

IFCC General Conference 2018

The International Consortium for Harmonization of Clinical Laboratory Results

Greg Miller
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USA

10th – 11th November 2018
Hotel Novotel Budapest City, Hungary

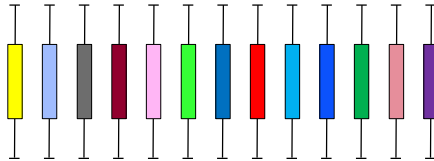
Advancing excellence in laboratory medicine for better healthcare worldwide



- ❖ Why was the ICHCL created
- ❖ What does the ICHCLR do

What is harmonization

Equivalent results among different measurement procedures for the same laboratory test



Standardization:

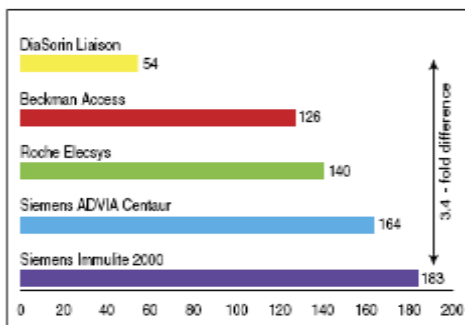
equivalent results are achieved by metrological traceability to a fit-for-purpose higher order reference system

Equivalent

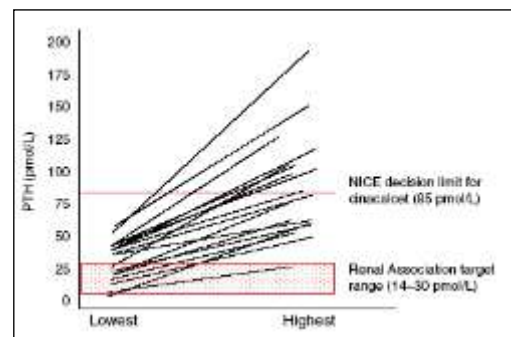


- **Equivalent does not mean identical**
- **Equivalent means within a total allowable error consistent with an acceptable risk of harm from decisions based on a lab test result**

The problem we need to fix!

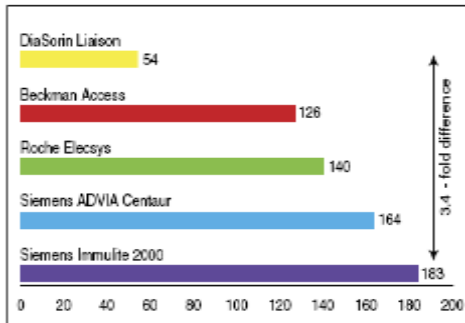


PTH concentration (pmol/L) in a single patient.



Treatment variation caused by comparing highest and lowest PTH concentrations in 18 patients.

How did this happen?



PTH concentration (pmol/L) in a single patient.

1. **Non-commutable reference materials**

2. **Methods do not measure the same quantity**

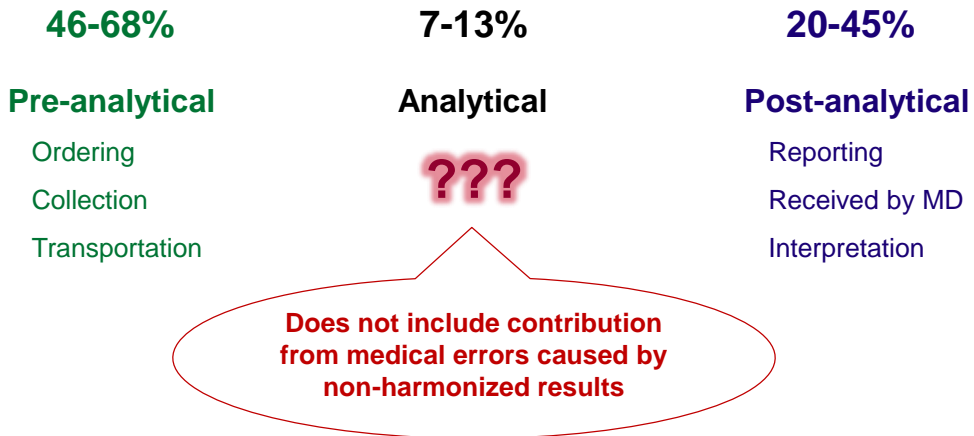
IFCC is addressing this problem

Almond et al. Ann Clin Biochem 2012; 49: 63–67.

For results to be harmonized / standardized:

- ✓ **All IVD medical devices must have metrological traceability to the same higher order reference system**
 - **must be fit-for-purpose**
- ✓ **All IVD medical devices must measure the same measurand**
 - **must have adequate selectivity for the measurand**

Source of lab testing errors



Plebani. Ann Clin Biochem 2010;47:101-10.

What is metrological traceability?

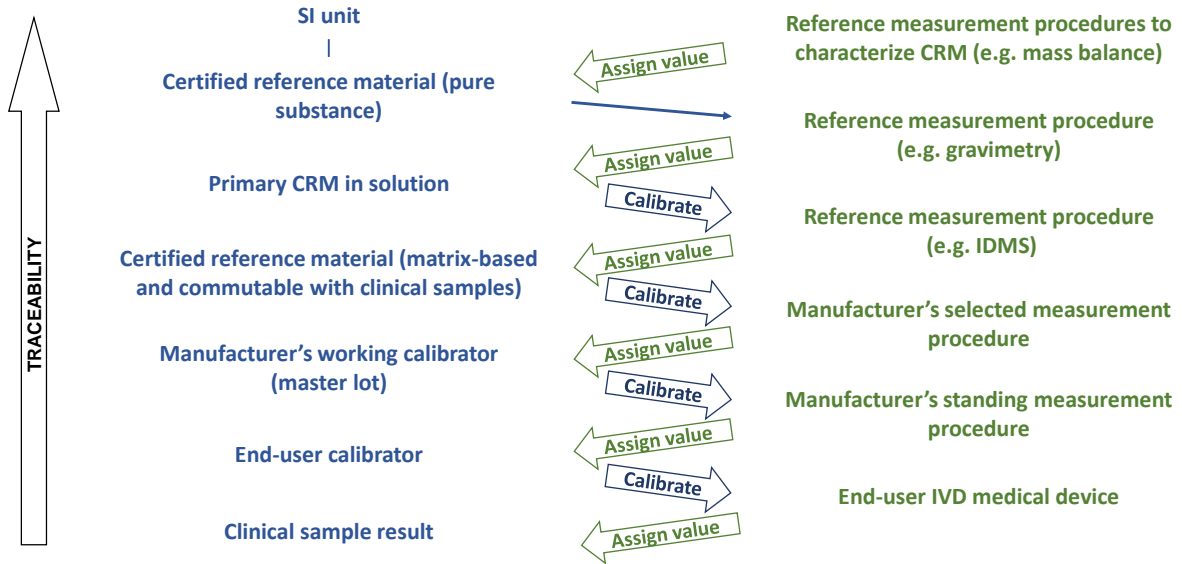
A

An unbroken chain of calibrations from a clinical sample result to a higher order reference system.

B

A process that specifies the source of calibration for an IVD medical device.

Metrological traceability: an unbroken chain of calibrations from a clinical sample result to a higher order reference system component (ISO 17511)



Commutability is?

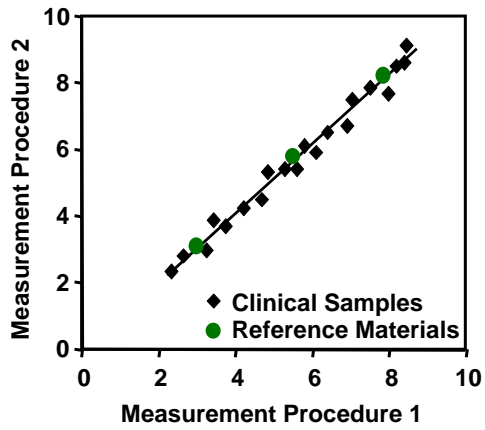
A

A property of results from measurement procedures.

B

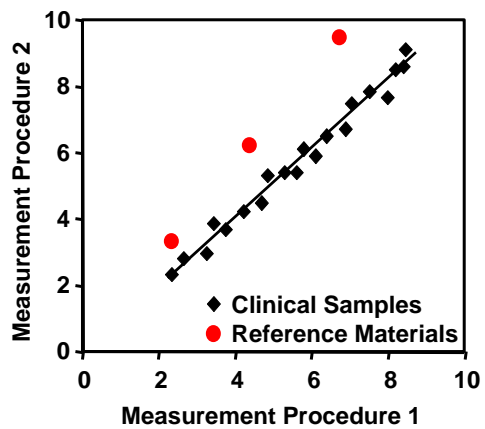
A property of a reference material for use with measurement procedures.

Commutable



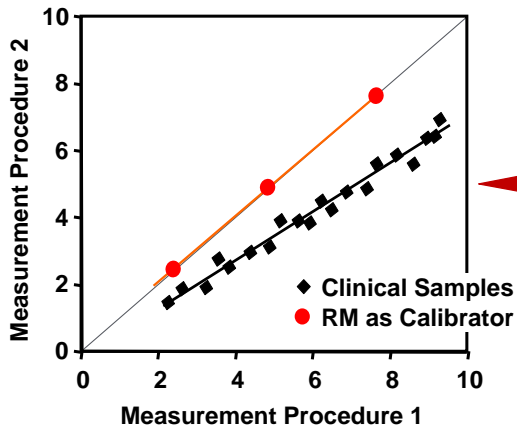
RM and CS results have the same relationship between measurement procedures

Non-Commutable

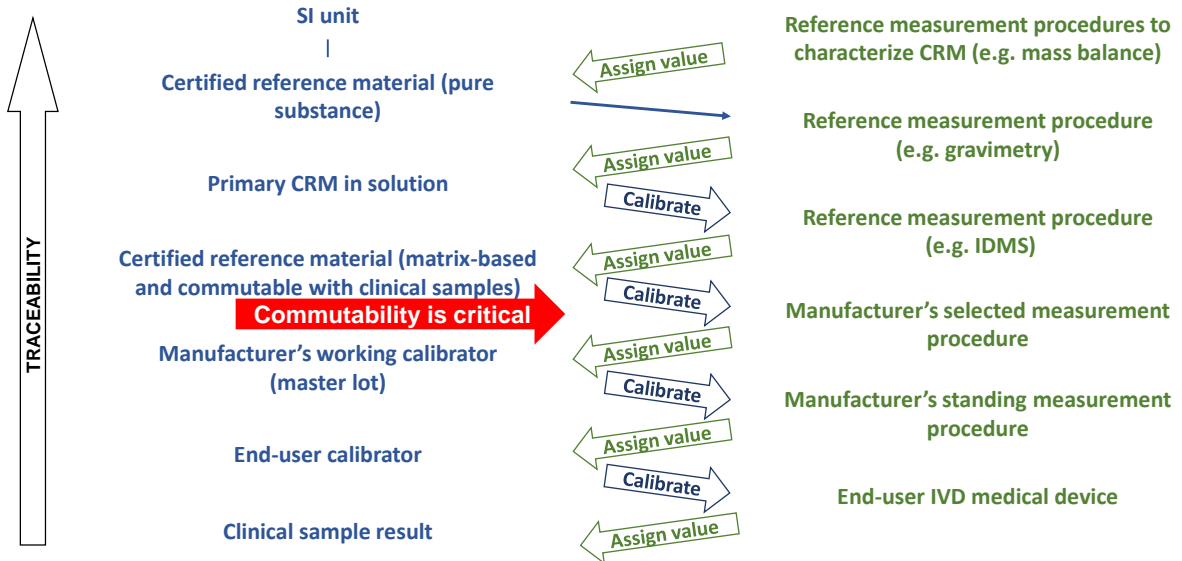


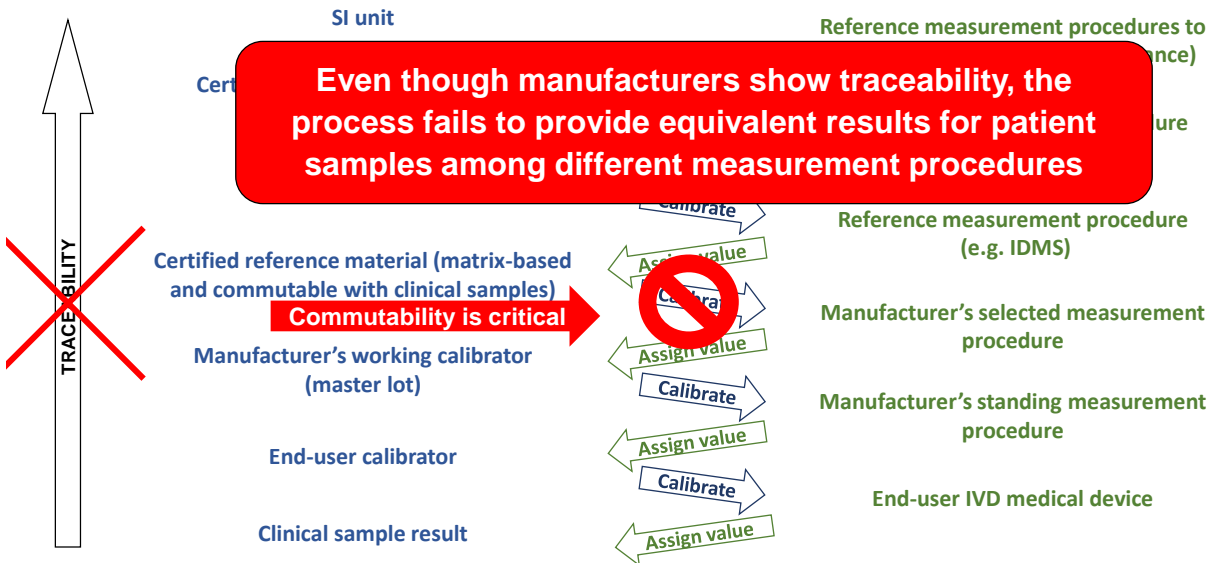
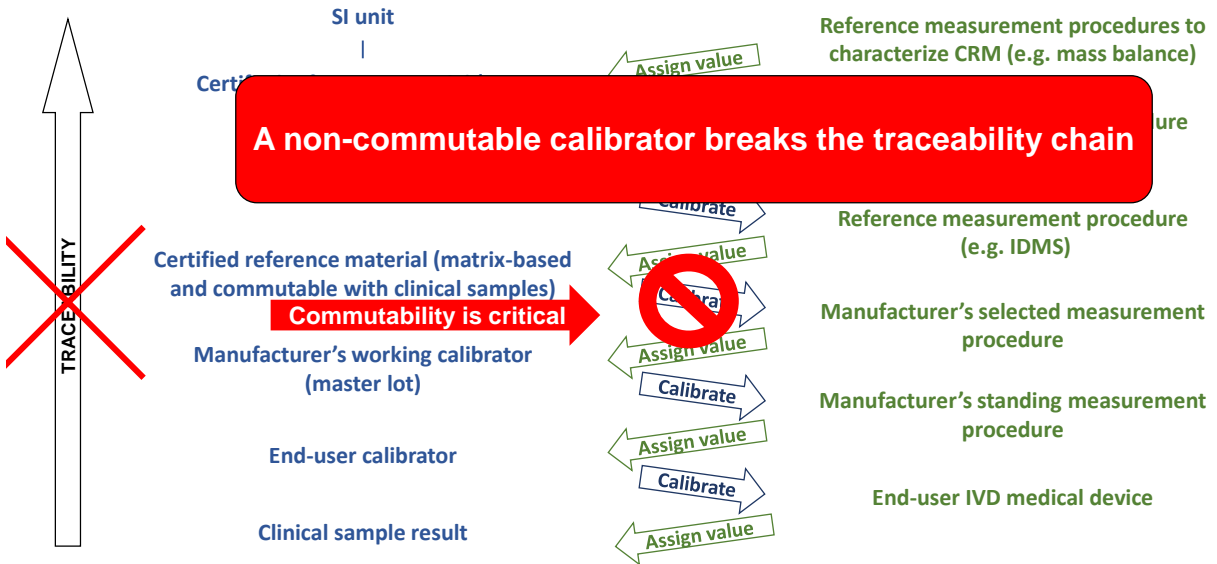
RM and CS results have a different relationship between measurement procedures

Non-Commutable Calibrator



causes CS results to be different





Commutability is important for:

Matrix-based CRMs used as calibrators

EQA materials used to assess harmonization

IFCC Working Group on Commutability

Recommendations for assessing commutability:

Part 1: general experimental design; *Clin Chem* 2018;64:447-54

Part 2: using the difference in bias between a reference material and clinical samples; *Clin Chem* 2018;64:455-64

Part 3: using the calibration effectiveness of a reference material; *Clin Chem* 2018;64:465-74



Approximately 100 measurands have reference system components

*** Not all matrix-based CRM's listed have been validated for commutability ***

**JCTLM now requires commutability assessment for
matrix-based CRMs**

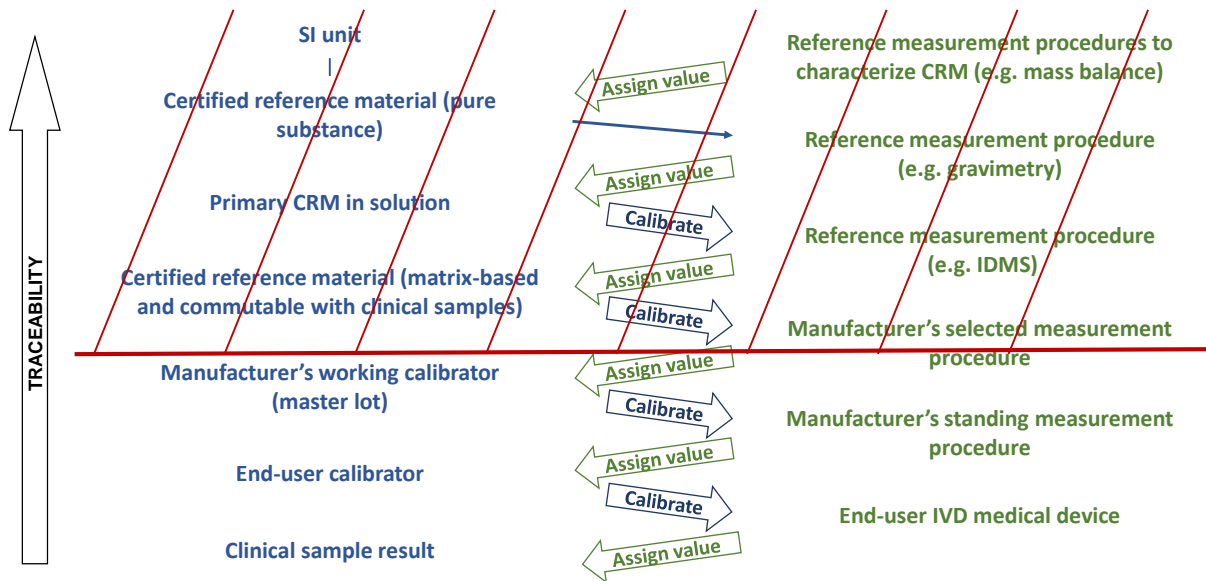


WHO International Standards and Reference Preparations have **historically not been validated for commutability and many are not commutable**

**WHO Consultation on Commutability of WHO Biological Reference Preparations for In Vitro Detection of Infectious Markers.
WHO Headquarters, Geneva, 18-19 April, 2013**

http://www.who.int/bloodproducts/norms/BS_2230_Addendum1_Commutability.pdf

Higher order references do not exist or are not fit-for-purpose for a large number of measurands



What happens when metrological traceability ends at the IVD manufacturer's master lot of working calibrator?

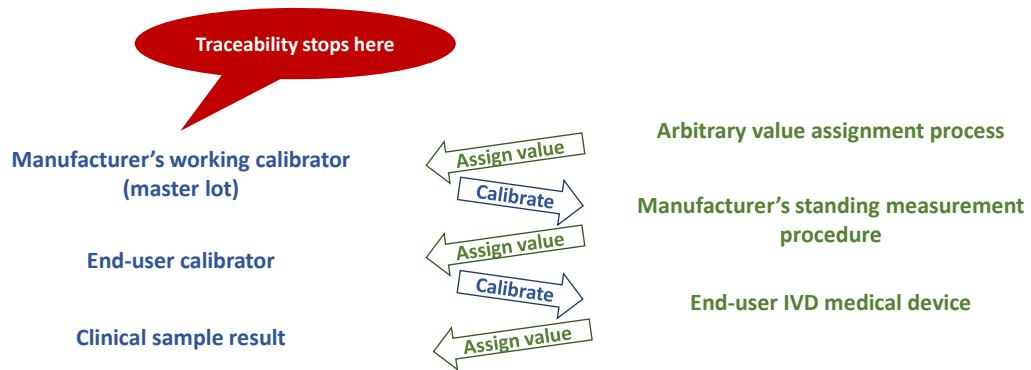
A

Clinical sample results can be different from different IVD medical devices.

B

Test results interpreted using decision values in guidelines can cause different medical actions for the same condition.

Still traceable; however different working calibrators cause different results from different end-user IVD medical devices



Key challenge #1: non-commutable matrix-based CRMs are used

***** such a reference system is not fit-for-purpose *****

Key challenge #2: there is no reference system for a large number of measurands

- ❖ Why was the ICHCL created
- ❖ What does the ICHCLR do

How do we address the situation when there is no suitable CRM or RMP?

A

Modify the clinical decision values for use with different IVD medical devices.

B

Apply a harmonization protocol to make the results equivalent from different IVD medical devices.



Harmonization

**One of the most important challenges
in laboratory medicine**

Clinical Chemistry 57:8
1108–1117 (2011)

Special Report

Roadmap for Harmonization of Clinical Laboratory Measurement Procedures


W. Greg Miller,^{1*} Gary L. Myers,² Mary Lou Gantzer,³ Stephen E. Kahn,⁴ E. Ralf Schönbrunner,⁵
Linda M. Thienpont,⁶ David M. Bunk,⁷ Robert H. Christenson,⁸ John H. Eckfeldt,⁹ Stanley F. Lo,¹⁰
C. Micha Nübling,¹¹ and Catharine M. Sturgeon¹²

- ✧ International Forum organized by AACC in October, 2010
- ✧ Agreement that metrological traceability to higher order CRM and RMP is preferred when possible
- ✧ Endorsed a harmonization approach when no CRM or RMP

The Roadmap

Develop an infrastructure to coordinate harmonization activities world wide:

1. Prioritize measurands by medical importance
2. Coordinate the work of different organizations
3. Promote processes for harmonization of results



The screenshot shows the homepage of the International Consortium for Harmonization of Clinical Laboratory Results. The header features a logo with test tubes and a search bar. The main navigation menu includes links for HOME, ABOUT, OVERSIGHT, MEASURANDS, RESOURCES, and CONTACT US. The main content area has a large title, 'The International Consortium for Harmonization of Clinical Laboratory Results', and two sections: 'OUR VISION' and 'OUR MISSION'. The background image shows a laboratory technician in a white coat and gloves holding two test tubes.

International Consortium
for Harmonization of Clinical Laboratory Results

Search

HOME ABOUT OVERSIGHT MEASURANDS RESOURCES CONTACT US

The International Consortium for Harmonization of Clinical Laboratory Results

OUR VISION

- ✓ Clinical laboratory test results will be equivalent independent of the clinical laboratory that produced the results

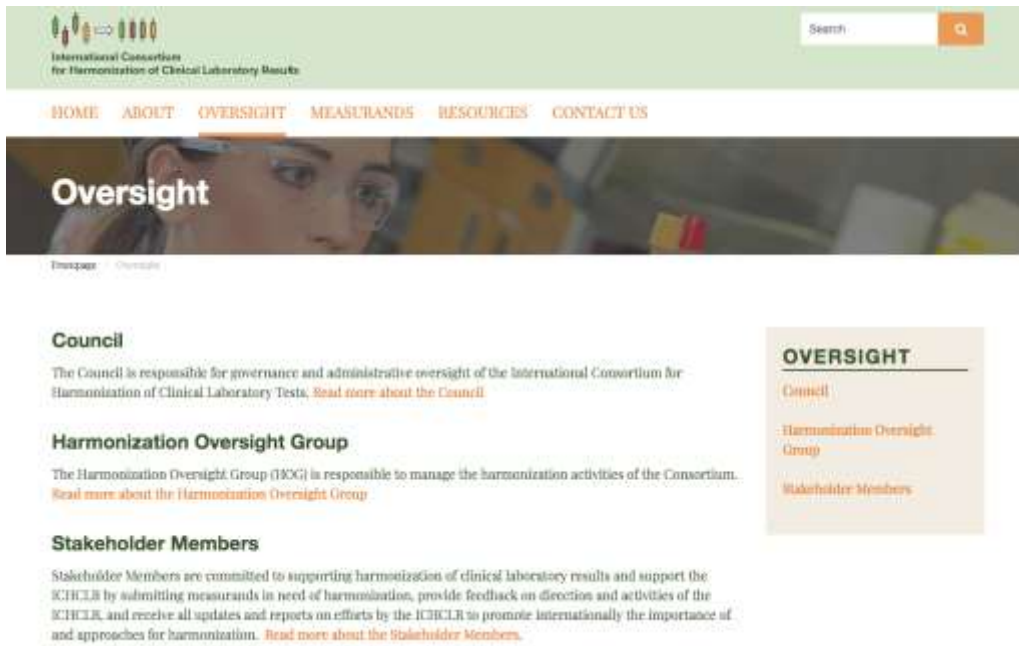
OUR MISSION

- ✓ To provide a centralized process to organize global efforts to achieve harmonization of clinical laboratory test results

www.harmonization.net

ICHCLR Timeline

- 2010** – AACC Conference recommends formation to address unmet needs; AACC supports an Organizing Committee
- 2011** – Roadmap recommendations in *Clinical Chemistry*
- 2013** – ICHCLR begins operation; AACC is Secretariat
- 2013** – www.harmonization.net is launched
- 2013** – ICHCLR/AACC/AdvaMedDx conference on regulatory issues; 2014 follow up meeting
- 2013** – NWIP to ISO TC-212 for a harmonization protocol
- 2017** – Insoft hosts www.harmonization.net
- 2018** – IFCC becomes Secretariat for ICHCLR



The screenshot shows the website for the International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR). The header includes the organization's name and a search bar. The main navigation menu includes: HOME, ABOUT, OVERSIGHT, MEASURANDS, RESOURCES, and CONTACT US. The current page is titled "Oversight" and features a large image of a person wearing a headset. The content area is divided into three sections: Council, Harmonization Oversight Group, and Stakeholder Members. A sidebar on the right lists the main navigation items under the heading "OVERSIGHT".

Council
The Council is responsible for governance and administrative oversight of the International Consortium for Harmonization of Clinical Laboratory Tests. [Read more about the Council.](#)

Harmonization Oversight Group
The Harmonization Oversight Group (HOG) is responsible to manage the harmonization activities of the Consortium. [Read more about the Harmonization Oversight Group.](#)

Stakeholder Members
Stakeholder Members are committed to supporting harmonization of clinical laboratory results and support the ICHCLR by submitting measurands in need of harmonization, provide feedback on direction and activities of the ICHCLR, and receive all updates and reports on efforts by the ICHCLR to promote internationally the importance of and approaches for harmonization. [Read more about the Stakeholder Members.](#)

OVERSIGHT

- Council
- Harmonization Oversight Group
- Stakeholder Members

www.harmonization.net



Overview Measurands

This section provides information on the status of harmonization or standardization of measurands. Priority based on medical impact are provided for measurands for which harmonization is needed or that have an incomplete or inactive implementation of harmonization activity. Additional information regarding the harmonization status and medical impact is available by clicking on the measurand name. Information on reference materials, reference measurement procedures, and reference laboratory services is provided by the links in the JCTLM column. Links to organizations actively addressing harmonization of particular measurands are provided for additional information on those projects.

Comments on measurand status can be sent using the [Contact Us](#) tab. [Download the form to submit a new measurand.](#)

Summary of Measurand Harmonization Activities

www.harmonization.net

Measurand	Unit	Matrix	Medical Impact of Harmonization *	Harmonisation Status *	Resources *	Organization *
Alkaline Phosphatase (ALP)		Serum	Medium	Incomplete	JCTLM	IFCC
Alanine Aminotransferase (ALT)		Serum	Medium	Incomplete	JCTLM	IFCC; EU-JRC (IRMM)
Albumin		Urine		Active		NKDEP; IFCC; JSCC
Albumin		Serum	Medium	Needed	JCTLM	
Alpha Fetoprotein		Serum		Adequate		
Amylase		Serum		Active	JCTLM	IFCC
Anti-DNA antibody (qualitative)		Serum	Low			
Anti-DNA antibody (quantitative)		Serum	Medium	Needed		
Anti-Hepatitis C Virus antibody (Anti-HCV Ab)		Serum		Adequate		
Antinuclear antibody (ANA)		fixed cells or serum		Active		International Workshops and Consensus Conferences
Antistreptolysin O		Serum	Low	Needed		
Aspartate Aminotransferase (AST)		Serum	Medium	Incomplete	JCTLM	IFCC
B-type Natriuretic Peptide (BNP)		Serum	High	Needed		

Measurand	U _i	Matrix	Medical Impact of Harmonization ^a	Harmonisation Status ^a	Resources ^a	Organization ^a
Alkaline Phosphatase (ALP)		Serum				IFCC
Alanine Aminotransferase (ALT)		Serum				IFCC EU-JRC (HMN)
Albumin		Urine				NKDEP ^b IFCC JSCC
Albumin		Serum				
Alpha Fetoprotein		Serum				
Amylase		Serum				IFCC
Anti-DNA antibody (qualitative)		Serum				
Anti-DNA antibody (quantitative)		Serum				
Anti-Hepatitis C Virus antibody (Anti-HCV Ab)		Serum				
Antinuclear antibody (ANA)		fixed cells or serum				International Workshops and Consensus Conferences
Antistreptolysin O		Serum				
Aspartate Aminotransferase (AST)		Serum				IFCC
B-type Natriuretic Peptide (BNP)		Serum	High	Needed		

B-type Natriuretic Peptide (BNP)

B-Type natriuretic peptide (BNP) is a marker of cardiac function and is used for diagnosis, risk stratification and follow-up of patients with chronic or acute heart failure. Laboratory assessments have determined that the agreement among results for different measurement procedures is not suitable to support uniform clinical decision values for interpretation of results (1,2). Both a candidate reference material (2) and a candidate reference measurement procedure (3) have been recently reported.

References


1. Clerico A, Zaninotto M, Prontera C, et al. State of the art of BNP and NT-proBNP immunoassays: The CardioOrmoCheck study. Clin Chim Acta 2012;414:712-9.
2. Semenov AG, Tamun NN, Apple FS, et al. Searching for a BNP standard: Glycosylated proBNP as a common calibrator enables improved comparability of commercial BNP immunoassays. Clin Biochem 2017;50:181-5.
3. Torra AF, Groves K, Biesenbruch S, et al. A candidate liquid chromatography mass spectrometry reference method for the quantification of the cardiac marker 1-32 B-type natriuretic peptide. Clin Chem Lab Med 2017;55:1397-1406.

Measurand	U _i	Matrix	Medical Impact of Harmonization ^a	Harmonisation Status ^a	Resources ^a	Organization ^a
Alkaline Phosphatase (ALP)		Serum	Medium	Incomplete	JCTLM	IFCC
Alanine Aminotransferase (ALT)		Serum	Medium	Incomplete	JCTLM	IFCC EU-JRC (HMN)
Albumin		Urine		Active		NKDEP ^b IFCC JSCC
Albumin					JCTLM	
Alpha Fetoprotein						
Amylase					JCTLM	IFCC
Anti-DNA antibody						
Anti-DNA antibody (quantitative)		Serum	Medium	Needed		
Anti-Hepatitis C Virus antibody (Anti-HCV Ab)		Serum		Adequate		
Antinuclear antibody (ANA)		fixed cells or serum		Active		International Workshops and Consensus Conferences
Antistreptolysin O		Serum	Low	Needed		
Aspartate Aminotransferase (AST)		Serum	Medium	Incomplete	JCTLM	IFCC
B-type Natriuretic Peptide (BNP)		Serum	High	Needed		

- JCTLM listing
- Links to commutable EQA programs

Measurand	Matrix	Medical Impact of Harmonization *	Harmonization Status *	Resources *	Organization *
Alkaline Phosphatase (ALP)	Serum	Medium	Incomplete	ICTLM	IFCC
Alanine Aminotransferase (ALT)	Serum	Medium	Incomplete	ICTLM	IFCC; EU-JRC (HMN)
Albumin	Urine		Active		NKDEP; IFCC; ISCC
Albumin					
Alpha Fetoprotein					
Amylase					IFCC
Anti-DNA antibody (qualitative)					
Anti-DNA antibody (quantitative)	Serum	Medium	Needed		
Anti-Hepatitis C Virus antibody (Anti-HCV Ab)	Serum		Adequate		
Antinuclear antibody (ANA)	fixed cells or serum		Active		International Workshops and Consensus Conferences
Antistreptolysin O	Serum	Low	Needed		
Aspartate Aminotransferase (AST)	Serum	Medium	Incomplete	ICTLM	IFCC
B-type Natriuretic Peptide (BNP)	Serum	High	Needed		

Organizations with harmonization/standardization activities for the measurand


Search

[HOME](#) [ABOUT](#) [OVERSIGHT](#) [MEASURANDS](#) [RESOURCES](#) [CONTACT US](#)

Resources

Below are resources for global harmonization of clinical laboratory measurement procedures.

Content

Council/HCG Meeting Summaries

Council/HCG Meeting Summaries

Read more >

Content

ICHCLIR Activity Reports

ICHCLIR Activity Reports

Read more >

Document

International Consortium for Harmonization of Clinical Laboratory Results: Operating Procedures

Read more >

Document

Toolbox of technical procedures for developing a process to achieve harmonization for a measurand

Read more >

www.harmonization.net

An integrated protocol to assess potential effectiveness of candidate reference measurement procedures, reference materials and clinical sample panels for harmonizing results.

Clinical Chemistry 60:7
945–953 (2014)

Drug Monitoring and Toxicology

Harmonization of Measurement Results of the Alcohol Biomarker Carbohydrate-Deficient Transferrin by Use of the Toolbox of Technical Procedures of the International Consortium for Harmonization of Clinical Laboratory Results

Cas Weykamp,^{1*} Jos Wielders,² Anders Helander,³ Raymond F. Anton,⁴ Vincenza Bianchi,⁵ Jan-Olof Jeppsson,⁶ Carla Siebelder,¹ John B. Whitfield,⁷ and François Schellenberg⁸ on behalf of the IFCC Working Group on Standardization of Carbohydrate-Deficient Transferrin

A harmonization protocol based on panels of clinical samples when there are no certified reference materials or reference measurement procedures.



Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

A "Step-Up" approach for harmonization

Katleen Van Uytvanghe, Linde A. De Grande, Linda M. Thienpont *

Laboratory for Analytical Chemistry, Faculty of Pharmaceutical Sciences, Gent University, Harelbekestraat 72, 9000 Gent, Belgium

Clin Chim Acta 2014; 432: 62-67

IFCC Committee for Standardization of Thyroid Function Tests developed much of the science supporting a practical harmonization protocol.

Clinical Chemistry 63:7
1248-1260 (2017)

Endocrinology and Metabolism

Harmonization of Serum Thyroid-Stimulating Hormone Measurements Paves the Way for the Adoption of a More Uniform Reference Interval

Linda M. Thienpont,^{1,2*} Katleen Van Uytendaele,³ Linde A.C. De Grande,¹ Dries Reynders,⁴ Barnali Das,⁵ James D. Faix,⁶ Finlay MacKenzie,⁷ Brigitte Decallonne,⁸ Akira Hishinuma,⁹ Bruno Lapauw,¹⁰ Paul Taelman,¹¹ Paul Van Crombrugge,¹² Annick Van den Bruel,¹³ Brigitte Velkeniers,¹⁴ and Paul Williams¹⁵
on behalf of the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)

Can the TSH approach be generalized?

A

Yes

B

No

Clinical Chemistry 63:7
1184-1186 (2017)

Editorials



Harmonization: Its Time Has Come

W. Greg Miller^{1*}



**REVISION
NOT PUBLISHED**

**17511 next revision: includes a harmonization protocol
as one approach to achieve metrological traceability**



NEW PROJECT
NOT PUBLISHED
NOT AN ISO STANDARD

NP 21151: *In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for **international harmonization protocols** intended to establish metrological traceability of values assigned to product (end user) calibrators and human samples*

New project approved (2014)



Committee draft (2018)

-- vote --

HERE 

Draft international standard (2019)

-- vote --

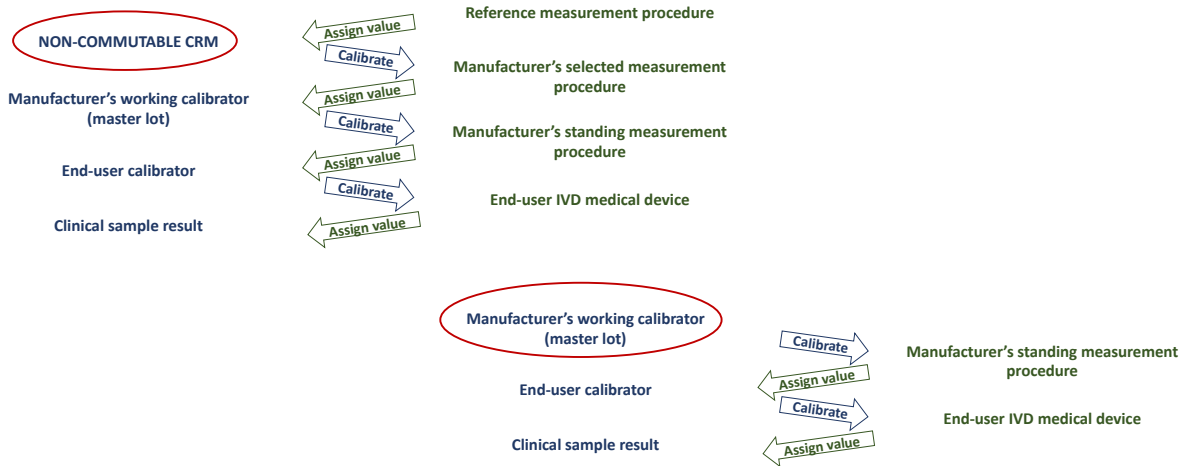
[Final draft international standard]

-- vote --

International standard

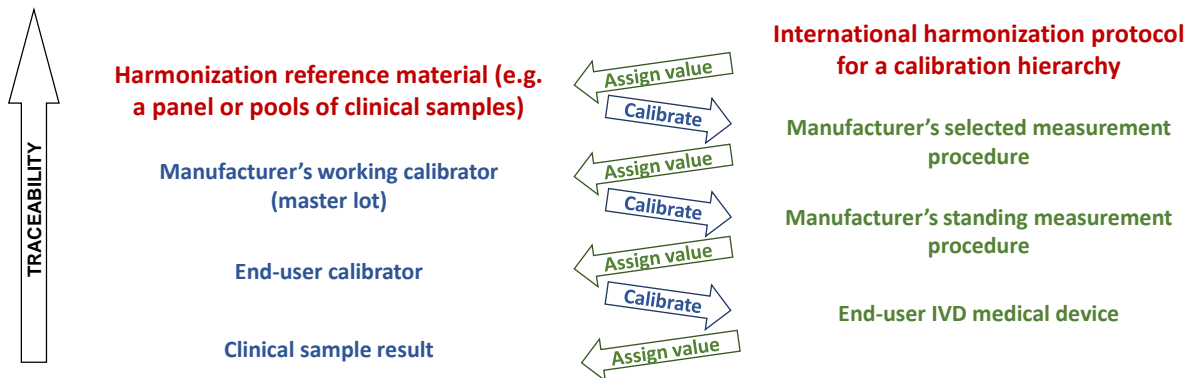
Metrological traceability: harmonization protocol

Replace these inadequate calibration hierarchies ...



Metrological traceability: harmonization protocol

... with metrological traceability to a harmonization protocol





Steps in the ISO NP 21151 **Draft International Standard**

**NOT PUBLISHED
NOT AN ISO STANDARD**

Harmonization protocol: qualify measurement procedures for inclusion

1. Measure the same quantity (molecular form)

- Correlated measurement responses
- Similar specimen specific influences = similar selectivity for the measurand

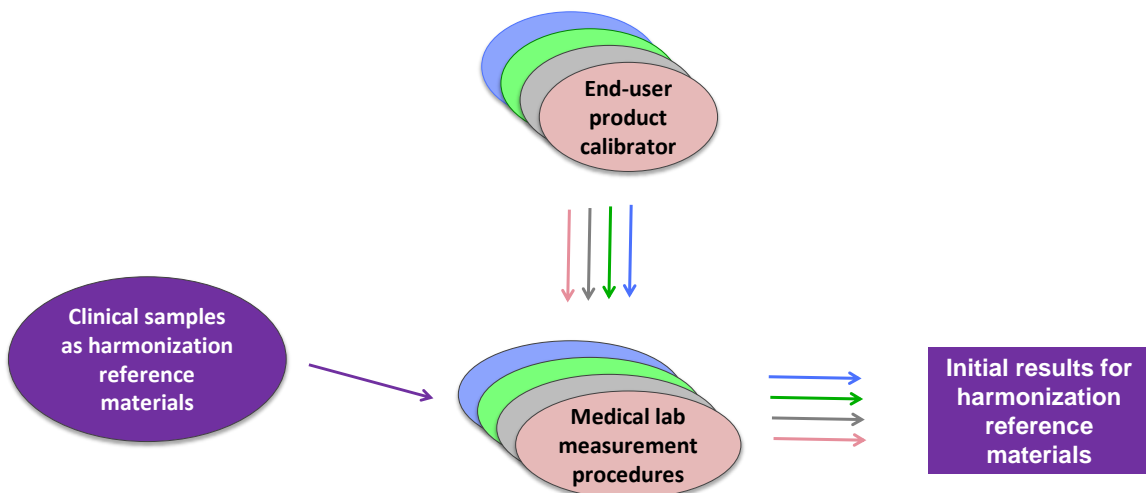
2. Adequate performance

- Precision
- Proportional response over concentration

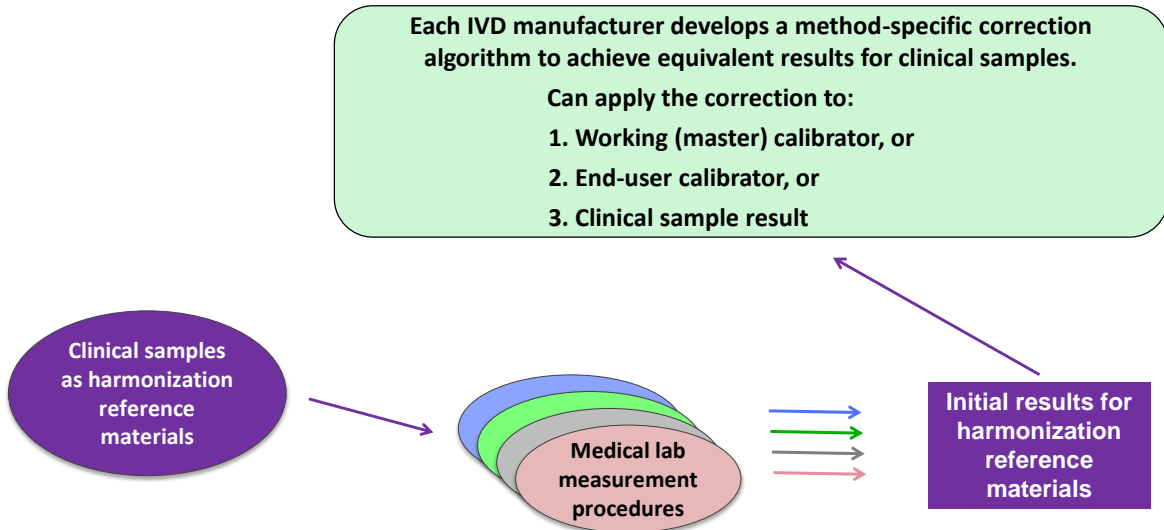
Harmonization protocol: reference materials



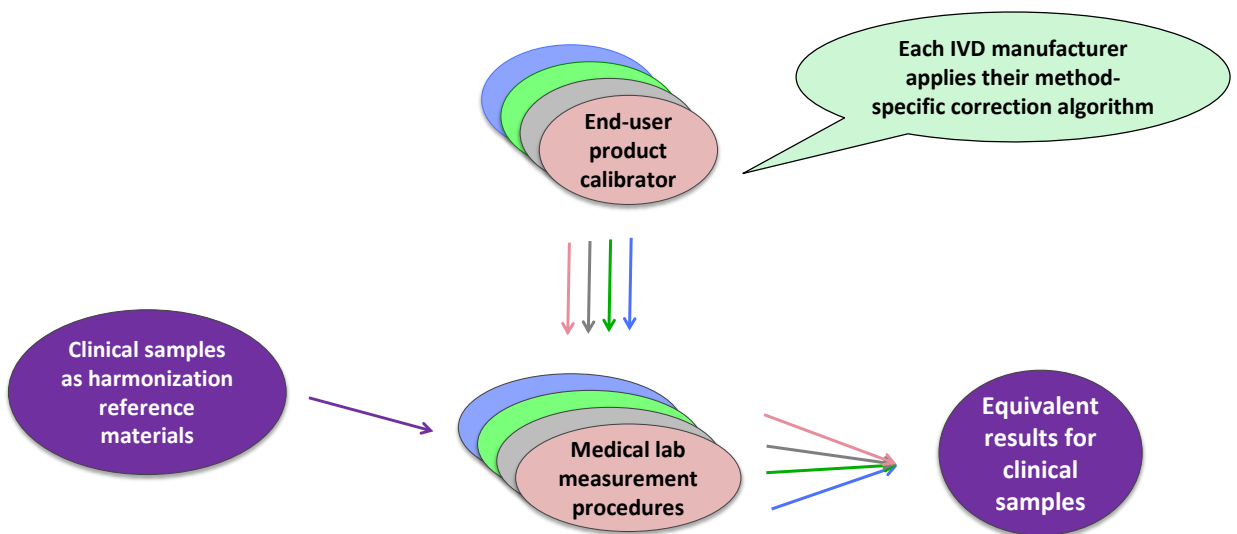
Harmonization protocol: initial results



Harmonization protocol: IVD-specific correction algorithm



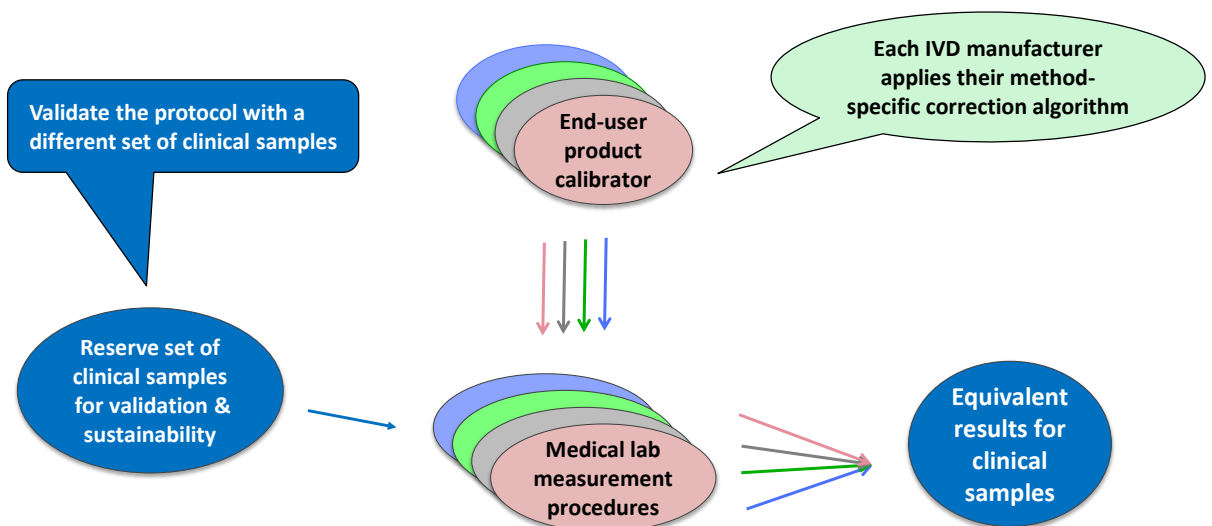
Harmonization protocol: equivalent results



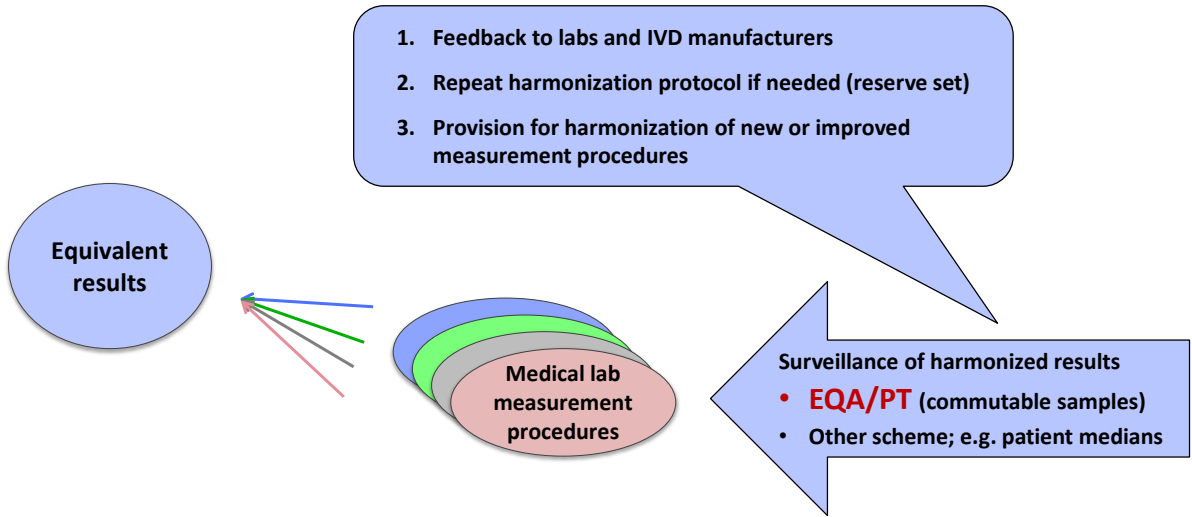
Harmonization protocol: validation / sustainability



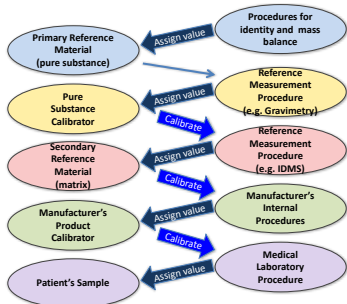
Harmonization protocol: validate the protocol



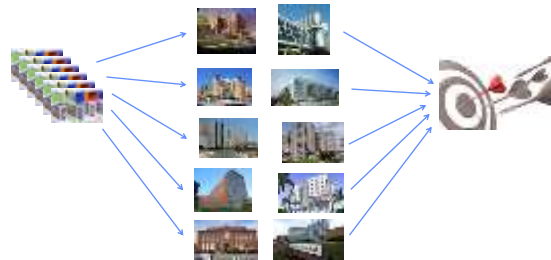
Harmonization protocol: surveillance over time



STANDARDIZATION / HARMONIZATION METROLOGICAL TRACEABILITY



ASSESSMENT EQA



Harmonization needs EQA feedback to the IVD industry

We need a mechanism for EQA providers to cooperate to:

1. Cover measurands on an annual or biennial cycle
2. Prepare aggregated data summaries among schemes

An organizing role for ICHCLR, EQALM, IFCC, ???




Regulation

A challenge to harmonization



What has changed by recalibration to achieve equivalent results

- **Numeric value**
 - **Reference interval**
 - **Measuring interval**
- 
- Changes are proportional to the numeric value change**

Nothing else is changed by recalibration

- **Precision**
- **Selectivity**
- **Interfering substances**

Should not require a full resubmission

**The important change is that
harmonized results reduce medical errors**

Patient safety is improved

**Agreed at a 2013 conference including
ICHCLR, AACC, AdvaMedDx, IVD industry, FDA**

www.harmonization.net/resources/

Summary

- **Harmonization of results is important to reduce medical errors**
- **The ICHCLR:**
 - **prioritizes measurands in need of harmonization**
 - **provides an information portal for global harmonization activities**
 - **promotes collaborative activities to achieve harmonized results**
- **Global cooperation is needed to achieve harmonization**

The path forward

- **We now have more tools**
- **We need to work as a team**
 - **Laboratory practitioners**
 - **IVD industry**
 - **Regulatory bodies**



The guiding principle

Perfect is the enemy of good