SYDPATH
ST VINCENT'S PATHOLOGY

ST VINCENT'S HOSPITAL SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Getting the Right Answer
The Importance of Traceability

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JCTLM

APFCB Visiting Lecturer 2015-6

Acknowledgements

ASIA-PACIFIC FEDERATION FOR CLINICAL BIOCHEMISTRY AND LABORATORY MEDICINE

JCTLM
Accurate results for patient care

ifcc
International Federation of Clinical Chemistry and Laboratory Medicine

aacb
testing for health

RCPAQAP
RCPA Quality Assurance Programs

RCPA
The Royal College of Pathologists of Australasia

EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

SYDPATH
ST VINCENT'S PATHOLOGY

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Contents

- History and philosophy
- Interpreting laboratory results
- Performing measurements
- The science and practice of Metrology
- Improving metrological traceability today
- (creatinine as an example)

Chia Measure: China 45 BC – AD 23

國立故宮博物院
NATIONAL PALACE MUSEUM

Taiwan

Combination of five volume measures.

2 he = 1 ho, 10 ho = 1 sheng, 10 sheng = 1 tou, 10 tou = 1 hu.

Inscription of 249 characters explains the origins, individual parts, and dimensions of the individual parts.

Chia Measure: China 45 BC – AD 23

國立故宮博物院
NATIONAL PALACE MUSEUM

Taiwan

Multiple copies made - Sent around the country

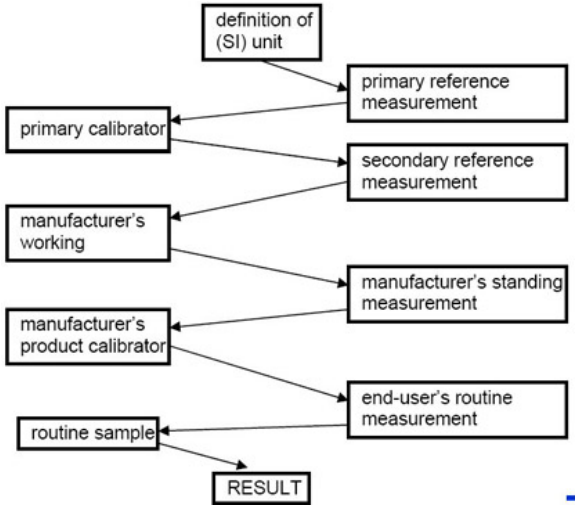
Standardised measurement and trade

Authenticity "certified" by inscription

→ same result in different times and places

Measurements

- Every civilisation and every craft has its tools for spreading measurement standards
- Traceability is the modern version
- Lets apply this to Laboratory Medicine ….



Terminology

- **Measurement** Traceability
- Trueness
- Bias
- “Getting the right answer”

Laboratory Medicine

- **Our goal:** To improve patient health
- **Our tools:** Laboratory tests
- **Our mechanism:** Support medical decisions

Numerical laboratory results

Example:

Mr Bill Bloggs (DoB 1 Jul 1950)

Sample Collected: 21 Aug 2012, 10:00 am

Test	Result	Units
Serum creatinine:	**125**	umol/L

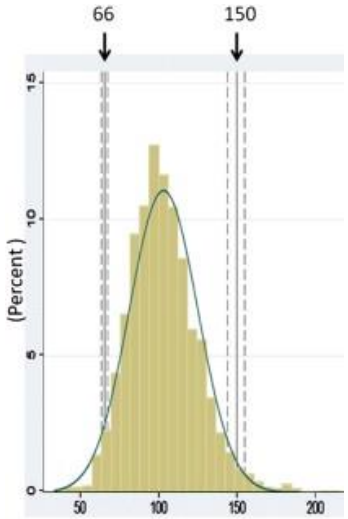
How is this number interpreted?

Interpreting laboratory results

All results are interpreted by **comparison.**

Comparison may be with:

- **A clinical decision point**



- **A population reference interval**

- **A previous result from the patient**

	5-Aug	1-Aug	
Creatinine:	**110**	**125**	umol/L

Professor Per-Hyltoft Peteresen, Sydney 2005

For valid comparisons …

- **Results** must be **unbiased** relative to the results used to create the **comparator**
- **Clinical Decision Point**
  - **Method used to perform the study**
- **Population reference interval**
  - **Method used for the reference interval study**
- **Previous result on the patient**
  - **Method used for the previous result**

Are Unbiased Results Important?

Bias: Adverse clinical effects

Biased results →

(results not comparable with the comparator):

- Wrong diagnosis
- Wrong management
- Incorrect monitoring

→ patient harm

Bia: Applying Evidence

Comparison may be with:

- **A clinical decision point**
- **Derived from the medical literature**

- Comparable results required for

evidence-based medicine

Bias: Financial issues?

- Unnecessary testing costs due to **analytical factors** (patient recalls, follow-up, treatment):
- Germany 1.5 Billion US$ per year
  - German Health Report 1998
- USA 7.5 Billion US$ per year
  - Willie May, Chief Analytical Chemistry NIST

→ ***Wasteful***

Murphy KE et al. J. Anal. At. Spectrom., 2002, 17, 469–477

Bias: E-Health

- Combining results in an Electronic Medical Record
- Valid only if results comparable
- The public expects this!

→ IT Ready

Without comparable results ..

Laboratory Medicine is:

Not safe

Not evidence-based

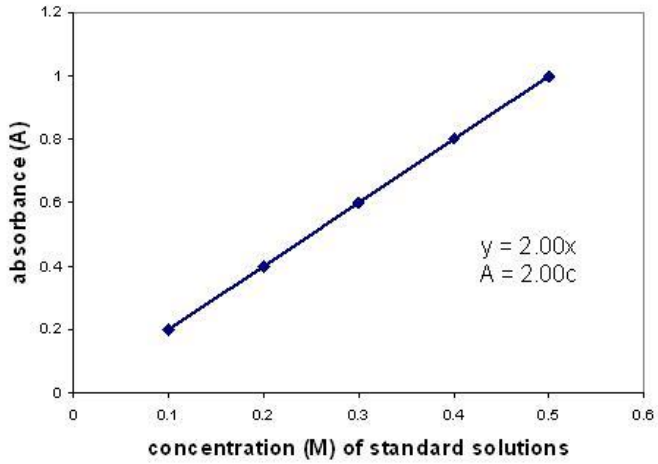
Wasteful

Not IT Ready

Laboratory Measurements

Laboratory Measurements

- All numerical **laboratory measurements** are made by **comparison**
- Analyte concentration in the **sample** is **compared** with concentration in the assay **calibrators**.
- Done using a standard curve



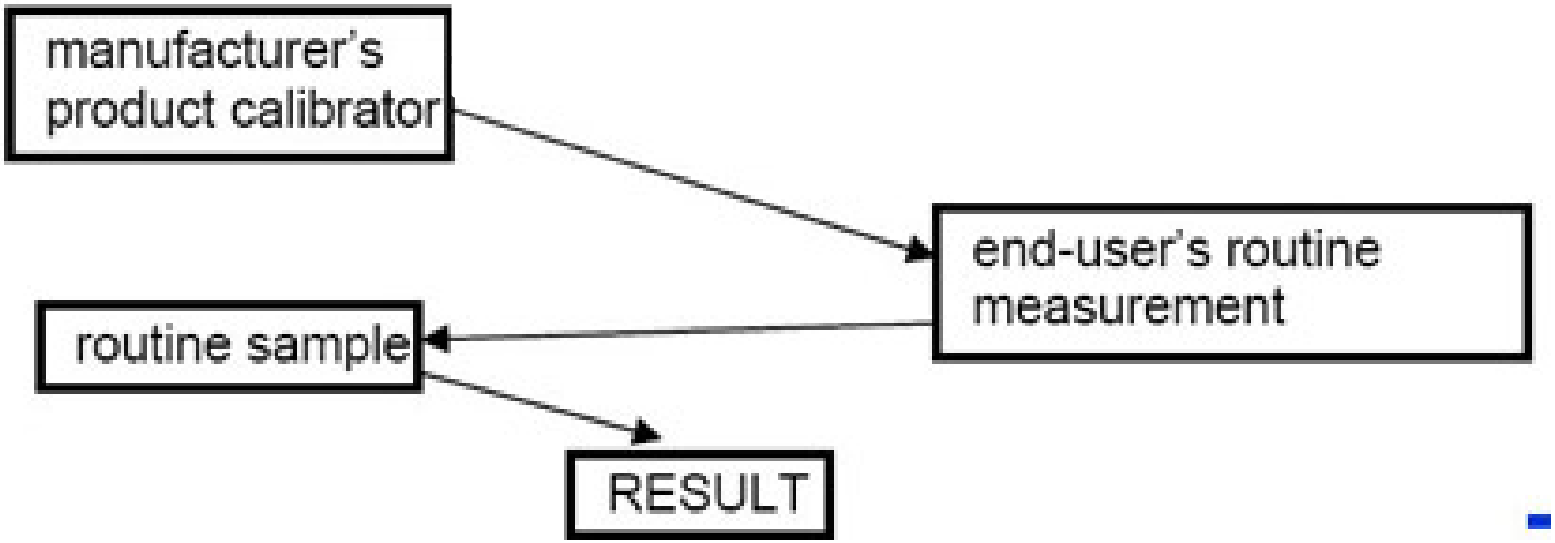
- **Value assignment of calibrators establishes assay trueness (bias)**

Materials

Methods

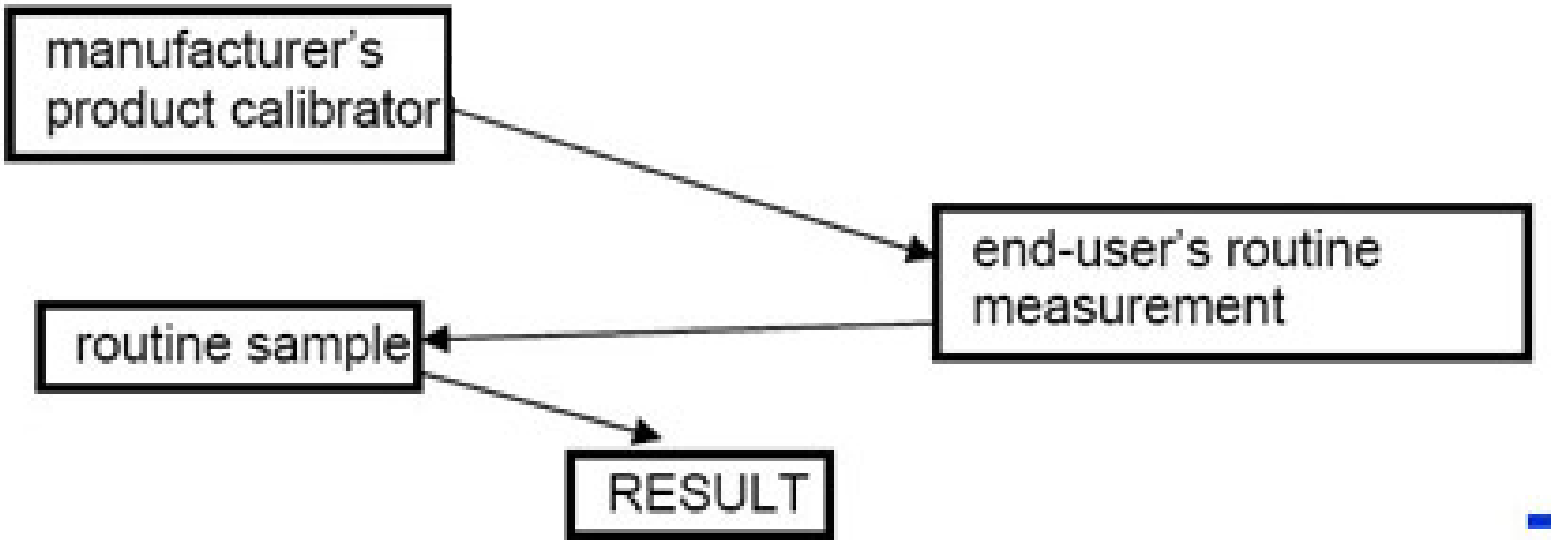
Calibrator value “sets” assay trueness / bias

How is the value of the calibrator set?



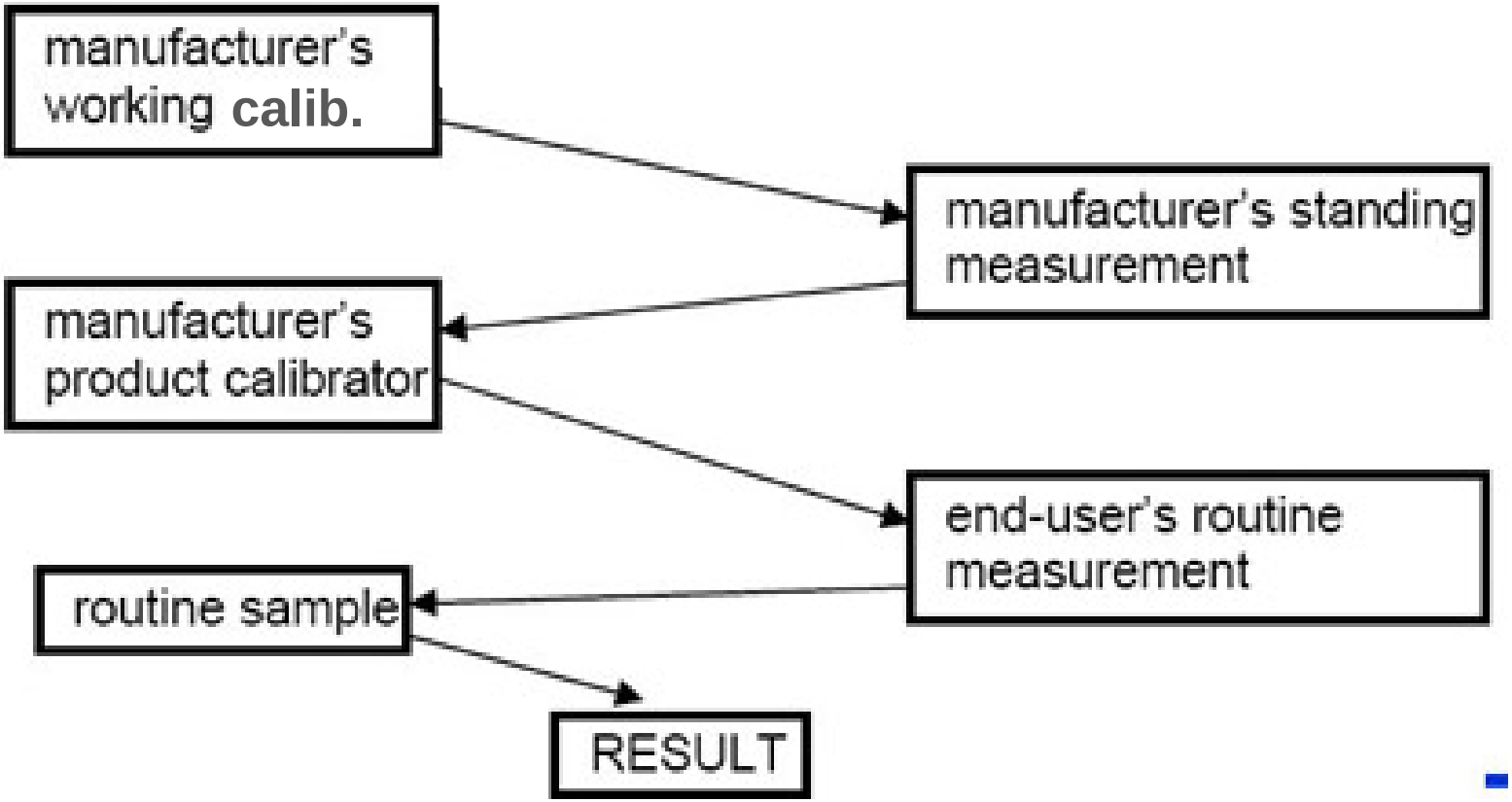
Materials

Methods



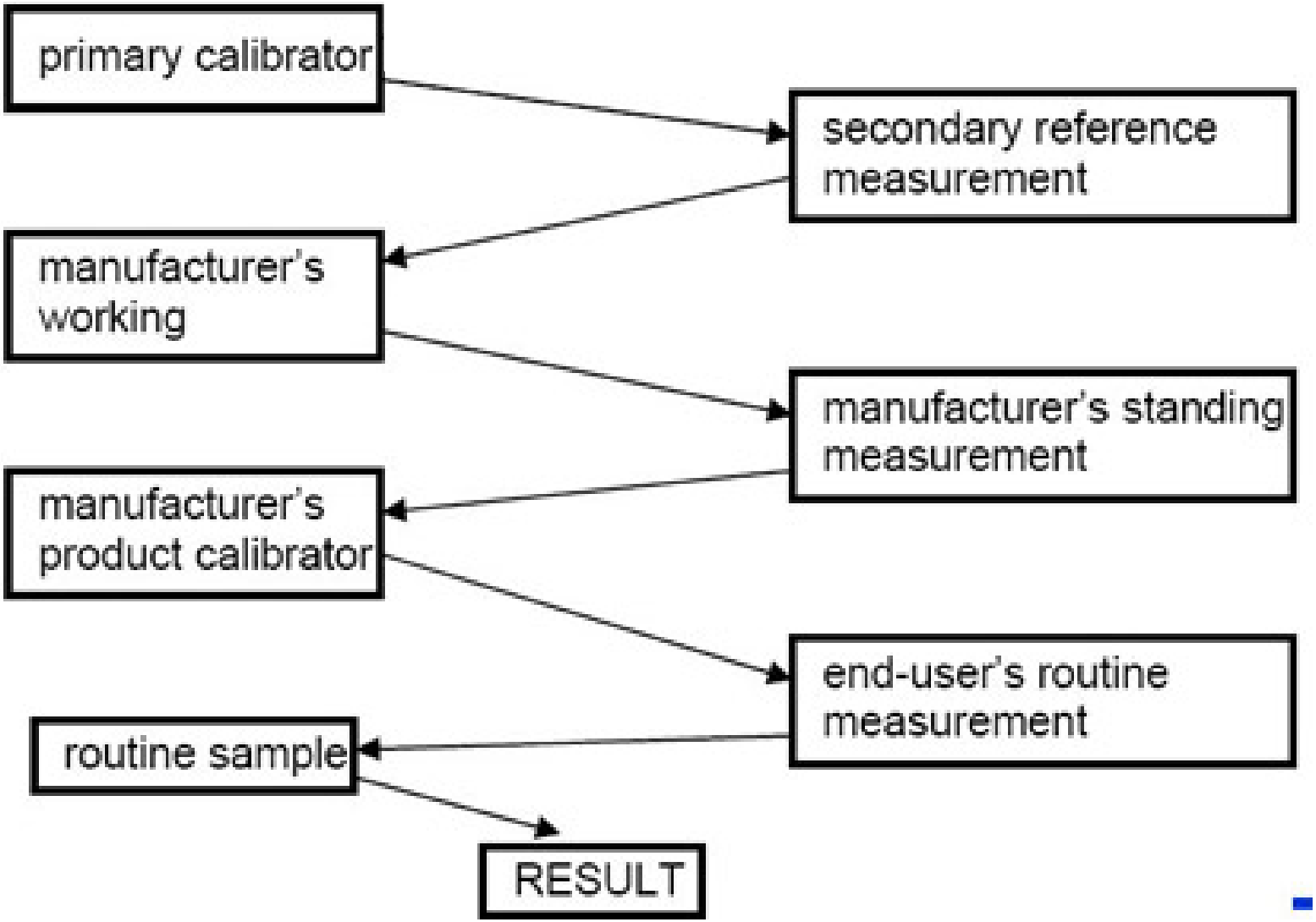
Materials

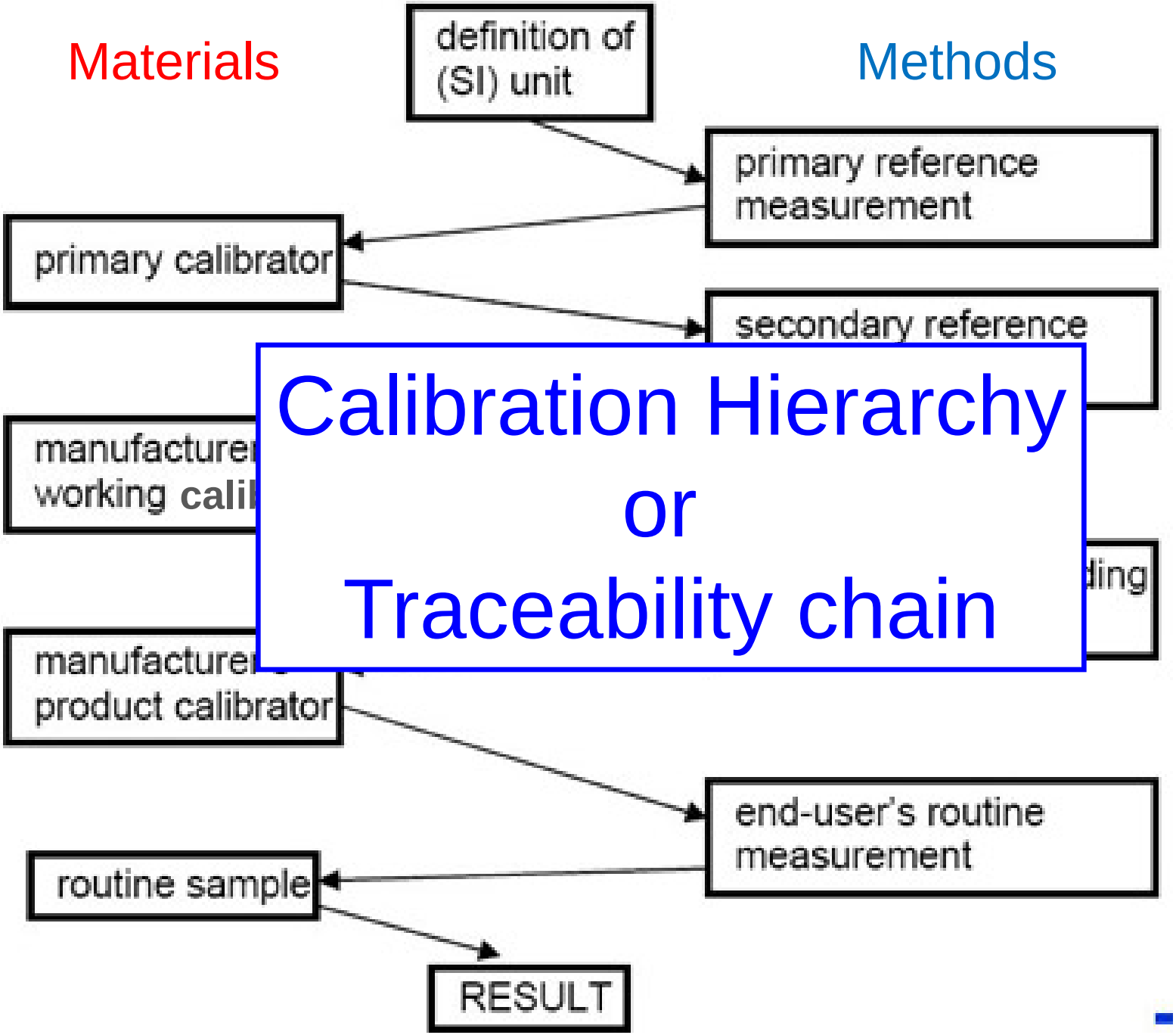
Methods

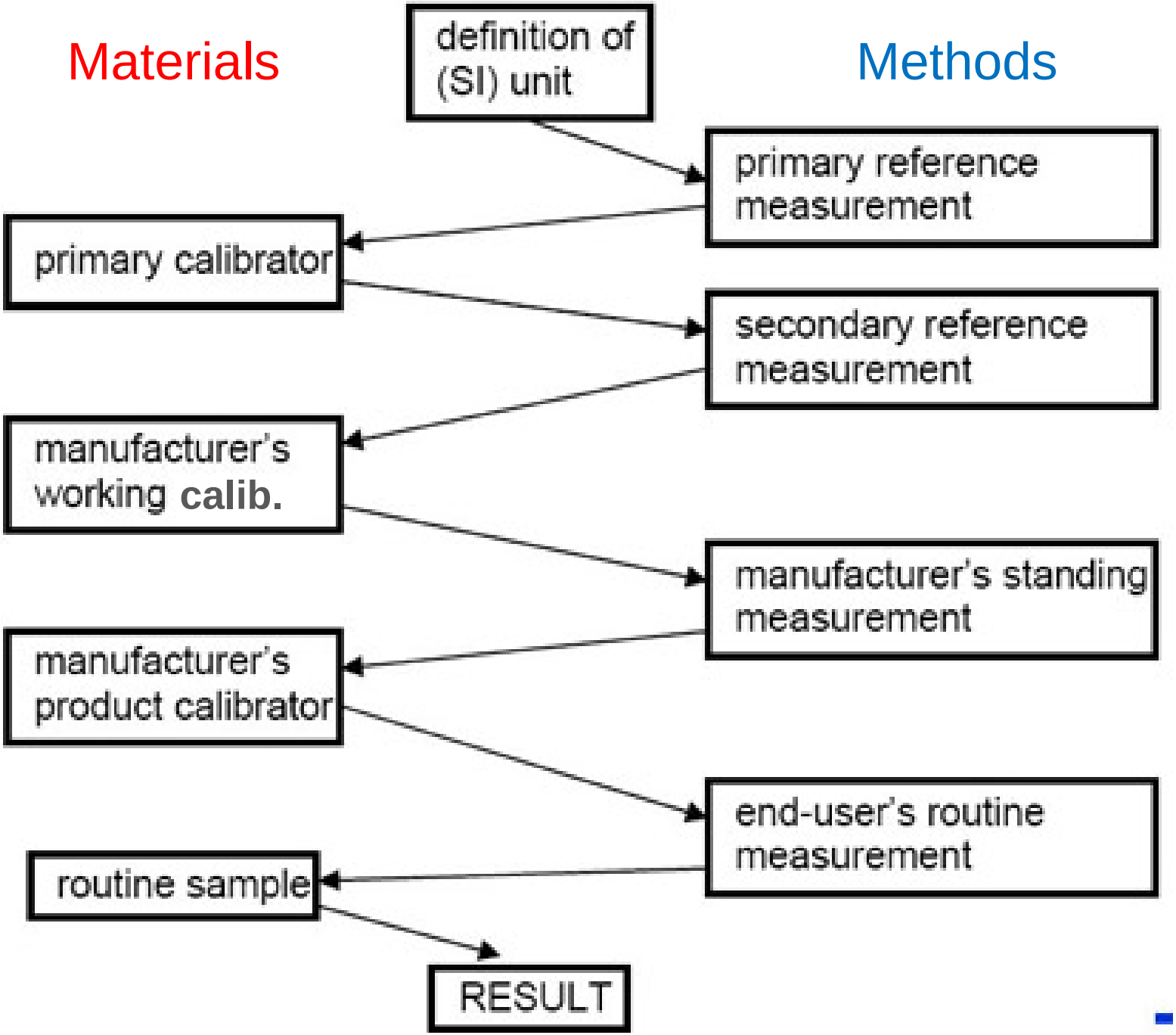


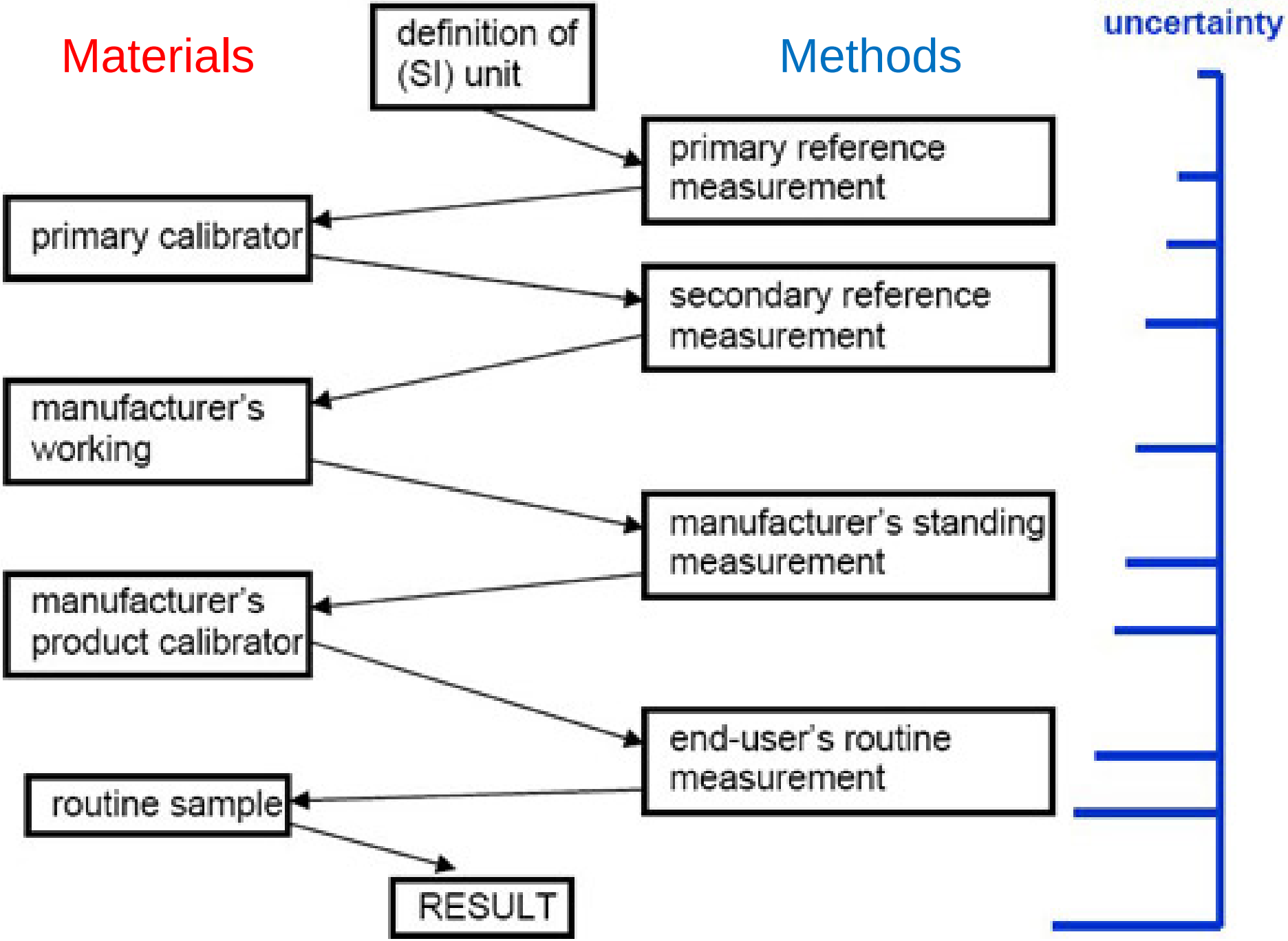
Materials

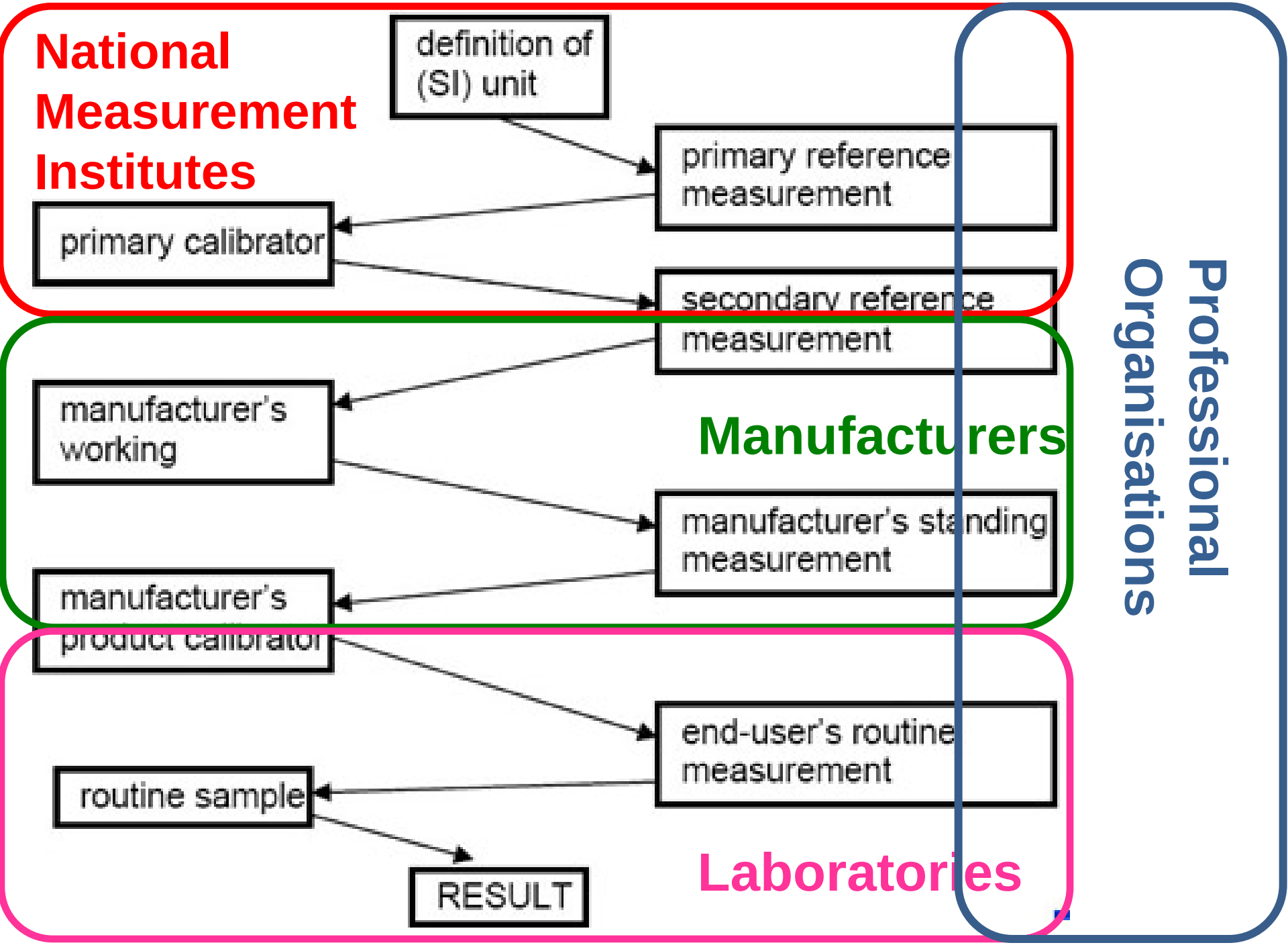
Methods



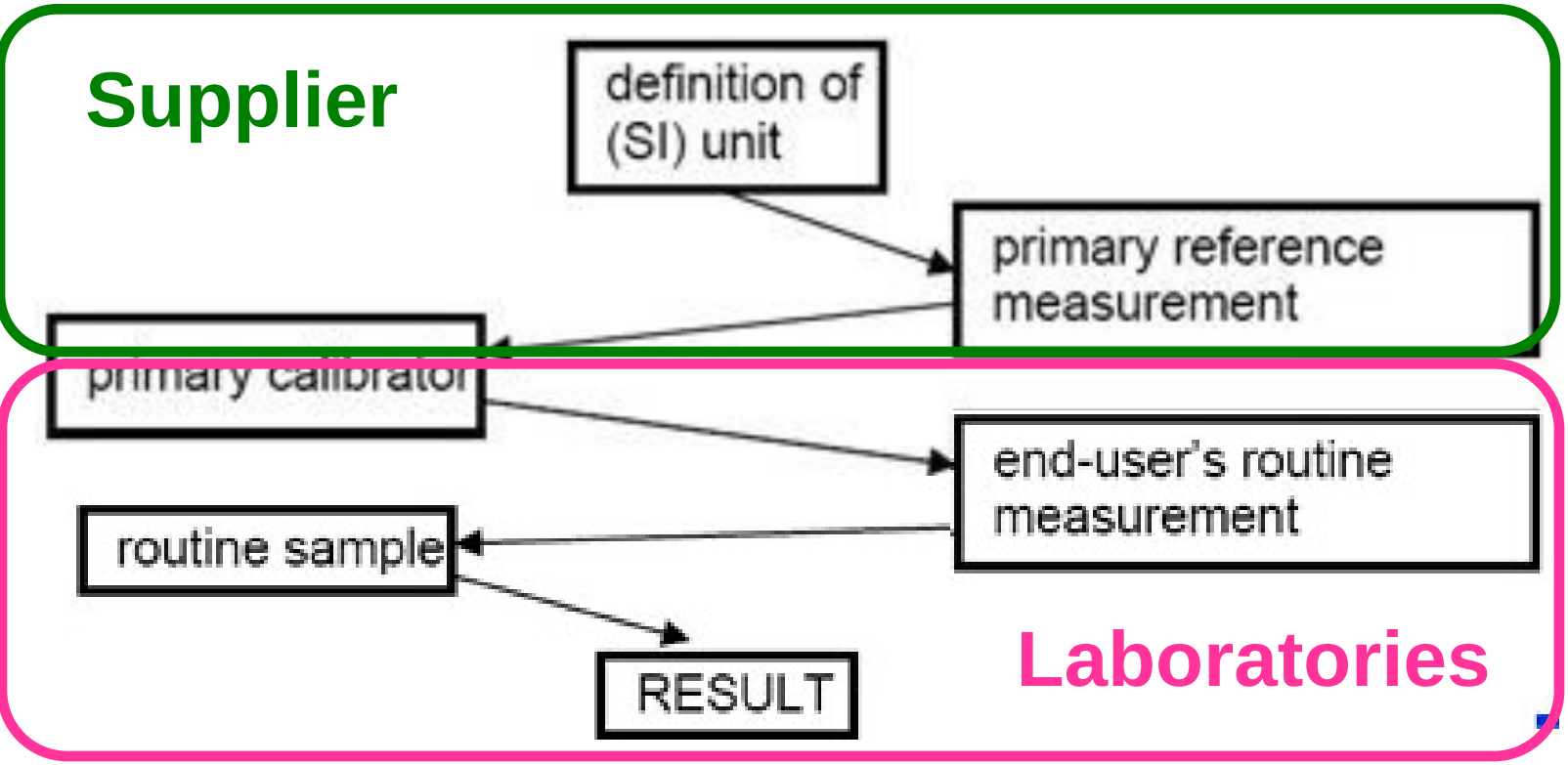

Materials
Methods
definition of (SI) unit
primary reference measurement
primary calibrator
secondary reference
manufacturer working cali
ding
manufacturer product calibrator
end-user's routine measurement
routine sample
RESULT
Calibration Hierarchy
or
Traceability chain


Materials
Methods
definition of (SI) unit
primary reference measurement
primary calibrator
secondary reference measurement
manufacturer's working calib.
manufacturer's standing measurement
manufacturer's product calibrator
end-user's routine measurement
routine sample
RESULT


Materials
definition of (SI) unit
Methods
uncertainty
primary reference measurement
primary calibrator
secondary reference measurement
manufacturer's working
manufacturer's standing measurement
manufacturer's product calibrator
end-user's routine measurement
routine sample
RESULT

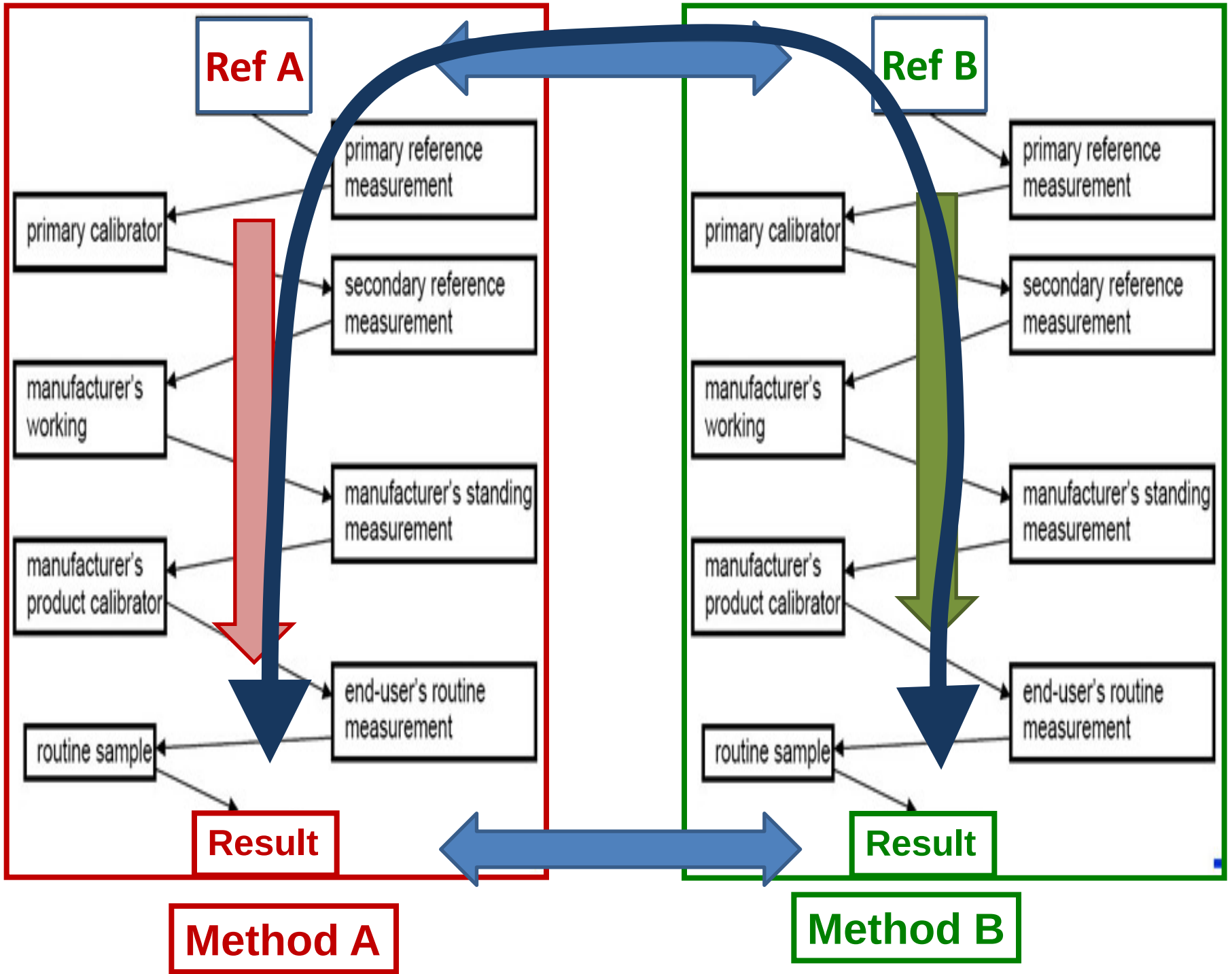

National Measurement Institutes
definition of (SI) unit
primary reference measurement
primary calibrator
secondary reference measurement
manufacturer's working
Manufacturers
manufacturer's standing measurement
manufacturer's product calibrator
end-user's routine measurement
routine sample
RESULT
Laboratories
Professional Organisations

Alternative traceability chain for some in-house assays



The top of the traceability chain

- All assays are “anchored” in one of the following
  - A Material
  - A Method (eg Enzymes)


Ref A
primary reference measurement
primary calibrator
secondary reference measurement
manufacturer's working
manufacturer's standing measurement
manufacturer's product calibrator
end-user's routine measurement
routine sample
Result
Method A
Ref B
primary reference measurement
primary calibrator
secondary reference measurement
manufacturer's working
manufacturer's standing measurement
manufacturer's product calibrator
end-user's routine measurement
routine sample
Result
Method B

Reference Materials

- **Certified Reference Materials**
  - Produced by National Measurement Institutes
  - Highly purified
  - Purity verified (and certified)
  - Very accurately weighed (and certified)
  - Reconstituted very accurately

- May also be **“Matrix matched”** eg urine, serum
  - Values assigned by comparison with pure materials

LGC Setting standards in analytical science

ERM European Reference Materials

CERTIFICATE OF ANALYSIS

ERM®- DA252a

Frozen Human Serum		
Constituent	Certified value [1] (mg/kg)	Uncertainty [2] (mg/kg)
Creatinine	3.1	0.5

1) The certified value is traceable to the standards and analytical procedures used at LGC.

2) The quoted uncertainty is the half-width of the expanded uncertainty calculated using a coverage factor, k, of 2.6, which gives a level of confidence of approximately 95 %.

This certificate is valid for 3 months from the date of shipment provided the sample is stored under the recommended conditions.

The minimum amount of sample to be used is 0.4 g.

NOTE

European Reference Material ERM®-DA252a was produced and certified under the responsibility of LGC according to the principles laid down in the Technical Guidelines of the European Reference Materials® co-operation agreement between BAM-LGC-IRMM. Information on these guidelines is available on the Internet (http://www.erm-crm.org).

Accepted as an ERM®, Teddington, September 2006
Certificate revised July 2008

Signed: _____

Dr Derek Craston, UK Government Chemist
LGC Limited

Other Reference materials

- **International conventional calibrator**
  - Eg WHO standards
- **Other suppliers**
  - Eg US Pharmacopoeia, commercial suppliers
- **Manufacturer's In-house materials**

Reference Methods

- For some analytes the a method **defines** the true result
- Examples: IFCC methods for AST, ALT, ALP
- Assays NOT calibrated with pure material

- For most analytes reference methods are **calibrated** by a material
- Examples: Isotope Dilution Mass Spectrometry

Who decides?

The top of the chain is vital to accuracy.

What Reference Material or Method is the top of the Traceability Chain?

Joint Committee on Traceability in Laboratory Medicine

- **JCTLM - Joining of:**
  - Metrology Community (BIPM)
  - Laboratory Medicine Community (IFCC)
  - Accreditation Community (ILAC)
- Different languages, different journals, different traditions, different history
- Aim to bring rigour and processes of metrology to laboratory medicine

JCTLM
Accurate results for patient care

BIPM

ifcc
International Federation of Clinical Chemistry and Laboratory Medicine

ilac

Metrology - BIPM

Bureau International de Poids et Mesures
(International Bureau of Weights and Measures)

(Pont de Sevres, Paris)

Metre Convention

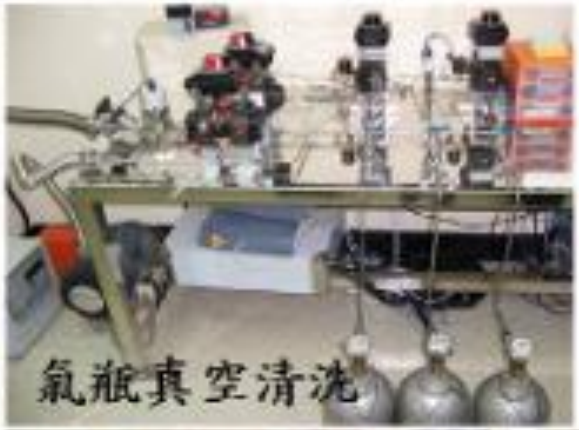
- The **Metre Convention (1875)**
- Treaty to oversee the keeping of metric standards (SI – Systeme Internationale).
- 56 signatory countries in 2012
- **“..to promote world wide uniformity in units of measurement..”**

- **Chinese Taipei is an associate member of the General Committee of Weights and Measures**

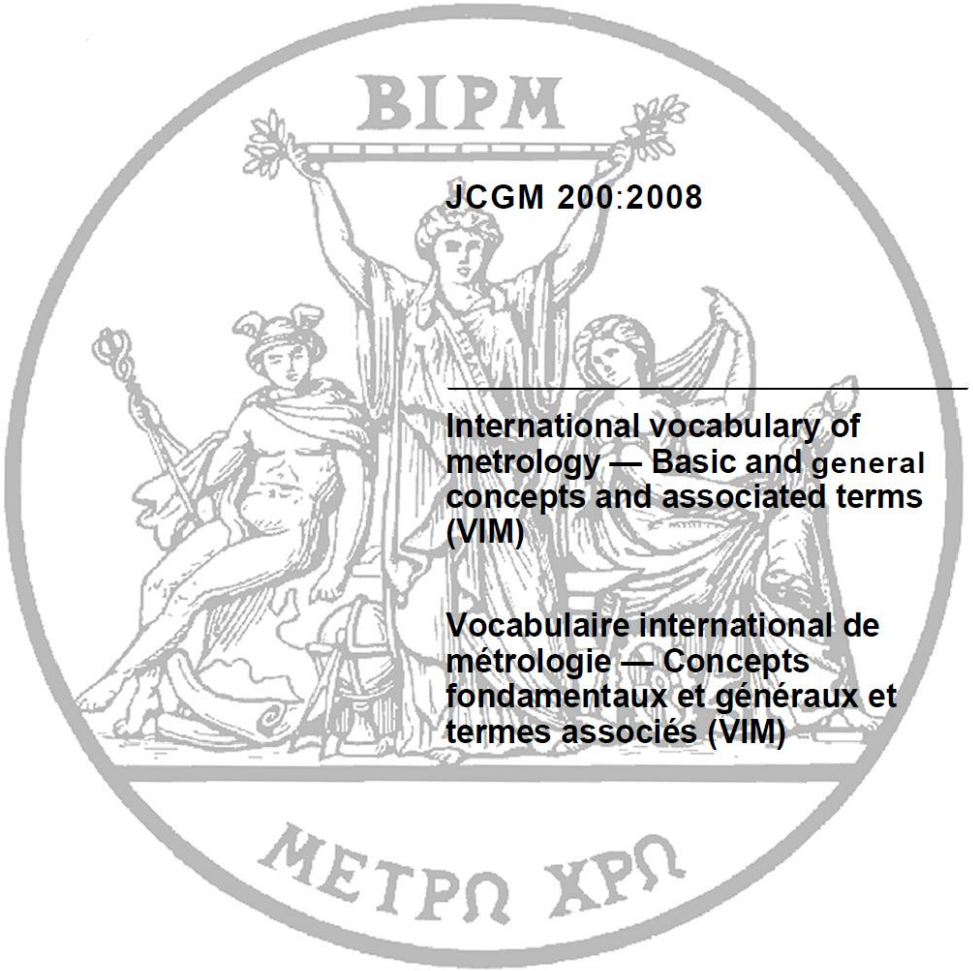
Metrology in practice

- **International network of Laboratories**
  - National Measurement Institutes
- **International Treaties**
  - Recognition of measurements
- **Metrology Research**
  - All aspects

國家度量衡標準實驗室
NATIONAL MEASUREMENT LABORATORY R.O.C.



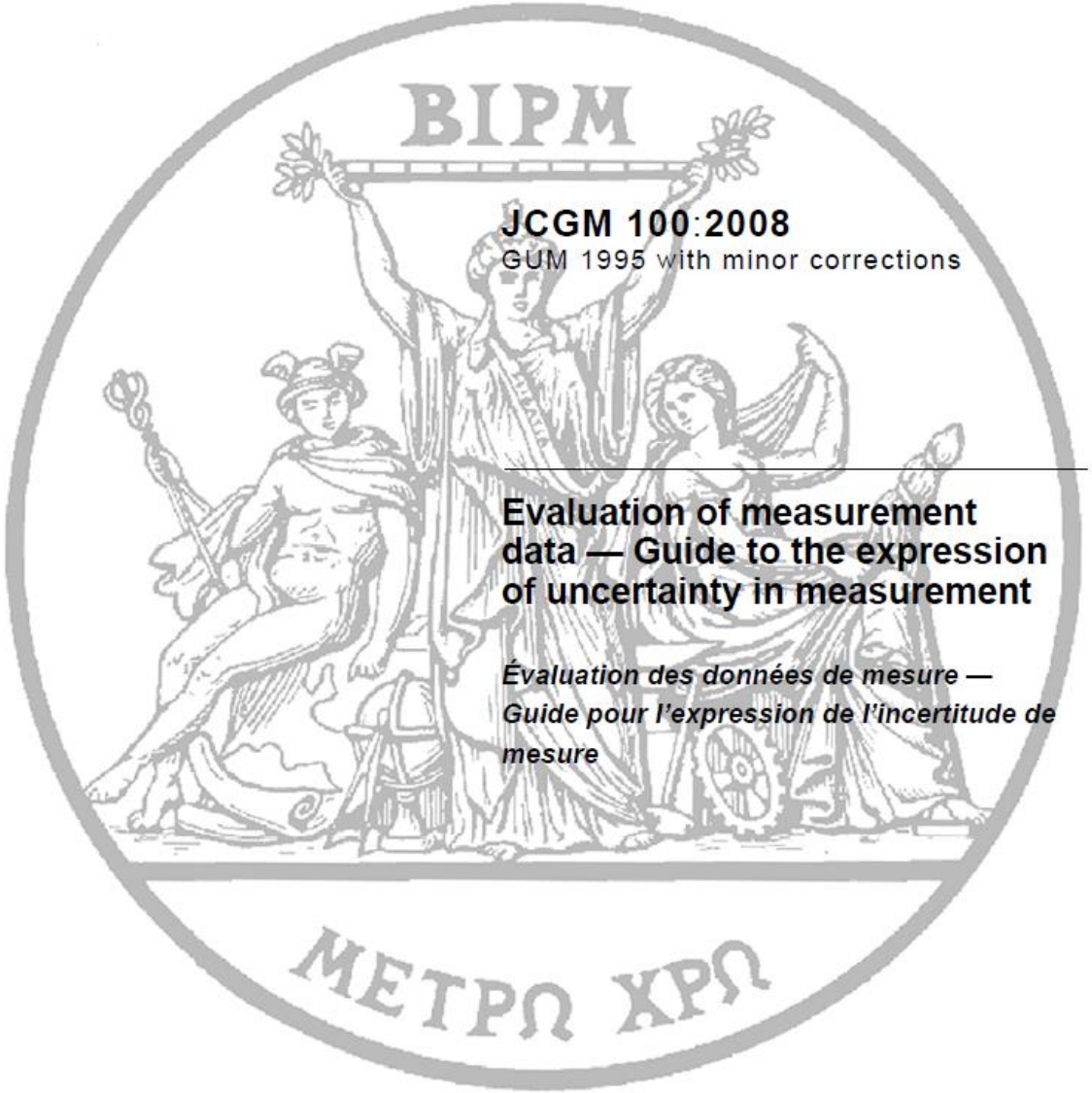
VIM – International Vocabulary of Metrology



- Measurand
- Measurement Uncertainty
- Traceability

“GUM”

Guide to the Uncertainty of Measurement



Systeme Internationale

Base quantity	SI base unit	
Name	Name	Symbol
length	metre	m
mass	kilogram	kg
time, duration	second	s
electric current	ampere	A
thermodynamic temperat	kelvin	K
amount of substance	mole	mol
luminous intensity	candela	cd

The kilogram

This international prototype, made of platinum-iridium, is kept at the BIPM under conditions specified by the 1st CGPM in 1889

Measurements in general

- Weighing a reagent
- Pipetting a volume
- Measuring absorbance
- Timing a reaction

- These are all possible because of metrology!

JCTLM Output

- **Database of “higher Order … ”**

- Reference Materials
- Reference Methods
- Reference Laboratories

Meets traceability requirements of European Union
Based on ISO standards

JCTLM database: Laboratory medicine and *in vitro* diagnostics

JCTLM Database

- **SURVEY FORM**
- List of reference materials no longer listed in the JCTLM Database
- Contact us
- Back to Search Form

JCTLM

- Why JCTLM?
- Joint Committee for Traceability in Laboratory Medicine (JCTLM)
- Leaflet

Analyte keyword search for reference materials, measurement methods/procedures and services

Type an analyte name in part or full, e.g. cholesterol

creatinine

Refine search by analyte category

All

Refine search by matrix category

All

Please select your requirement :

- (•) Higher-order reference materials
- ( ) Reference measurement methods/procedures
- ( ) Reference measurement services

Reset ×

Search →

Search by Analyte

Results of the search

Your search criteria produced 7 summary results.
Select one or several higher-order reference material summary descriptions amongst the following list and click on 'View' to access more information.

Select all items from the list

Sort by : (•) Analyte ( ) Matrix/Material ( ) Organization

Select	Analyte	Analyte category	Matrix/Material	Organization
☐	creatinine	metabolites and substrates	creatinine crystalline material	NIST
☐	creatinine	metabolites and substrates	creatinine crystalline material	NMIJ
☐	creatinine	metabolites and substrates	frozen human serum	CENAM
☐	creatinine	metabolites and substrates	frozen human serum	NIST
☐	creatinine	metabolites and substrates	human serum	IRMM
☐	creatinine	metabolites and substrates	human serum	LGC
☐	creatinine	metabolites and substrates	human serum	NIST

Deselect all items from the list

View

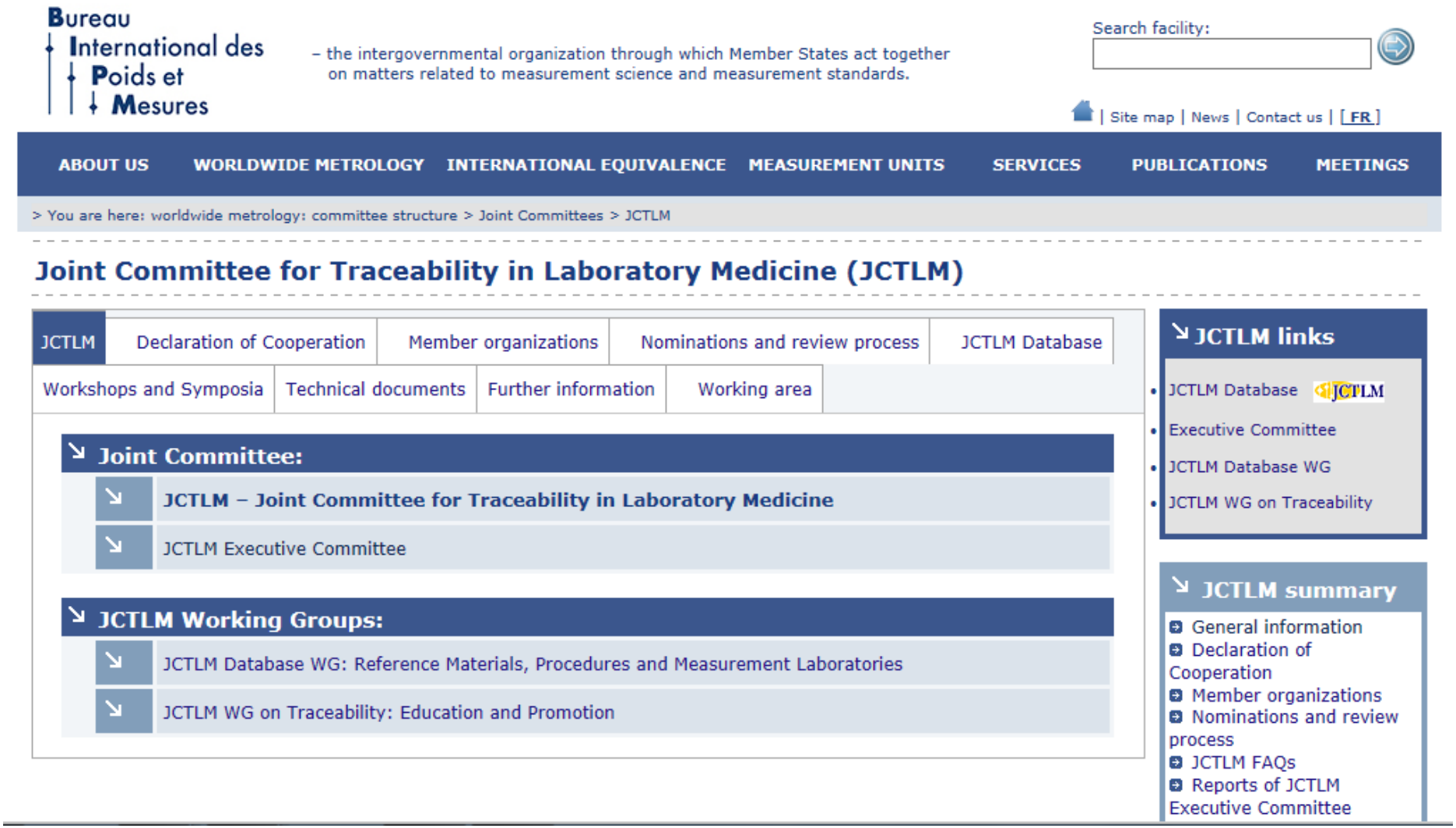
JCTLM Database

The JCTLM database currently lists:

- 298 RM for 175 measurands
- 180 RMP for 80 measurands
- 146 RMS for 39 measurands.

JCTLM
Accurate results
for patient care

Further Information (www.bipm.org/jctlm/)



3 Pillars of Laboratory Standardisation

1. Primary reference material
2. Primary reference method
3. Primary reference laboratory

4 Pillars of Laboratory Standardisation

1. Primary reference material
2. Primary reference method
3. Primary reference laboratory
4. **External Quality Assurance**
   Traceable, commutable

5 Pillars of Laboratory Standardisation

1. Primary reference material
2. Primary reference method
3. Primary reference laboratory
4. External Quality Assurance
5. **Reference Intervals / Clinical Decision limits**

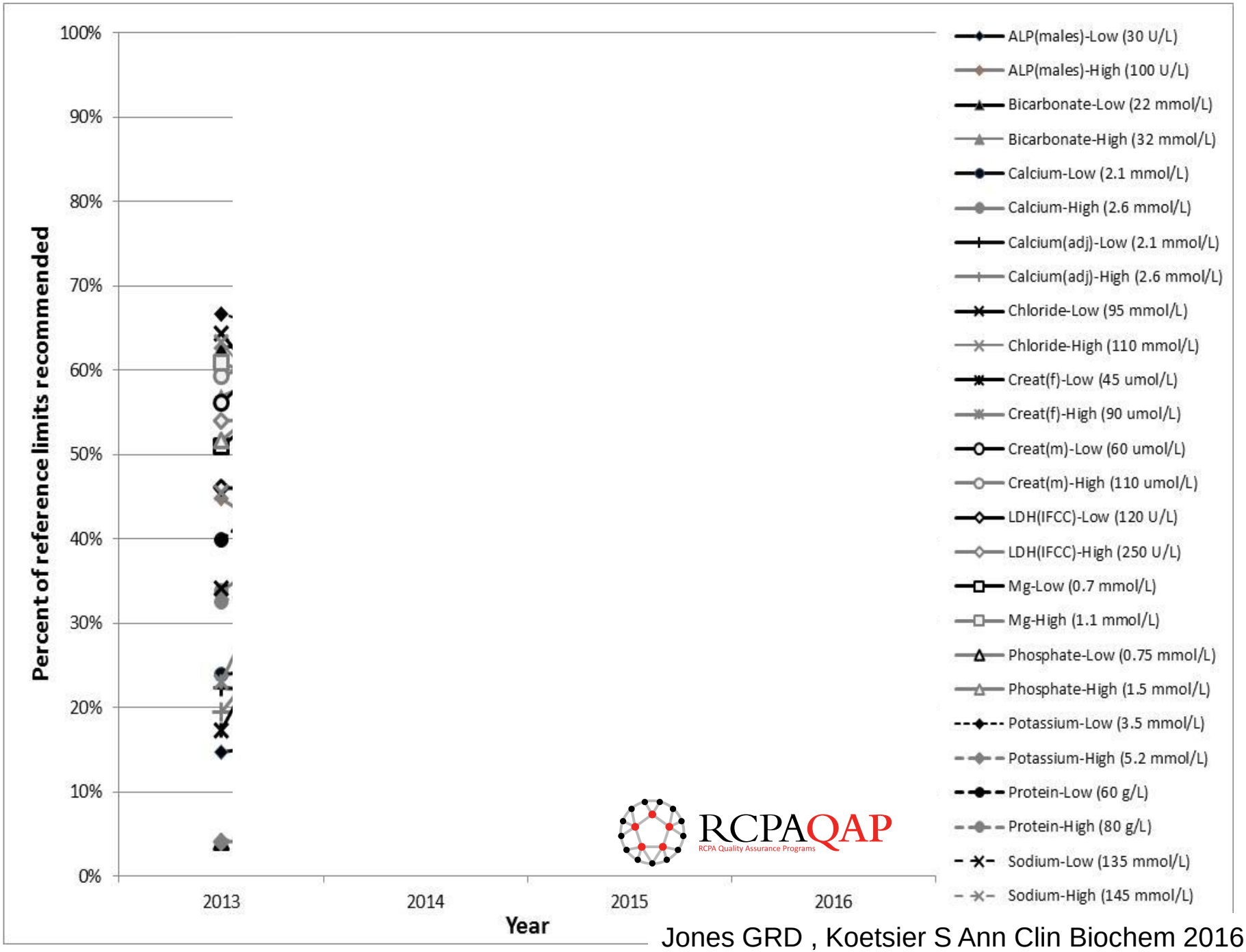
Common Reference Intervals

- Australian Project
- 2013 – 2015
- 12 Common tests
- Sodium, Potassium, Calcium …

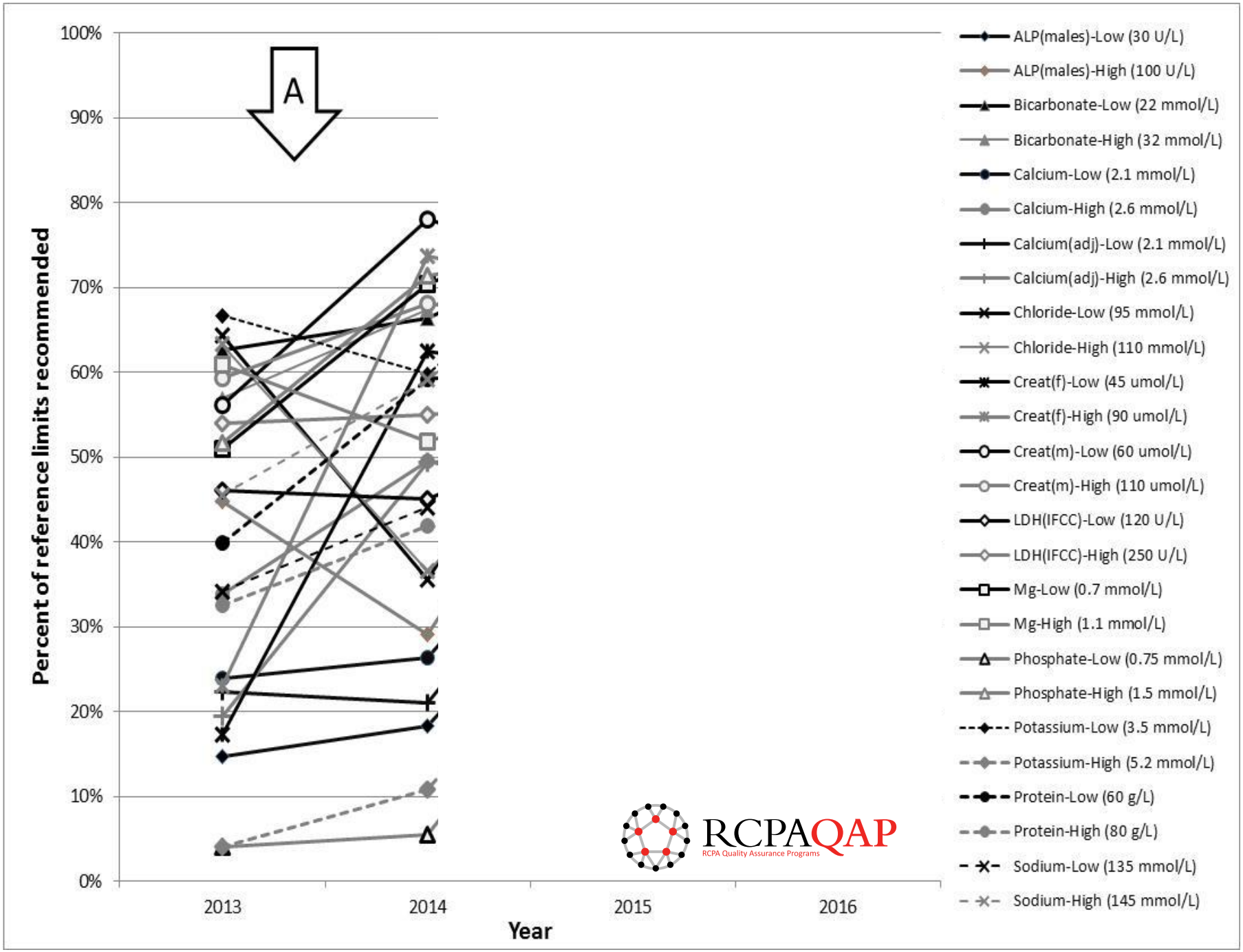
aacb testing for health

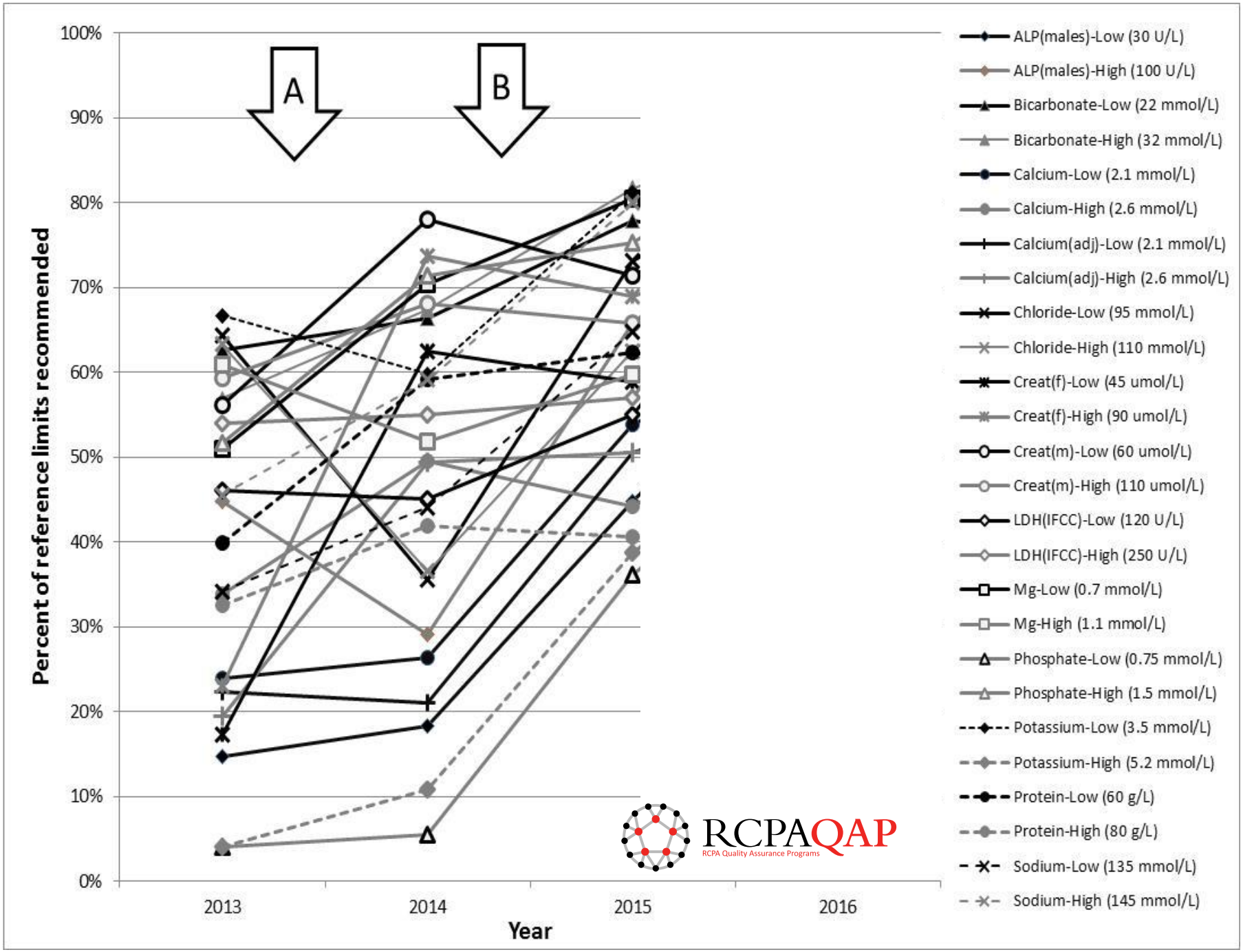
RCPA The Royal College of Pathologists of Australasia

RCPAQAP RCPA Quality Assurance Programs



Jones GRD , Koetsier S Ann Clin Biochem 2016


A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percent of reference limits recommended
2013
2014
2015
2016
Year
RCPAQAP
RCPA Quality Assurance Programs
ALP(males)-Low (30 U/L)
ALP(males)-High (100 U/L)
Bicarbonate-Low (22 mmol/L)
Bicarbonate-High (32 mmol/L)
Calcium-Low (2.1 mmol/L)
Calcium-High (2.6 mmol/L)
Calcium(adj)-Low (2.1 mmol/L)
Calcium(adj)-High (2.6 mmol/L)
Chloride-Low (95 mmol/L)
Chloride-High (110 mmol/L)
Creat(f)-Low (45 umol/L)
Creat(f)-High (90 umol/L)
Creat(m)-Low (60 umol/L)
Creat(m)-High (110 umol/L)
LDH(IFCC)-Low (120 U/L)
LDH(IFCC)-High (250 U/L)
Mg-Low (0.7 mmol/L)
Mg-High (1.1 mmol/L)
Phosphate-Low (0.75 mmol/L)
Phosphate-High (1.5 mmol/L)
Potassium-Low (3.5 mmol/L)
Potassium-High (5.2 mmol/L)
Protein-Low (60 g/L)
Protein-High (80 g/L)
Sodium-Low (135 mmol/L)
Sodium-High (145 mmol/L)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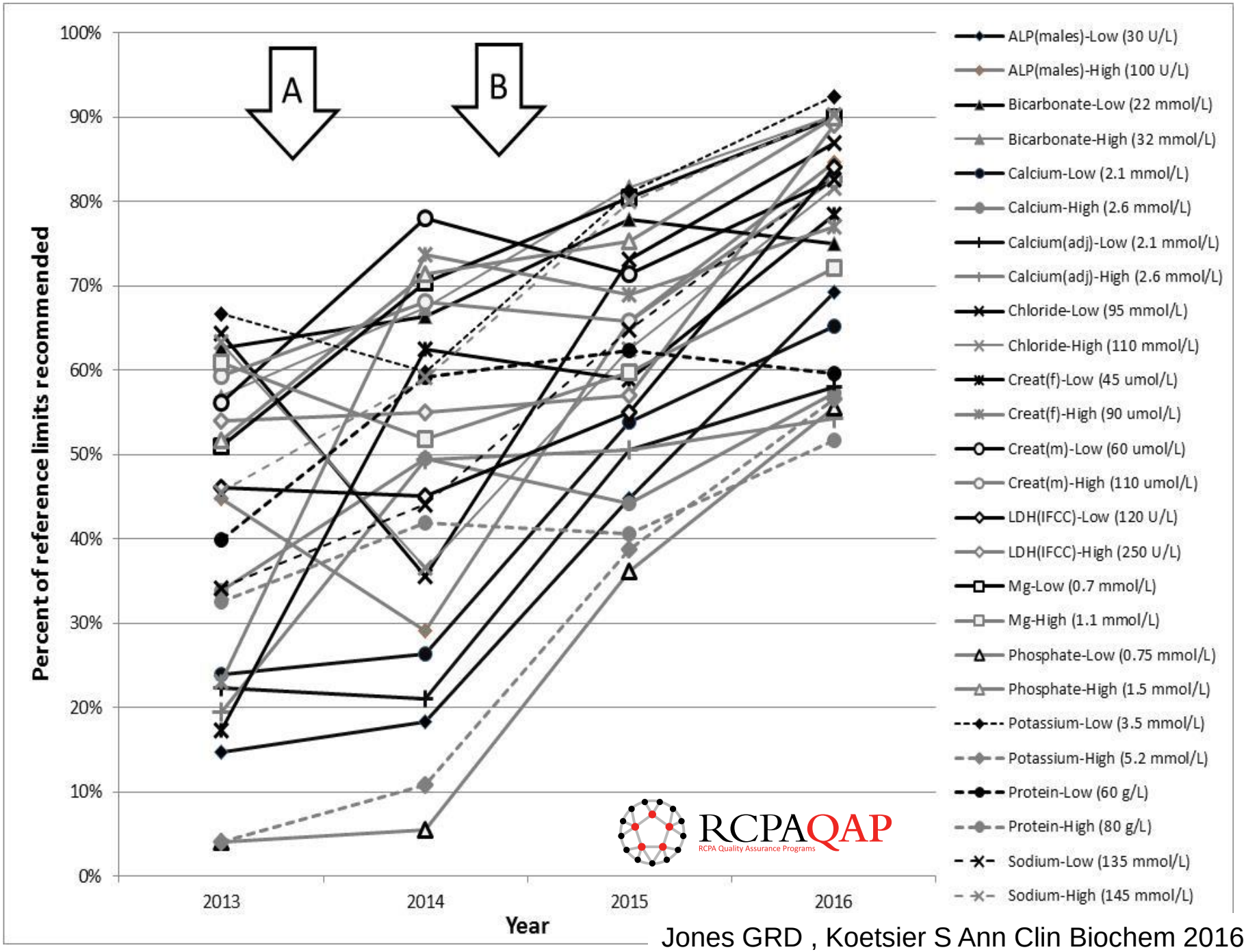

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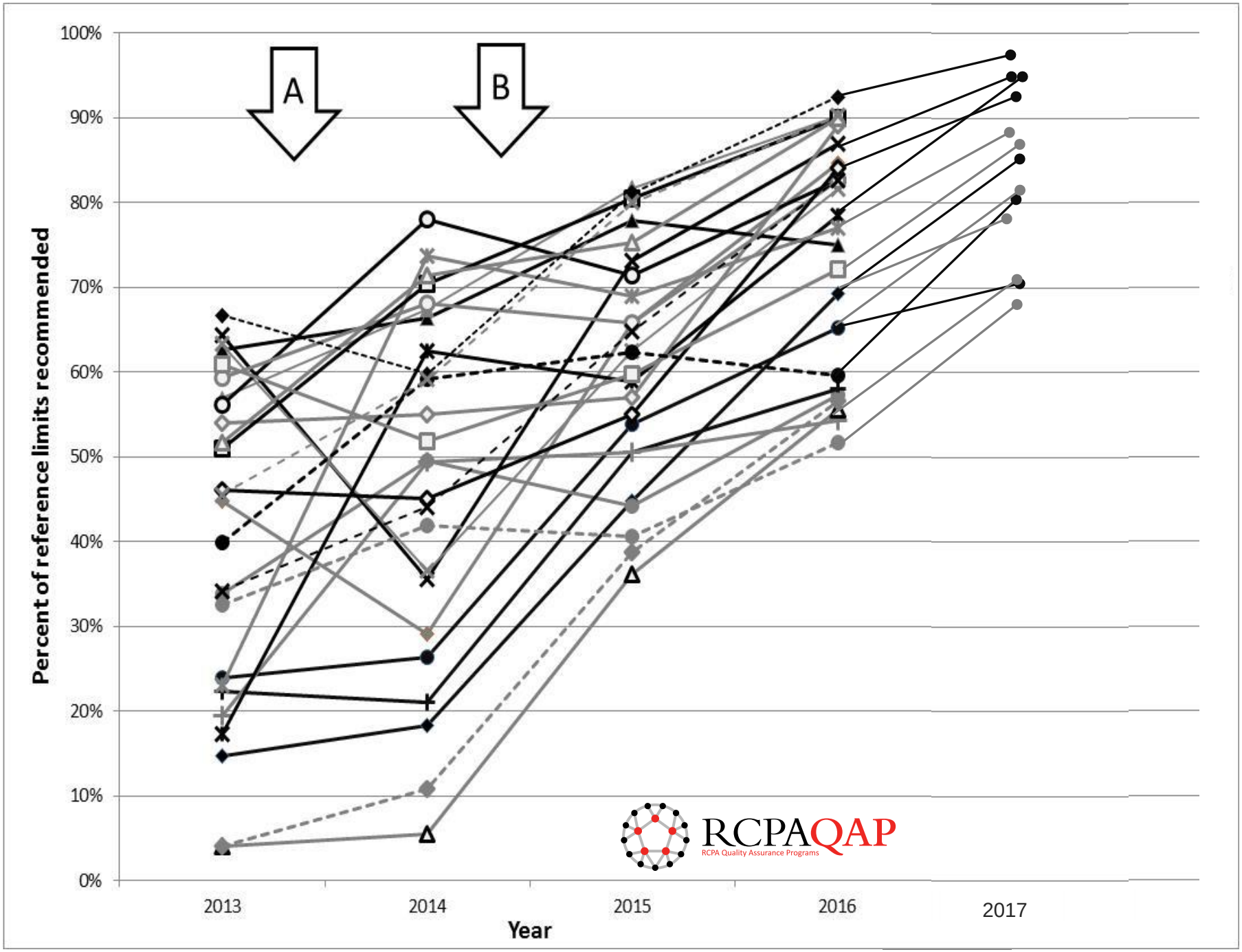
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Percent of reference limits recommended
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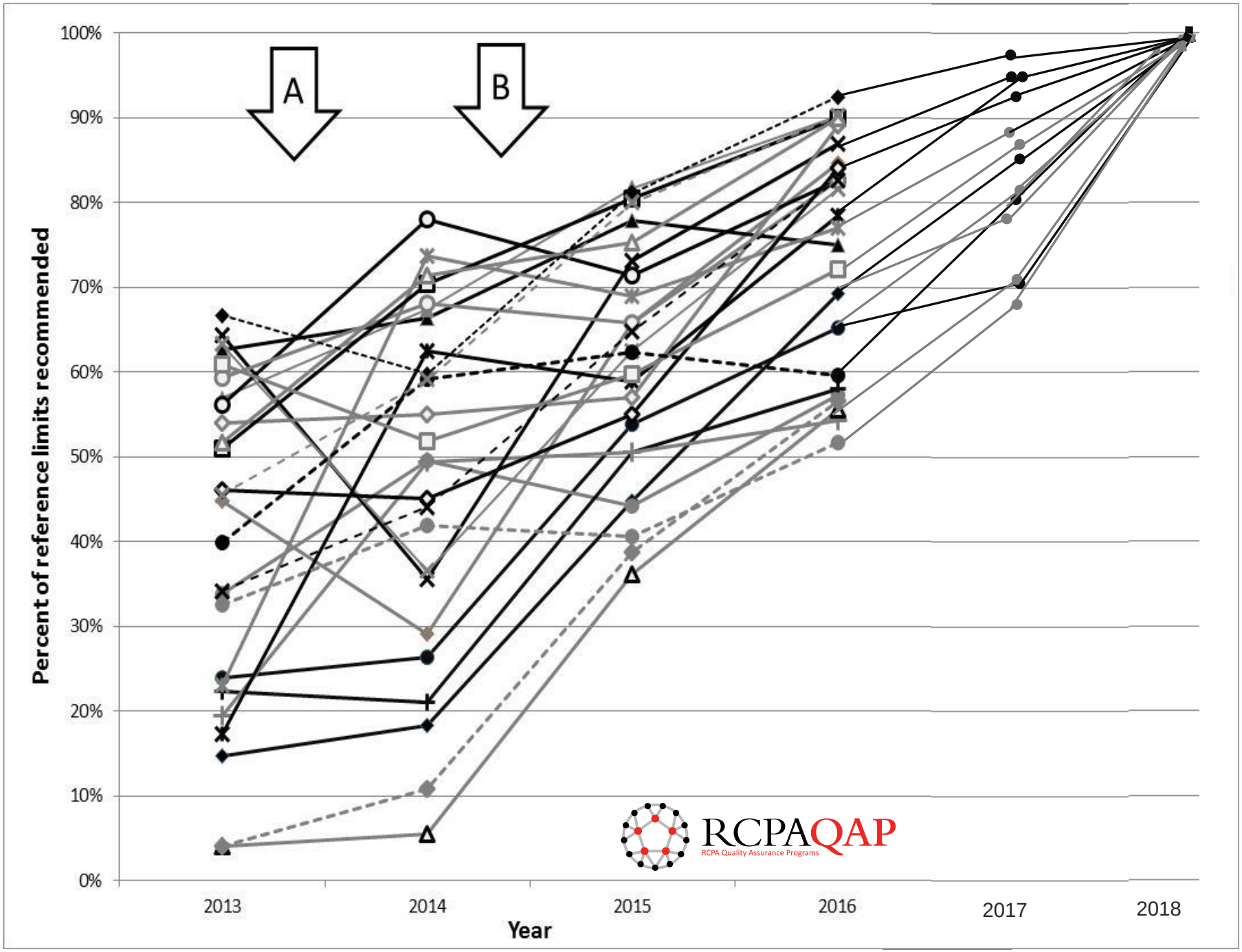
RCPA Quality Assurance Programs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2013
2014
2015
2016
2017
2018
Year
RCPAQAP
RCPA Quality Assurance Programs

What can we do?

Professional Organisations

Manufacturers

Laboratories

Measurement Institutes

Regulators

Accreditation agencies

Researchers

Professional organisations: APFCB - 2016

Symposium 2

IFCC-SD

IFCC-SD Standardization Globally Activity

Ian Young (GB)
Kina Höglund (SE)
Graham Beastall (UK)

Symposium 6

JSCC

Standardization and Harmonization in Japan

Shigeru Ueda (JP)
Susumu Osawa (JP)
Naotaka Hamasaki (JP)

Symposium 10

KSCC

Standardization Effort in Korea

Junghan Song (KR)
Yeo-Min Yun (KR)
Gye-Cheol Kwon (KR)

Symposium 14

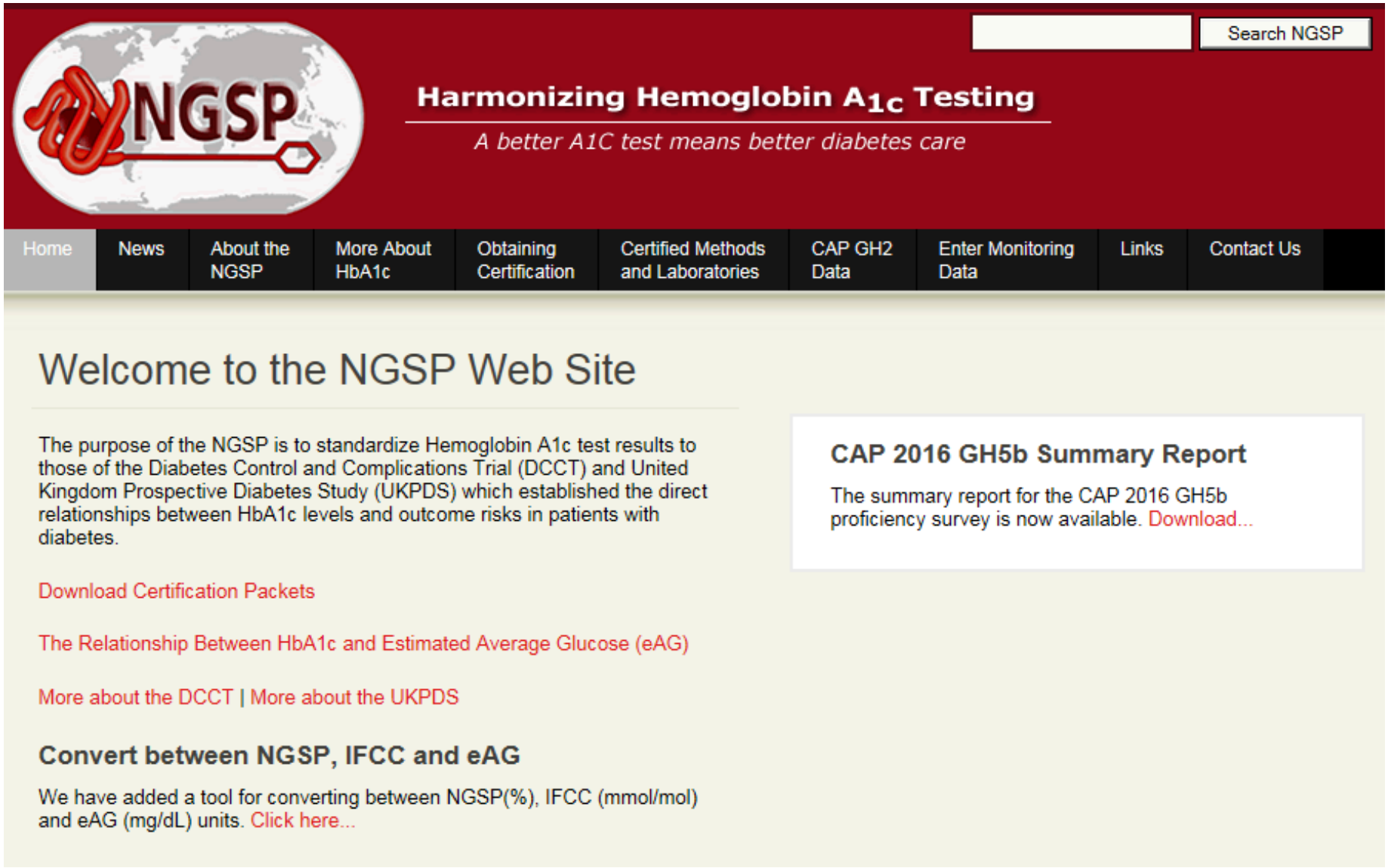
EFLM

EFLM Harmonization of Total Testing Process

Ferruccio Ceriotti (IT)
Ana-Maria Simundic (HR)
Mauro Panteghini (IT)
Éva Ajzner (HU)

All activities need international alignment

NGSP: HbA1c


Search NGSP
NGSP
Harmonizing Hemoglobin A1c Testing
A better A1C test means better diabetes care
Home
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More About HbA1c
Obtaining Certification
Certified Methods and Laboratories
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Welcome to the NGSP Web Site
The purpose of the NGSP is to standardize Hemoglobin A1c test results to those of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) which established the direct relationships between HbA1c levels and outcome risks in patients with diabetes.
Download Certification Packets
The Relationship Between HbA1c and Estimated Average Glucose (eAG)
More about the DCCT | More about the UKPDS
Convert between NGSP, IFCC and eAG
We have added a tool for converting between NGSP(%), IFCC (mmol/mol) and eAG (mg/dL) units. Click here...
CAP 2016 GH5b Summary Report
The summary report for the CAP 2016 GH5b proficiency survey is now available. Download...

Laboratory Qualit

Lab Standards Home
Cholesterol Reference Method Laboratory Network
Ensuring the Quality of Urinary Iodine Procedures
Hormone Standardization
Lead and Multielement Proficiency Program
Lipid Standardization Program
Newborn Screening Quality Assurance Program
Proficiency in Arsenic Speciation
Vitamin A Laboratory - External Quality Assurance
Contact Us

Related Links
Division of Laboratory Sciences

Key Resources

- HoSt Testosterone Certified Procedures
  [PDF - 297 KB]
  Updated September 2016
- VDSCP Vitamin D Certified Procedures
  [PDF - 312 KB]
  Updated September 2016
- HoSt Estradiol Certified Procedures
  [PDF - 292 KB]
  Updated September 2016

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: Testosterone Certified edures
PDF - 297 KB]
Updated September 2016
VDSCP Vitamin D Certified

of population subgroups with unsafe levels
- Minimize retesting of patients referred to another doctor

Laboratory Quality Assurance and Standardization Programs

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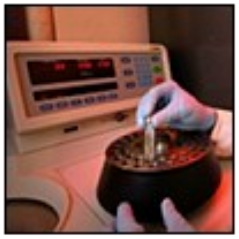
- Newborn Screening Quality Assurance Program
- Proficiency in Arsenic Speciation
- Vitamin A Laboratory - External Quality Assurance
- Contact Us

Related Links
Division of Laboratory

Lipid Standardization Program



The Centers for Disease Control and Prevention (CDC) maintains a Lipid Standardization Program (LSP) that provides accuracy-based standards for measuring total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-I (apo A-I), and apolipoprotein B (apo B) in U.S. and international laboratories.

The LSP is unique among external quality-control systems (EQAS) in that it provides a way to establish, assess, and improve the accuracy—or trueness—of analytical measurements over time. The LSP provides traceability to CDC's reference measurement procedures (RMPs) for the measurement of TC, TG, and HDL-C. Traceability to designated comparison methods (DCMs) at Northwest Lipid Metabolism and Diabetes Research Laboratories (NWLMDRL) for apolipoproteins is provided through the LSP. In this way, the LSP standardizes the resulting measured values of these lipids, lipoproteins, and apolipoproteins no matter what analytical system is used. Measurement standardization ensures the credibility of results and valid comparability among different

Program Information
- About the Program
- Eligibility Requirements
- FAQs
- General Information
- Reference Materials
- Reference Measurement Procedures
- Resources
- Standardization Process
- Suggested Reading & References
- Contact the Program

Key Resources

Certification Programs

- NGSP – HbA1c
- CDC - Lipids
- CDC - Steroids

- All use/contribute to JCTLM listed materials / methods / services
- All collaborate with international partners

CDC Home

Centers for Disease Control and Prevention

CDC 24/7: Saving Lives. Protecting People.™

Research

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

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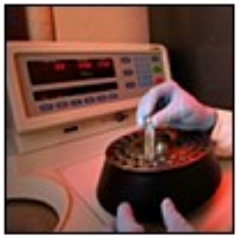
Lipid Standardization Program



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Commenced 1950's
Related to Framingham Study
Remains vital today
Linked to JCTLM-listed methods

Program Information

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sources

The role of Manufacturers

1. Actions

- Traceable to best international references (JCTLM)
- Good traceability practice (low uncertainty)
- Confirmed low bias of final product

2. Words

- Describe references used (JCTLM)
- Describe uncertainty
- Demonstrate quality of final product
- Include in IFU / sales material

Routine Laboratories

- Choose methods which are:
  - Traceable to good references (JCTLM listed)
  - Have low uncertainties for calibrators
  - Minimise changes over time
- Select and promote unbiased comparators
  - Common decision points
  - Common reference intervals
- Confirm performance with traceable EQA

Conclusions

- Assay traceability is vital for lab medicine
  - Patient safety
  - Cost effectiveness
  - Evidence based medicine
  - IT-application
- Metrology already backs most of what we do
  - Weights, volumes, currents, lights
- Traceability is a global activity
- We all need to play our role in traceability
- Good results are our contribution to healthcare

Traceability – The Modern Tool