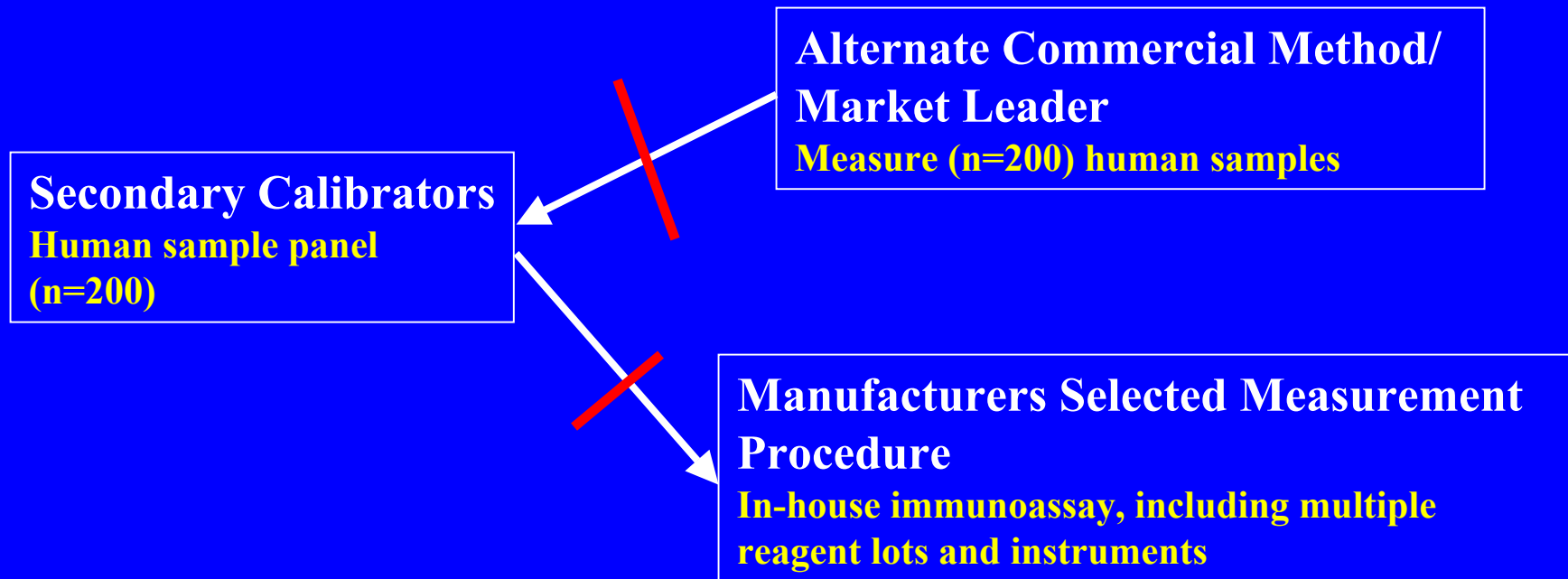
## **Example 3: *Commercial Troponin I Method***

### **What is the calibrator traceable to?**

- Alternate Commercial Method - Market Leader?
- Selected Measurement Procedure?
- Working Calibrator?
- Something Else?

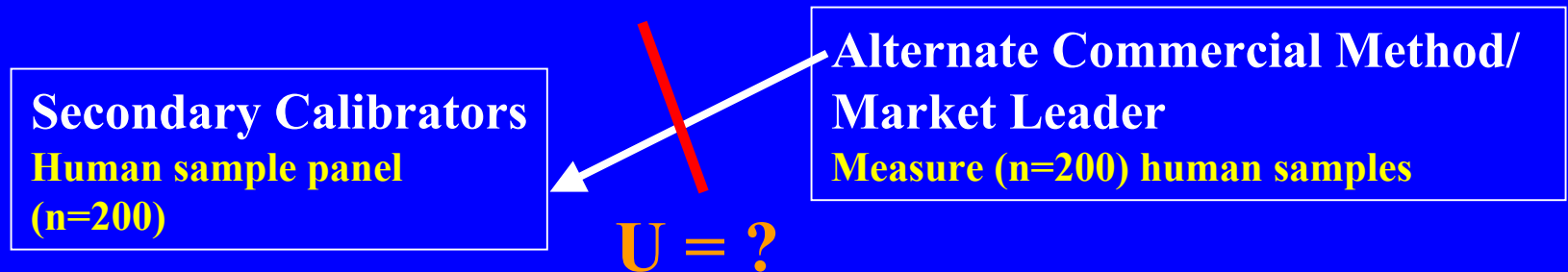
# Example 3: *Commercial Troponin I Method*

**Beware and Avoid Lateral Traceability!**



# Example 3: *Commercial Troponin I Method*

## Beware and Avoid Lateral Traceability!

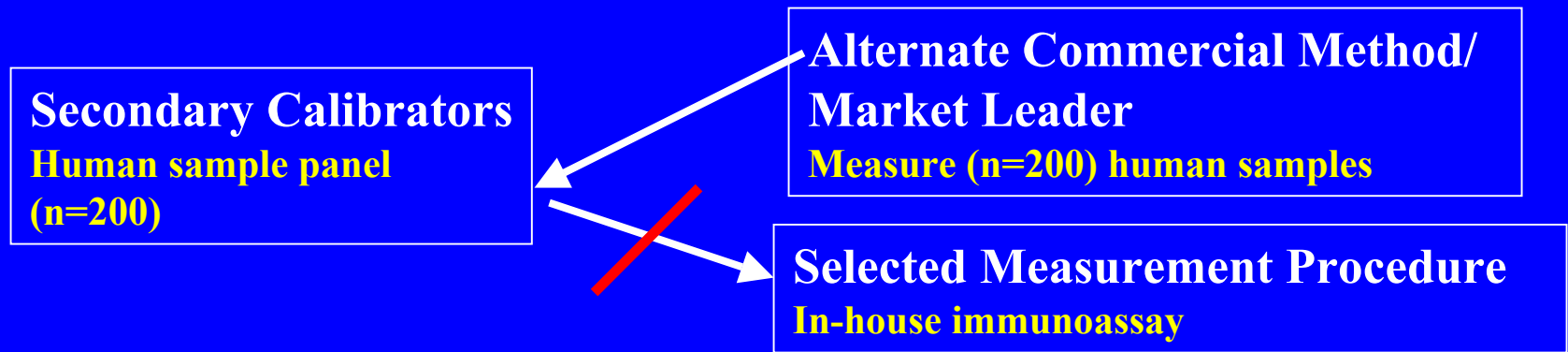


### Points to Consider & Questions to Ask...

- Frequency of method comparison between Alt Commercial Method & in-house Immunoassay (Selected Method)?
  - ◆ Once? More often?
- Is variation of Alternate Commercial Method controlled and known?
  - If NO, Alt Com Method is at SAME METROLOGICAL LEVEL as Manufacturer's Method in routine customer use

# Example 3: *Commercial Troponin I Method*

## Beware and Avoid Lateral Traceability!



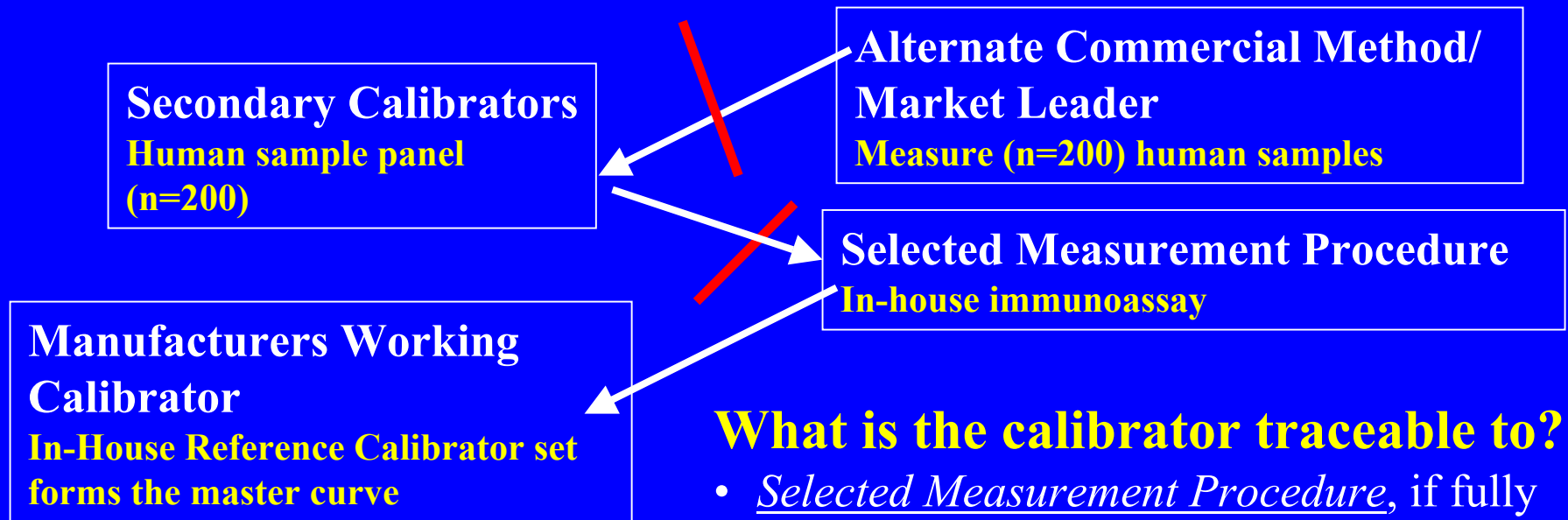
## Points to Consider/Questions to Ask...

- Alternate Commercial Method - NOT a Higher Order method
- Selected Measurement Procedures are calibrated with a Secondary Calibrator or higher, or International Conventional Calibrator.
- Is the Human Sample panel (n=200) with values measured by the Alt Commercial Method actually a Secondary Calibrator set?
  - ⇒ **NO! Secondary Calibrators can only be value-assigned against methods calibrated either with Primary Calibrators or Conventional International Calibrators.**



# Example 3: *Commercial Troponin I Method*

## Beware and Avoid Lateral Traceability!



### What is the calibrator traceable to?

- Selected Measurement Procedure, if fully validated and variation in assigning values to working calibrators is known, or...
- Working Calibrator, if retained for longterm use, & stability monitored and controlled ; no longterm reference back to Selected MP or higher.

# **Calibration Traceability Requirements - *Recommendations for Manufacturer Documentation***

Calibration Traceability tech report - include in Calibrator Product Technical File - for each analyte/method/system combination supported. Document...

- Calibrator Value Assignment process map
  - Follow format in ISO/CD 17511, e.g. Fig. 1
- Descriptions of measurement procedures (including protocols) & reference materials applied at each level
- Reference to process/test method validation reports - each measurement step; each value transfer step
- Estimates of uncertainties at each level
  - Calculations of combined uncertainty
- References to documentation/literature publications describing relevant reference materials and methods
- Certificates from higher order reference materials

# **Calibration Traceability Requirements - *Recommendations for Manufacturer Documentation***

Other items to include in calibrator technical file...

- Procedures for replacement of intermediate elements of traceability chain (e.g. working calibrators or master calibrator lots) when supplies/inventories are depleted or expired
- Methods/procedures and certificates of analysis from 3<sup>rd</sup> party labs and/or suppliers of reference materials.
  - Include providers of assayed patient sample panels used as secondary or working calibrators.
- In-house or external Reference Labs certification of conformity to ISO/CD 15195, if available

# Calibration Traceability Requirements - *Recommendations for Manufacturer Documentation*

- Information to be Provided on Product Labeling
  - Provide brief, high level summary of Calibrator Value Assignment process chain map
  - Most important to identify highest order available reference methods and materials applied
  - If applicable, define and explain known biases vs. reference methods
  - Define commutability of the calibrator
    - Define which methods the assigned values apply to
    - Important to limit commutability claims only to methods for which the calibrator is validated for use

# Calibration Traceability Requirements - *Recommendations for Manufacturers \_\_ Key Learnings*

- Use ISO language correctly
- Traceability requires re-verification over time
  - Unbroken series of linked steps
  - Avoid claiming traceability to metrological levels not supported by ongoing process to re-verify
- Always trace to higher order (materials & methods)
  - Beware Lateral Traceability
- Uncertainty is additive; fewer steps is best
- When standards don't exist, traceability only to manufacturer's in-house reference system is OK
- Validate each step in the chain

# **Calibration Traceability - *Selected References***

- 1) Guide to the Expression of Uncertainty in Measurement (GUM), 1<sup>st</sup> Edition, ISO, Geneva, 1995**
- 2) International Vocabulary of Basic and General Terms in Metrology (VIM), 2<sup>nd</sup> Edition, ISO, Geneva, 1993**
- 3) Buettner J., Reference Methods as a Basis for Accurate Measuring Systems. Eur J Clin Chem Clin Biochem, 1991; 29: 223-235**
- 4) Dybkaer R., Reference materials - A main element in a coherent reference measurement system. Eur J Clin Chem Clin Biochem 1991; 29:241-246**
- 5) Eurachem. Quantifying Uncertainty in Analytical Measurement. 1<sup>st</sup> edit. 1995. [Eurchem/CITAC Guide, 2<sup>nd</sup> Edition, 1999 (under development)]**
- 6) National Institute of Standards and Technology. (Taylor BN, Kuyatt CE) Guidelines for evaluating and expressing uncertainty of NIST measurement results. NIST Technical Note 1297. Washington: US Department of Commerce. 1994.**
- 7) ILAC-G2:1994, Traceability of Measurements, ILAC, 1996  
[<http://www.ilac.org>]**

# Assigning Traceable Values to Commercial IVD Calibrators

**Neil Greenberg, PhD, DABCC**

Ortho-Clinical Diagnostics, Rochester, NY

*US Delegate to ISO TC212 WG2*

*ADVAMED Delegate to JCTLM*

## **Thank You!**

**[ngreenbe@ocdus.jnj.com](mailto:ngreenbe@ocdus.jnj.com)**