St Vincent's Hospital

A facility of St Vincents & Mater Health Sydney

SYDPATH

ST VINCE

Survey assay and … performance i… …a:

Traceability and External Quality Assurance

…ceability by …te quality control

Graham Jones

Department of Chemical Pathology

St Vincent's Hospital, Sydney

EUROMEDLAB
MILANO 2013
19-23 MAY

20th IFCC-EFLM European Congress
of Clinical Chemistry and Laboratory Medicine

45th Congress of the Italian Society of
Clinical Biochemistry and Clinical Molecular Biology (SIBioC)

POST-CONGRESS SATELLITE MEETINGS
May 24th, 2013

CIRME

UNIVERSITÀ DEGLI STUDI
DI MILANO

7th CIRME International Scientific Meeting
Metrological traceability and assay standardization

Stresa, Italy

Positions

- Chemical Pathologist in Sydney
- Chair of Chemical Pathology Advisory Committees for RCPA and RCPAQAP
- Member JCTLM executive
- Co-Chair IFCC WP on CKD
- Co-Chair Australian Working parties on:
  - eGFR
  - Urine albumin
  - HbA1c for diagnosis
  - Common reference intervals

Overview

- Introduction
- Uses for QAP results
- Selected Examples
  - Key papers
  - Australian Developments
- Conclusions

“ 3 Pillars of Traceability”

- Reference Materials
- Reference Measurement Procedures
- Reference Measurement Services

“ 4 Pillars of Traceability”

- Reference Materials
- Reference Measurement Procedures
- Reference Measurement Services
- Common Reference intervals

“ 5 Pillars of Traceability”

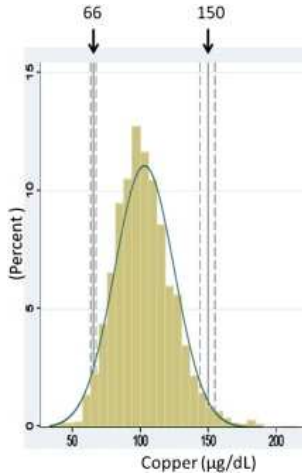
- Reference Materials
- Reference Measurement Procedures
- Reference Measurement Services
- Common Reference intervals
- **External Quality Assurance**
  - Mauro Pantegini

Interpreting laboratory results

All numerical laboratory 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	
Sodium:	**140**	**145**	mmol/L

Per-Hyltoft petersen, 2004

Valid comparisons

- For a valid comparison the results from the **comparator** must be comparable to **your results**
- **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*

*May be your laboratory or elsewhere

Why?

- For safe, evidence-based medicine, laboratories must provide consistent, comparable results.

- Patient safety
- Application of evidence
- Waste avoidance

Today’s assays

- Excellent reference materials *(for some)*
- Excellent reference methods *(for some)*
- Excellent reference laboratories *(for some)*
- Clear processes for manufacturers
- Clear performance goals for manufacturers *(for some)*
- Accredited routine laboratories

….. It’s all OK?

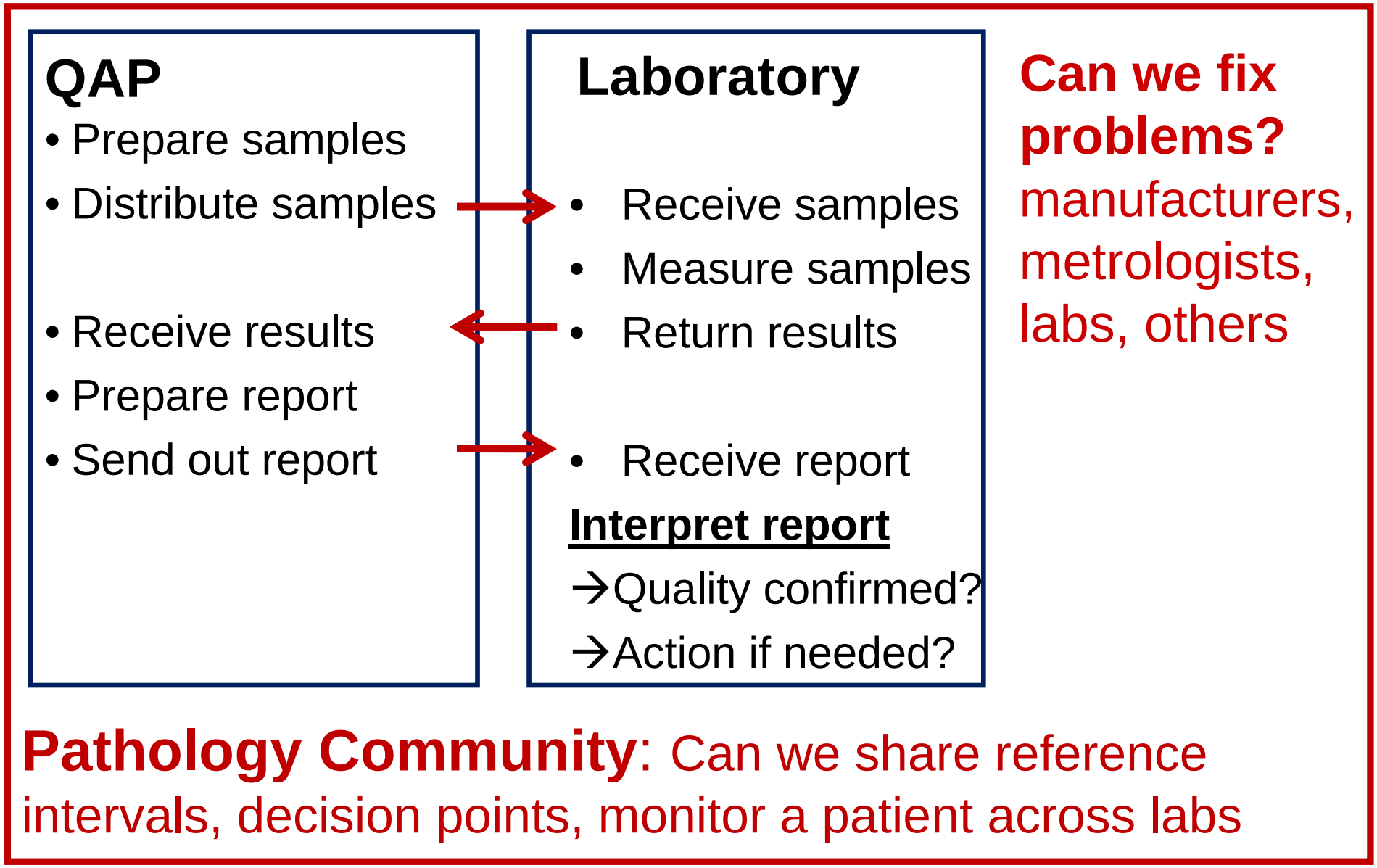
Laboratory Medicine Procedures

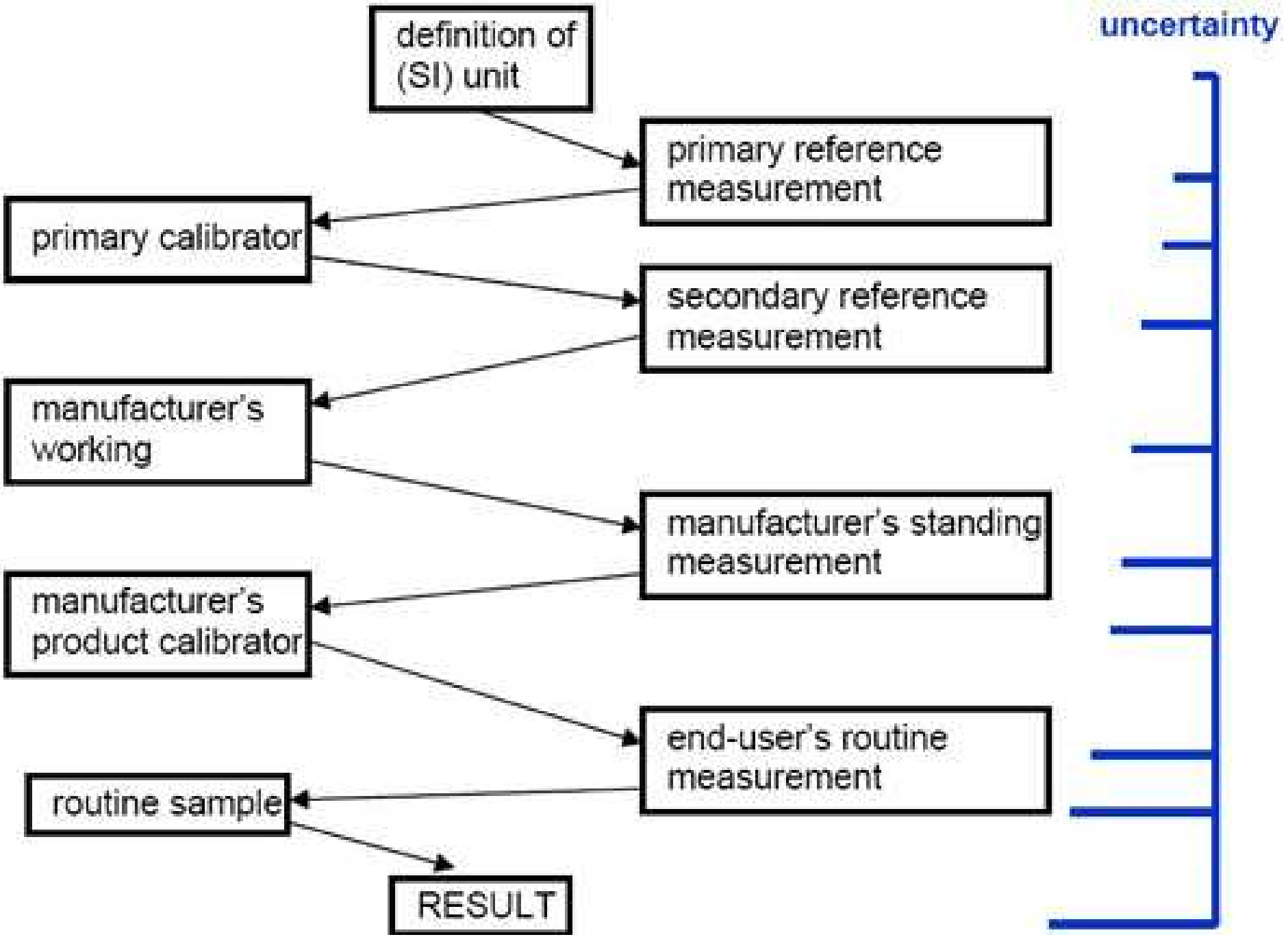
- **Write down** how to do it right
- **Do** it right
- **Prove** we have done it right
  - Assay verification / validation
  - Internal quality control
  - External quality assurance

A metrologist…

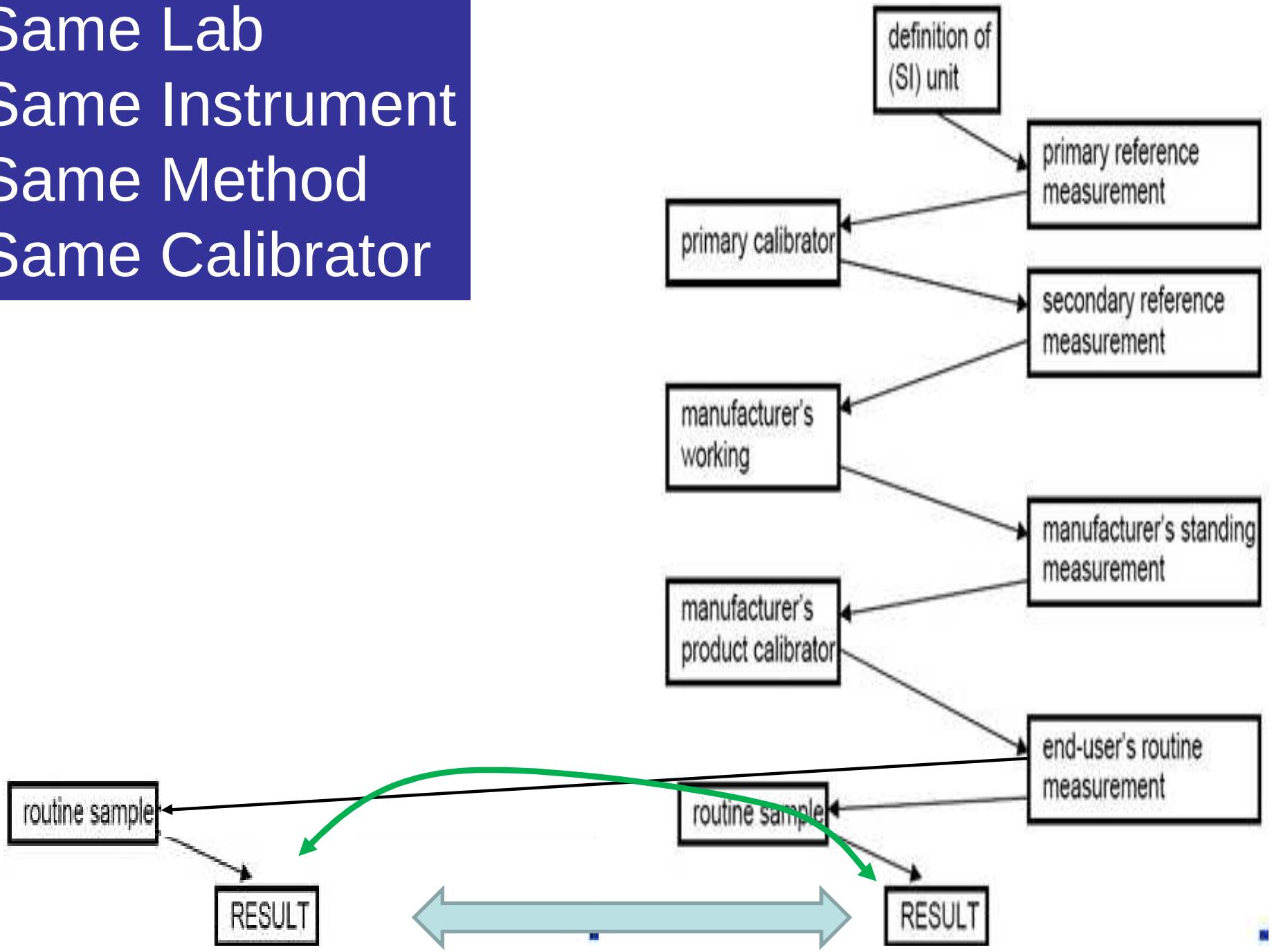
- Someone who trusts nothing and trusts no-one
  - *Anonymous Australian metrologist*

Quality Assurance Process

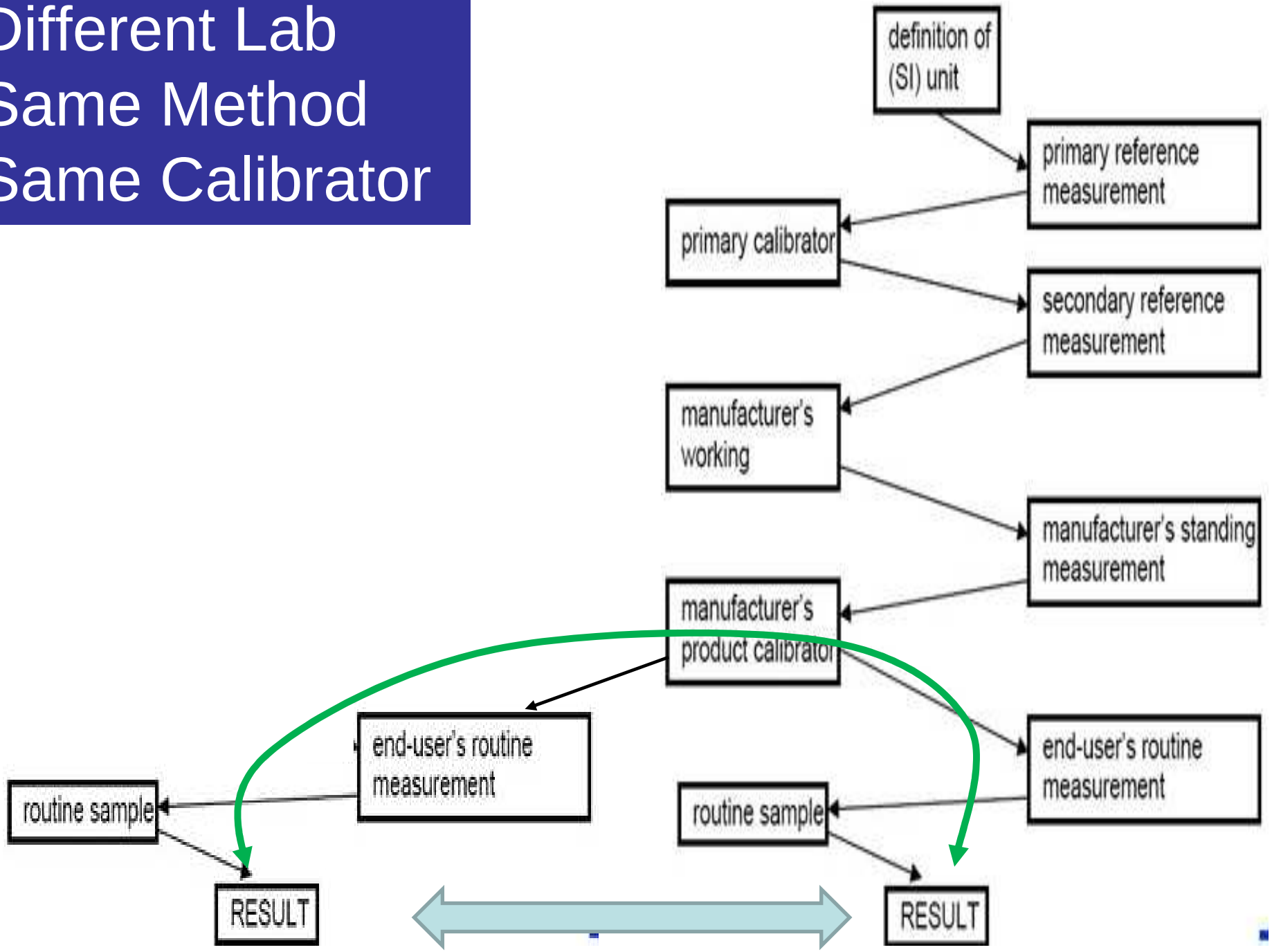



definition of (SI) unit
primary reference measurement
primary calibrator
secondary reference measurement
manufacturer's working
manufacturer's standing measurement
manufacturer's product calibrator
end-user's routine measurement
routine sample
RESULT
uncertainty

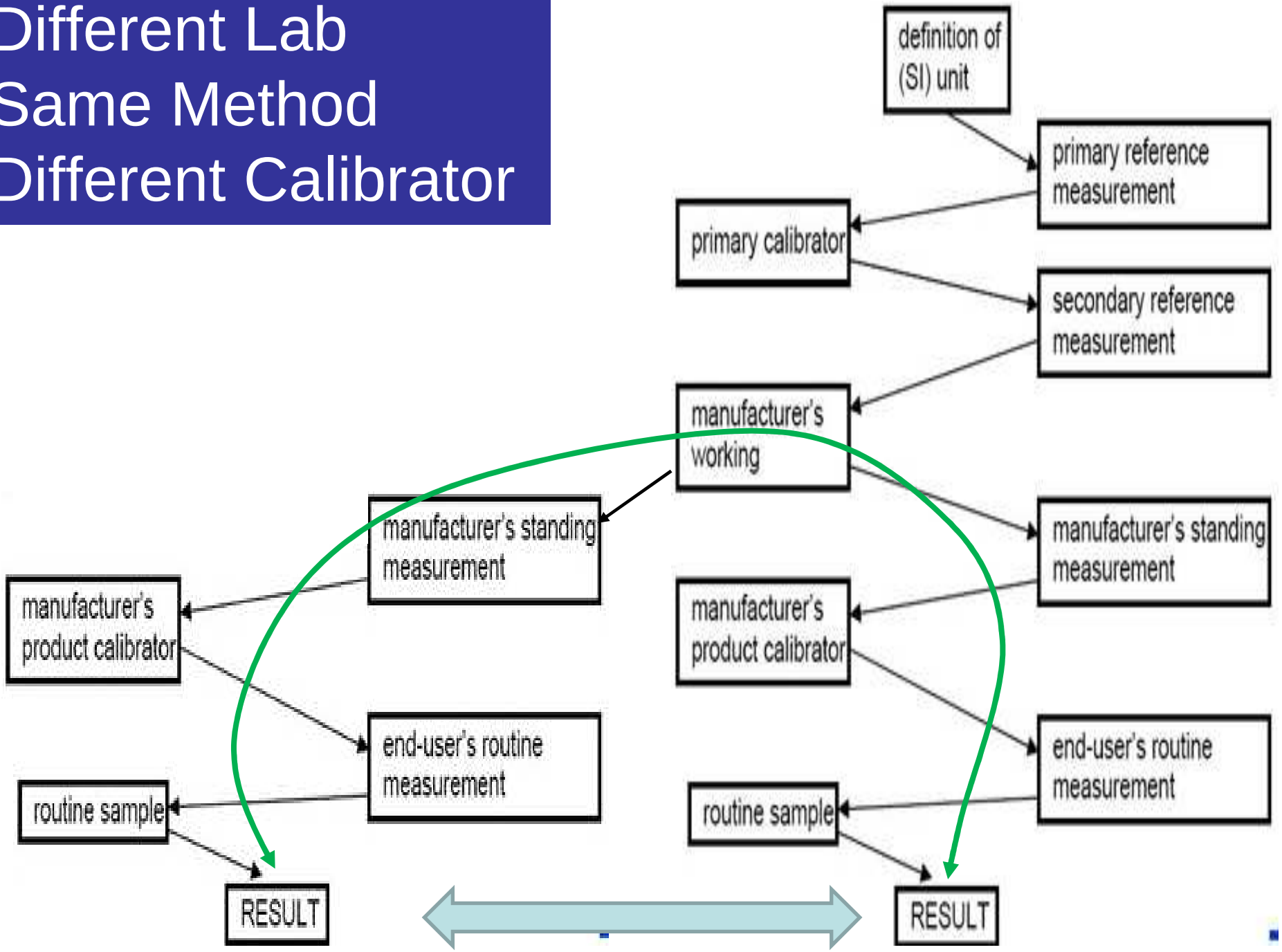
Same Lab
Same Instrument
Same Method
Same Calibrator



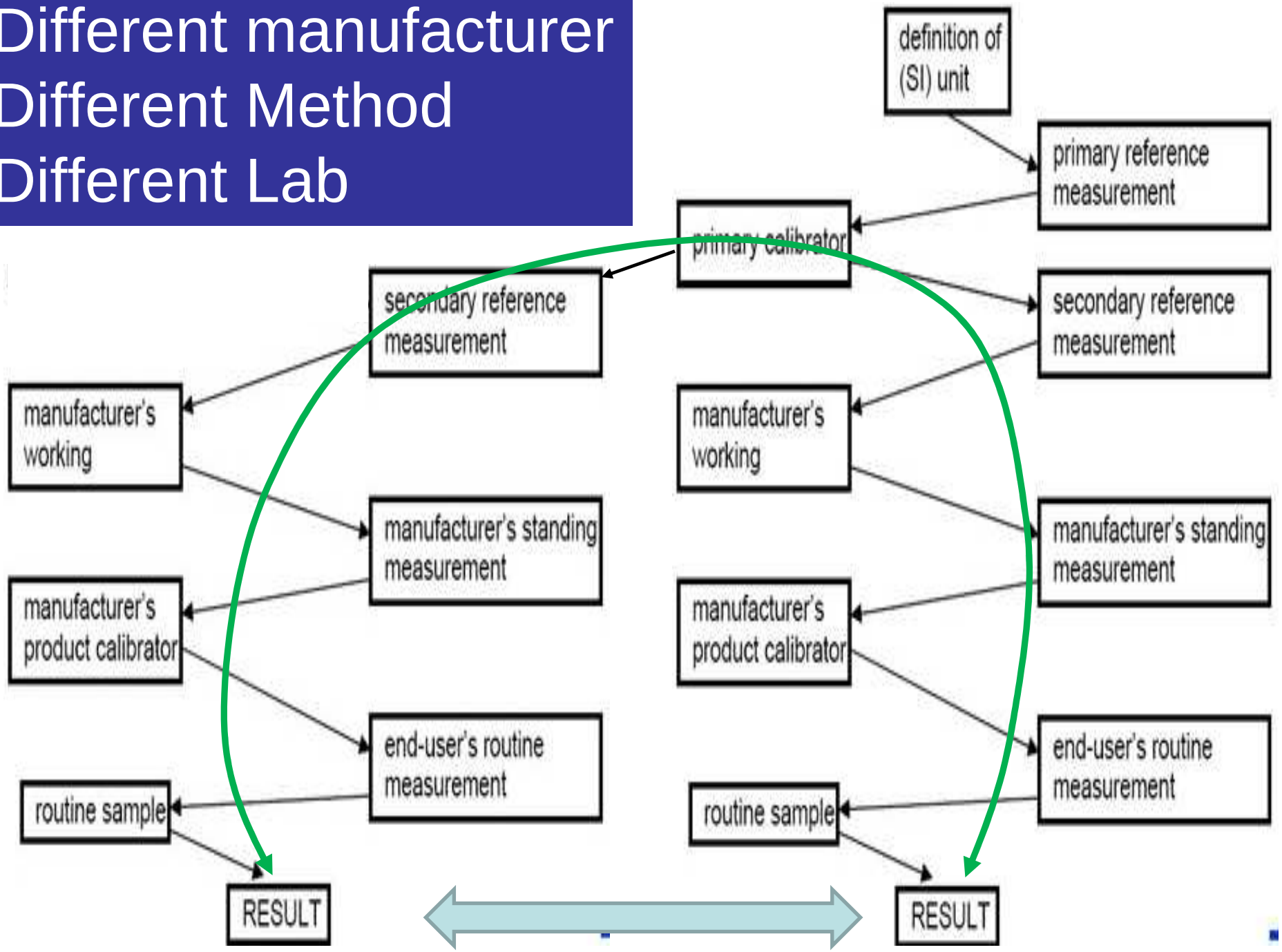
Different Lab
Same Method
Same Calibrator



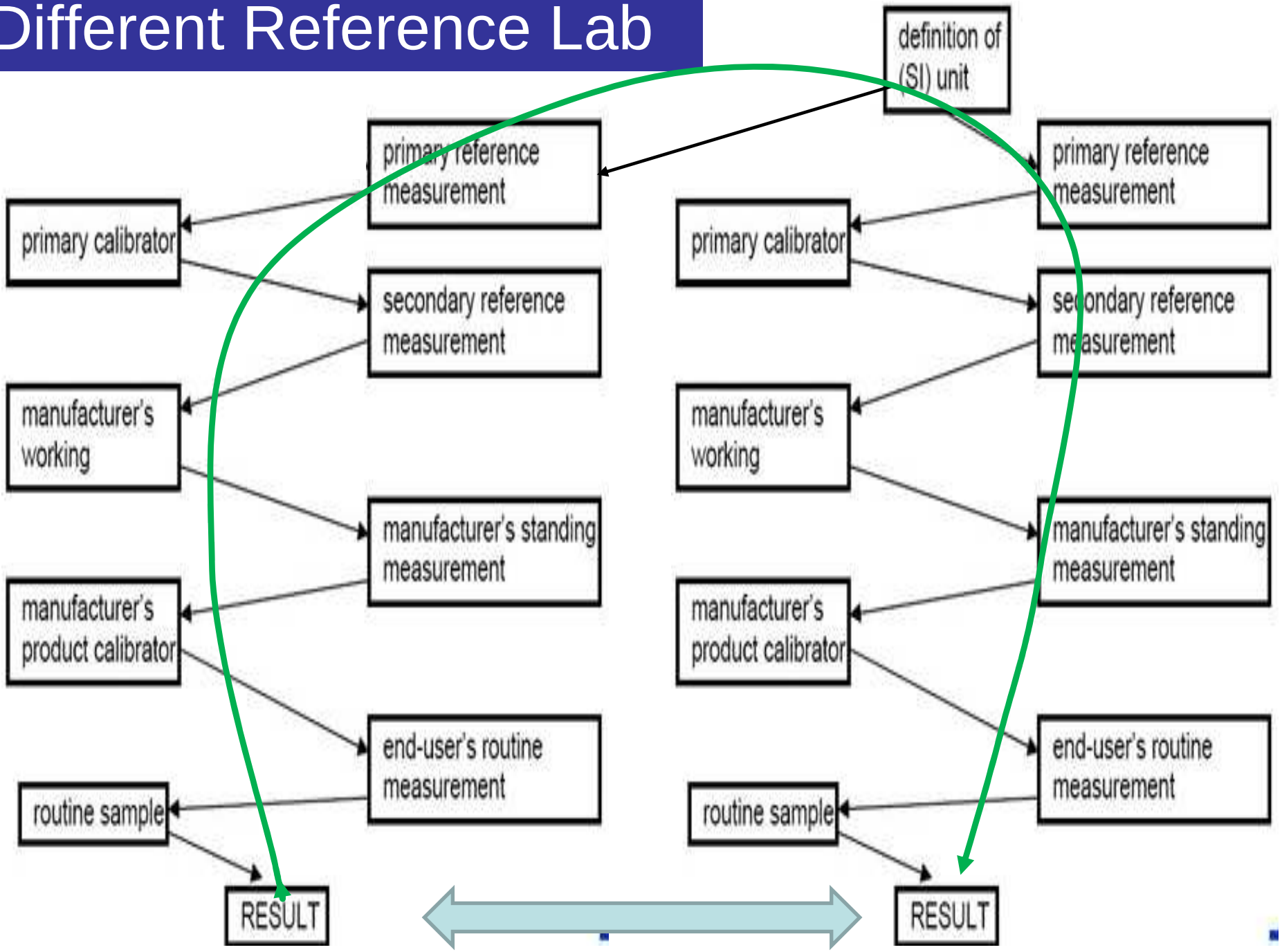
Different Lab
Same Method
Different Calibrator

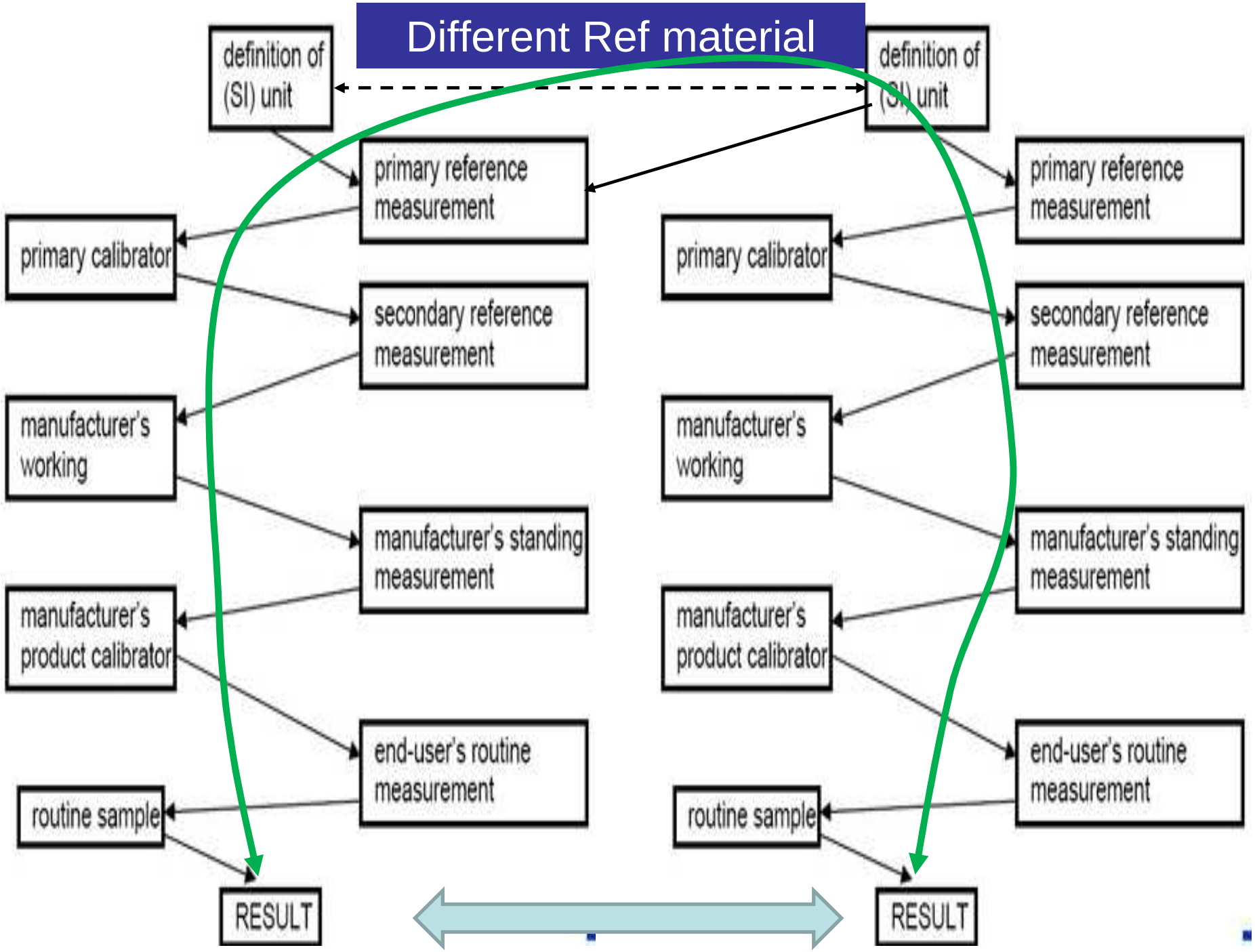


Different manufacturer
Different Method
Different Lab



Different Reference Lab




Different Ref material
definition of (SI) unit
definition of (SI) unit
primary reference measurement
primary reference measurement
primary calibrator
primary calibrator
secondary reference measurement
secondary reference measurement
manufacturer's working
manufacturer's working
manufacturer's standing measurement
manufacturer's standing measurement
manufacturer's product calibrator
manufacturer's product calibrator
end-user's routine measurement
end-user's routine measurement
routine sample
routine sample
RESULT
RESULT

Comparing Results

- Required to assess clinical utility
- Can be many, many steps in ***comparability chain***

- **EQA can confirm comparability:**
  - With reference method
  - With other results
    - Same method
    - Different laboratories
    - Different methods
- Can inform decisions about use of results
- NEEDS: commutable materials; quality standards

Some examples

EUROPEAN COMMISSION
DIRECTORATE GENERAL JRC
JOINT RESEARCH CENTRE
IRMM
Institute for Reference Materials and Measurements

IMEP®

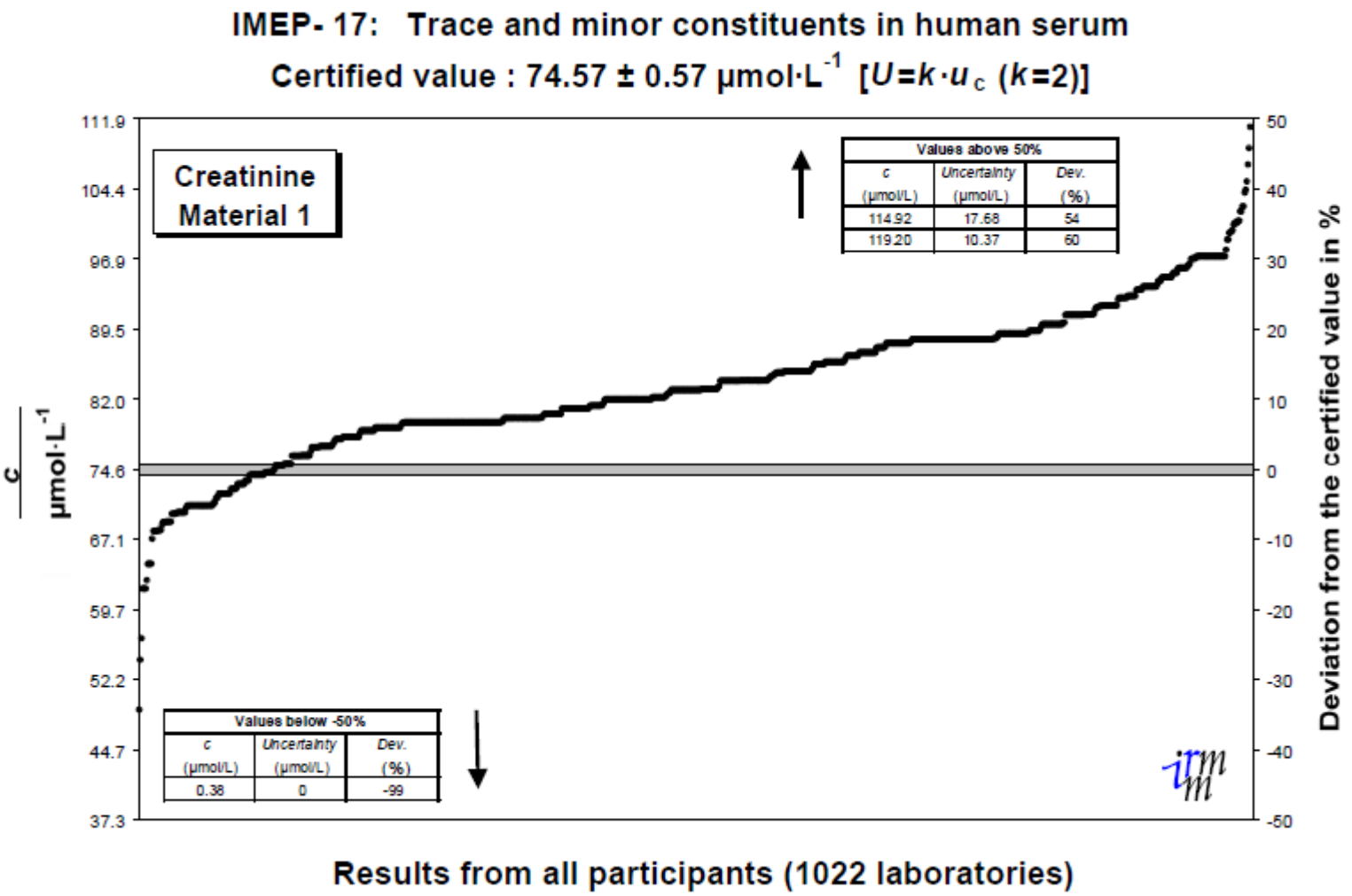
IRMM
Isotope Measurements Unit

GE/R/IM/42/02
Revised 2003-06-03

The International Measurement Evaluation Programme

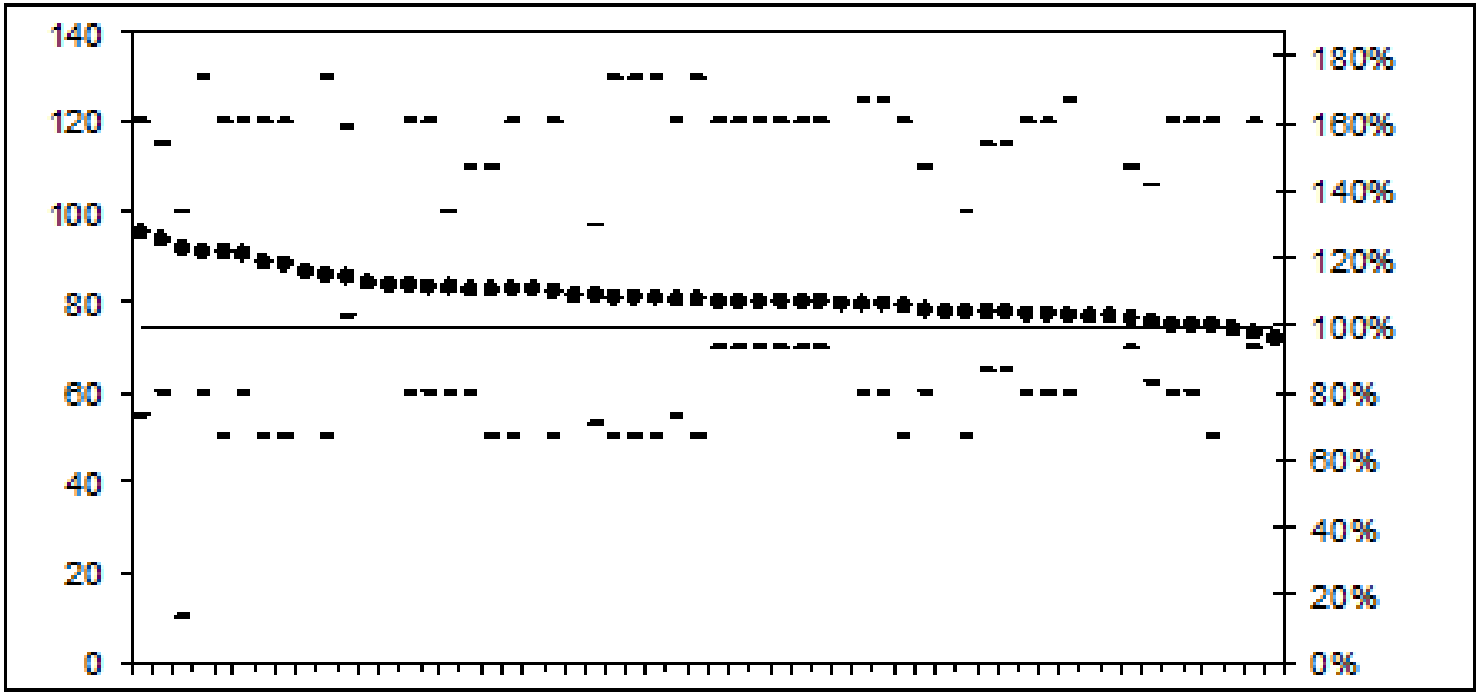
IMEP-17
Trace and Minor Constituents in Human Serum
EUR 20657 EN
Report to Participants

IMEP-17


IMEP- 17: Trace and minor constituents in human serum
Certified value : 74.57 ± 0.57 µmol·L-1 [U=k·uc (k=2)]
Creatinine
Material 1
Values above 50%
c (µmol/L) | Uncertainty (µmol/L) | Dev. (%)
114.92 | 17.68 | 54
119.20 | 10.37 | 60
Values below -50%
c (µmol/L) | Uncertainty (µmol/L) | Dev. (%)
0.38 | 0 | -99
111.9
104.4
96.9
89.5
82.0
74.6
67.1
59.7
52.2
44.7
37.3
c / µmol·L-1
50
40
30
20
10
0
-10
-20
-30
-40
-50
Deviation from the certified value in %
Results from all participants (1022 laboratories)

IMEP-17 – Local Use - creatinine

Figure 1. Summary of data for creatinine results from Sample 1 and upper and lower reference intervals from Australian and New Zealand laboratories. X axis: laboratories in descending order of serum creatinine. Y axis: creatinine measurements for Sample 1 and upper and lower reference limits for each laboratory. The straight horizontal line is the IMEP target.



Key Example Paper:

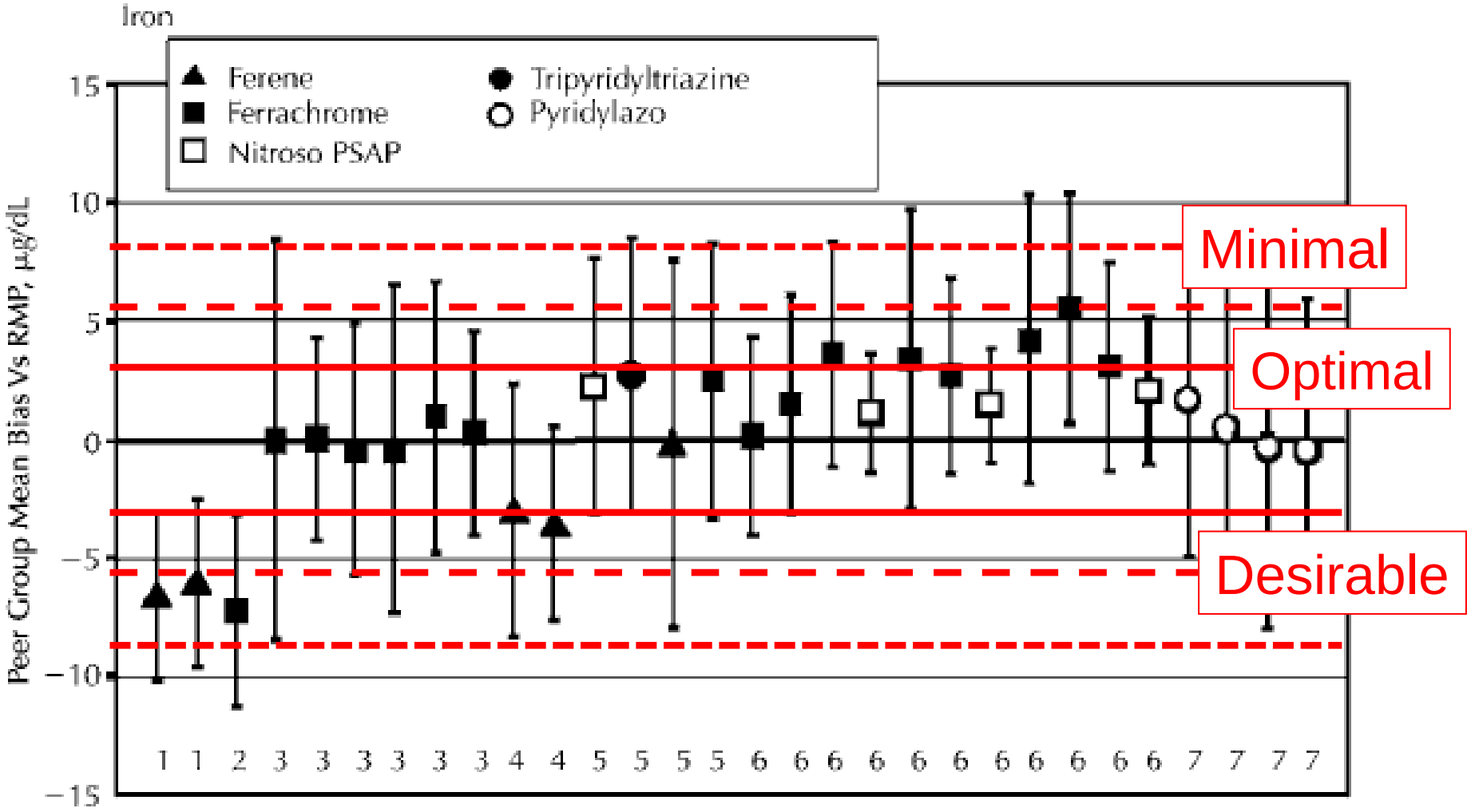
State of the Art in Trueness and Interlaboratory Harmonization for 10 Analytes in General Clinical Chemistry

W. Greg Miller, PhD; Gary L. Myers, PhD; Edward R. Ashwood, MD; Anthony A. Killeen, MD, PhD; Edward Wang, PhD; Glenn W. Ehlers, BS/MT, MBA; David Hassemer, MS; Stanley F. Lo, PhD; David Seccombe, MD, PhD; Lothar Siekmann, PhD; Linda M. Thienpont, PhD; Alan Toth, BS

- **Commutable Material**
- **Reference method measurements**
- **Valid quality criteria**

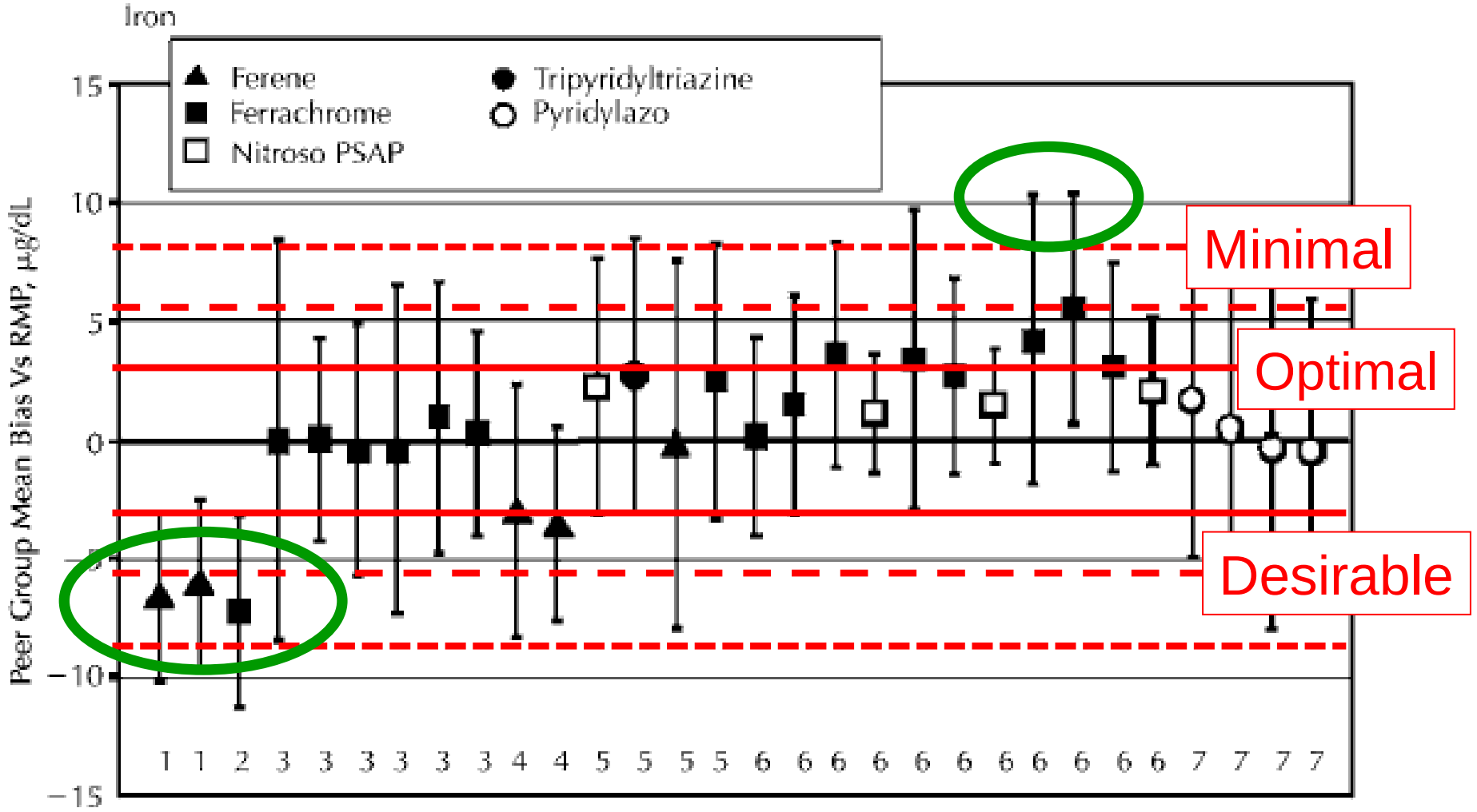
Arch Pathol Lab Med. 2008;132:838–846

Miller et al, Iron



All methods at “minimal level”, most at “desirable level”

Responses: Labs, Manufacturers, Profession?



Profession: Most labs can use same reference intervals

Why Results might be different

- **Materials:** *selection*, *purity,* value assignment, stability, homogeneity, preparation
- **Methods:** bias, precision, analytical specificity
- **Traceability chain:** number of steps, concentrations for transfer, summation of all errors

- There is always more uncertainty with more steps
- There is always more variation with more analysers, more methods, more laboratories

Similar Studies

Commutable material, value assigned, quality limits

Limitations:

- Expensive
- Limited sample numbers
- Limited sample concentrations

- CAP, UK-NEQAS, SKML, (RCPAQAP)…

IFCC - RELA

RELA Home

Welcome

login

Registration/ Accou

RELA in progress

order RELA 2012

enter RELA 2012 results

former RELA results

Choose year...

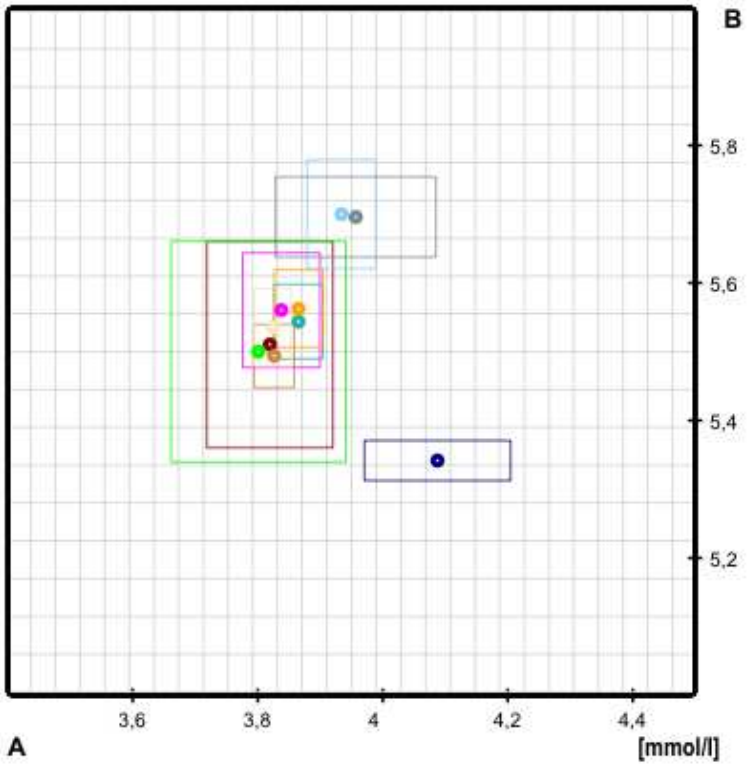
RELA 2011

All or choose Lab ...

select lab analytes | full address

Potassium | show result plot

with limits of equivalence



For highlighting a specific result please click on the corresponding result line.

Labcode	A	e.u. A	B	e.u. B	Method
3	3,837	0,063	5,561	0,083	ICP-OES after digestion of organic sampl
16	3,82	0,1	5,51	0,15	FES
18	3,826	0,031	5,494	0,045	ICP/MS
24	3,8	0,14	5,5	0,16	FES
25	3,934	0,055	5,7	0,08	FES
27	3,866	0,039	5,543	0,055	FES
39	3,823	0,03	5,536	0,057	flame atomic emission spectrometry
63	3,958	0,128	5,696	0,058	FES
106	4,088	0,116	5,342	0,03	FAAS
127	3,865	0,039	5,562	0,056	ICP-IDSMS

grey lines indicate a one-percent grid

e.u. - expanded uncertainty

Clinica Chimica Acta 414 (2012) 234–240

Contents lists available at SciVerse ScienceDirect

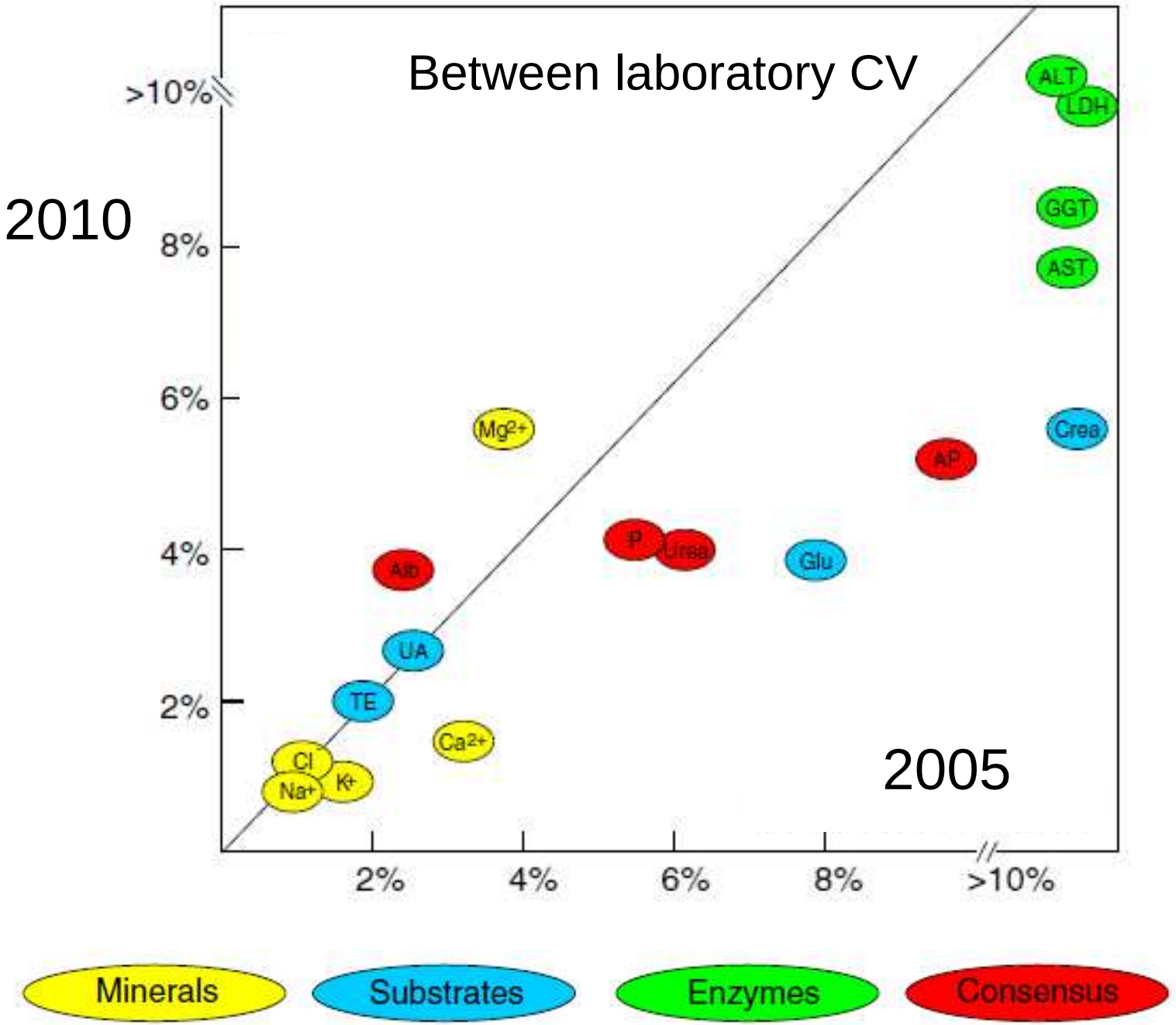
Clinica Chimica Acta

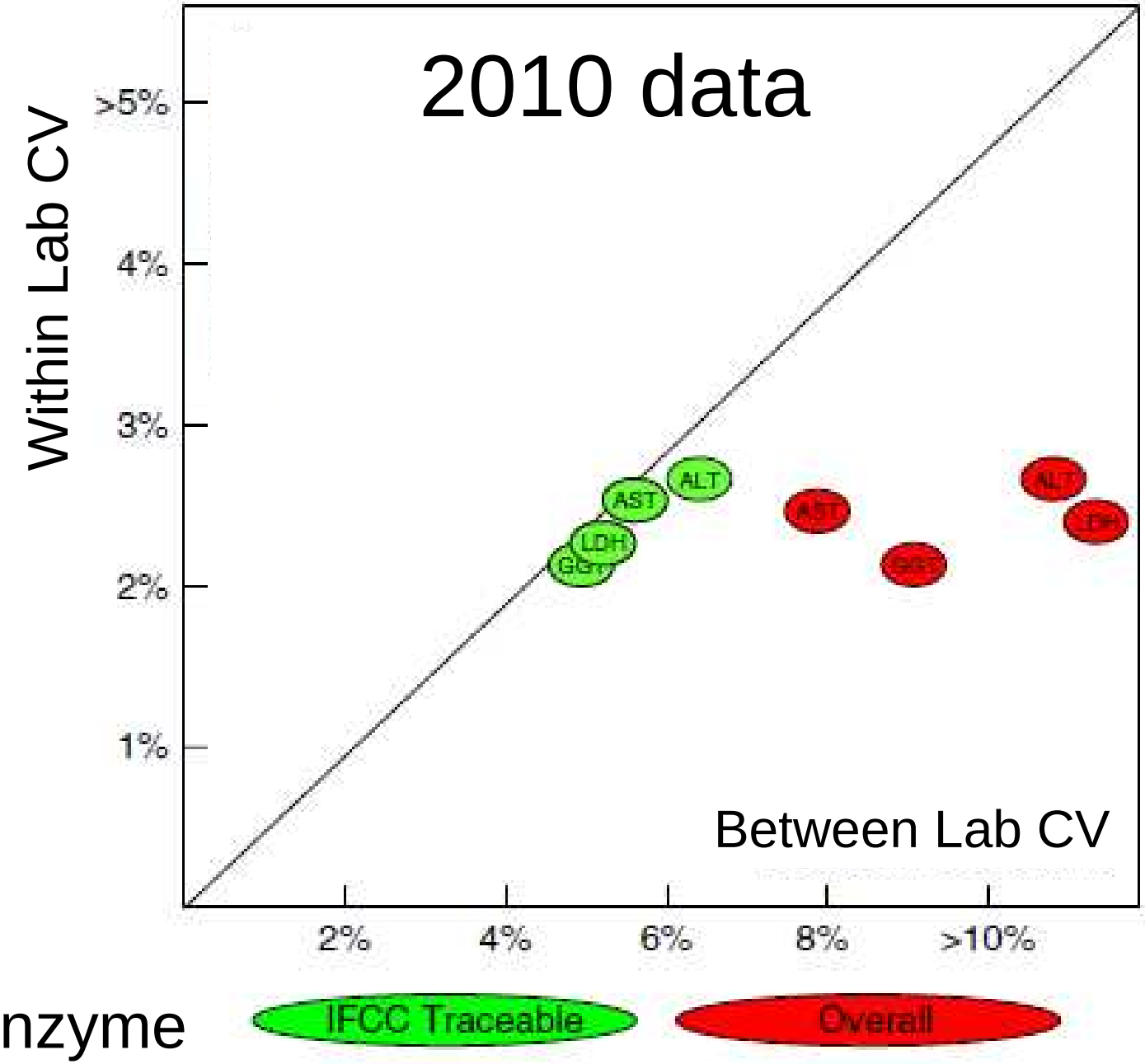
journal homepage: www.elsevier.com/locate/clinchim

Systematic monitoring of standardization and harmonization status with commutable EQA-samples—Five year experience from the Netherlands

Christa Cobbaert [a,*], Cas Weykamp [b], Paul Franck [c], Robert de Jonge [d], Aldy Kuypers [e], Herman Steigstra [f], Jacqueline Klein Gunnewiek [g], Douwe van Loon [h], Rob Jansen [f]

Clinica Chimica Acta 414 (2012) 234–240


Between laboratory CV
2010
2005
>10%
8%
6%
4%
2%
2%
4%
6%
8%
>10%
ALT
LDH
GGT
AST
Crea
AP
Mg2+
P
Urea
Glu
Alb
UA
TE
Ca2+
Cl-
Na+
K+
Minerals
Substrates
Enzymes
Consensus

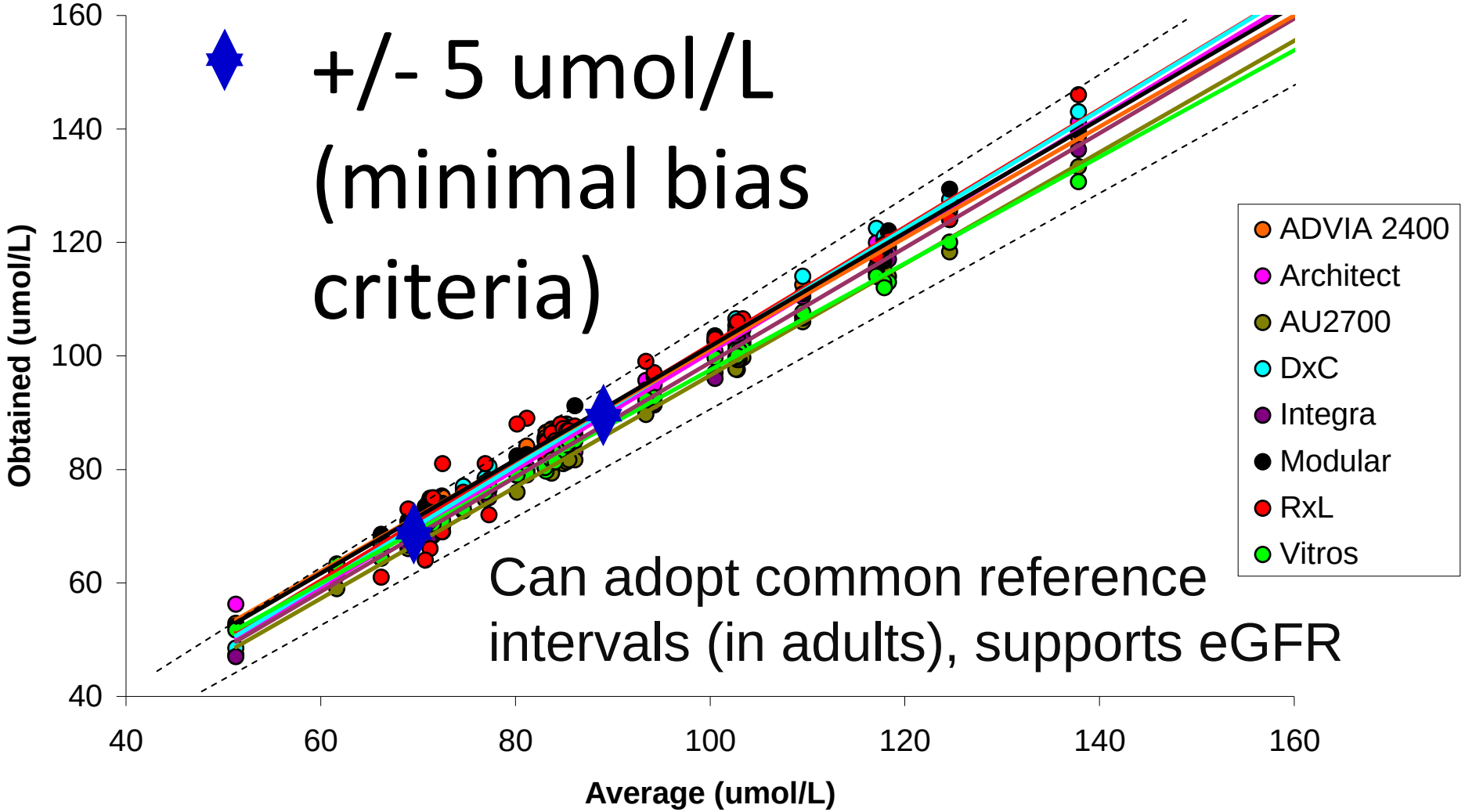


"Enzyme harmonisers"

Australian Activities

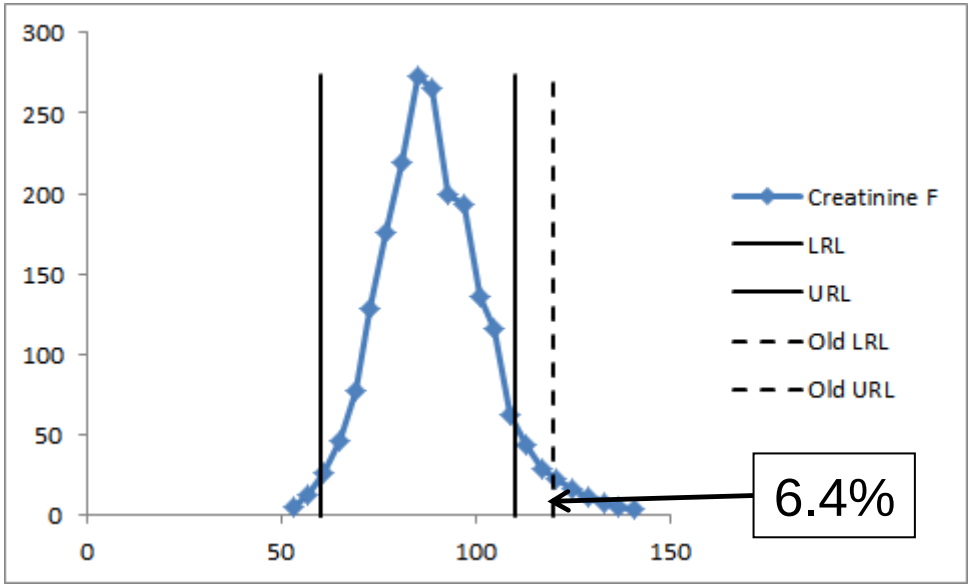
- AACB Harmonisation activities
  - Common reference intervals / decision points
  - Critical alert limits
- RCPA
  - Loinc Codes
  - Units
- All activities use “EQA” data
- Many use RCPAQAP

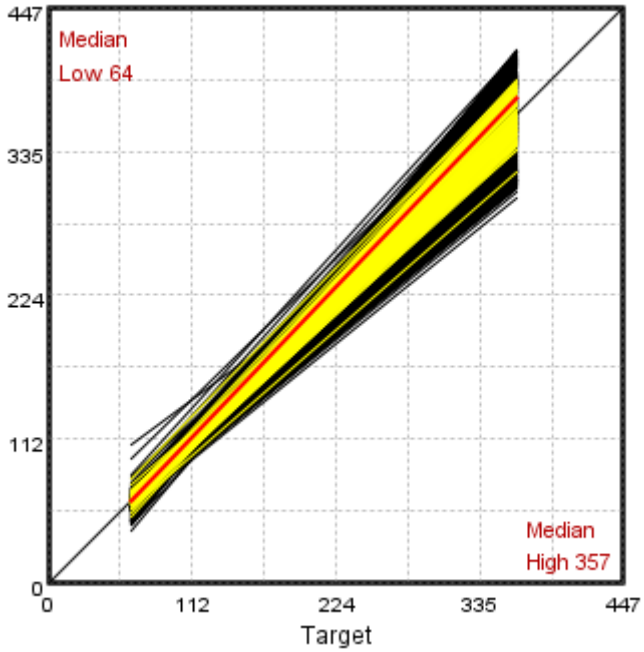
Creatinine - Australia
2011 survey, 7 methods, 21 labs

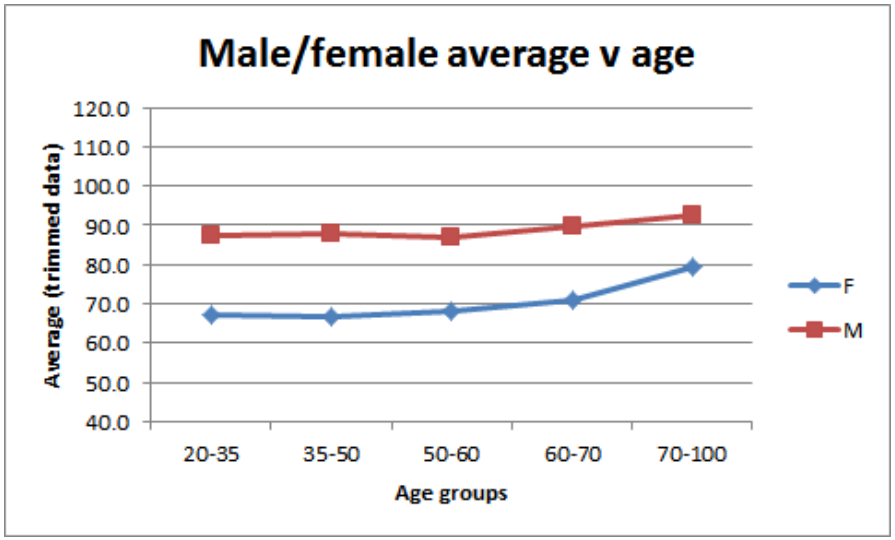


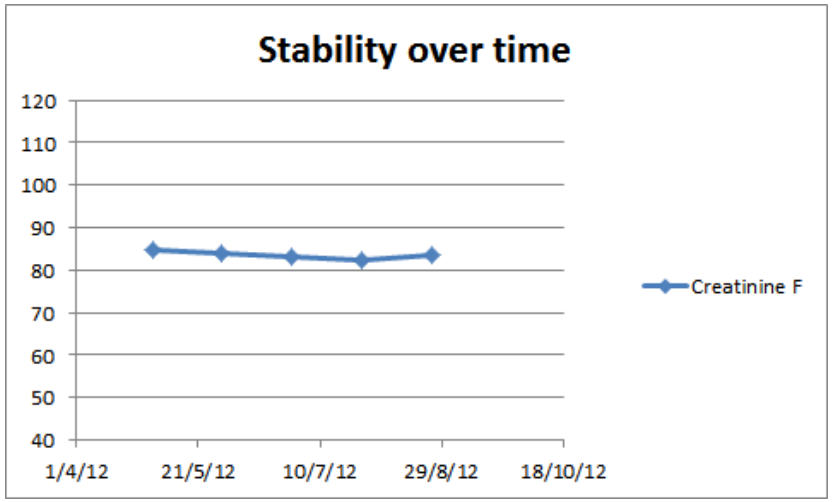
With thanks to Gus Koerbin (ACT) and AACB

Serum Creatinine - Male

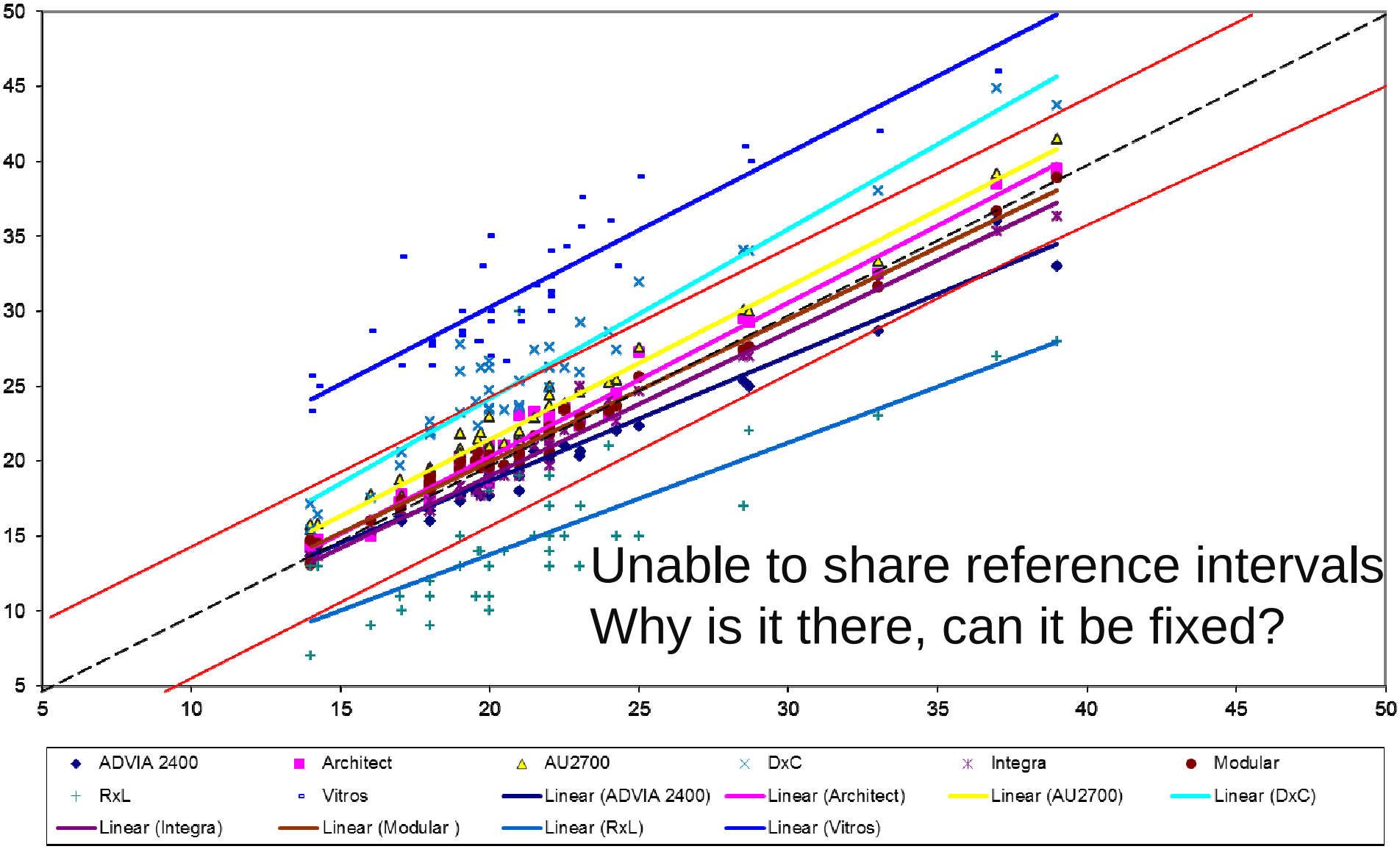




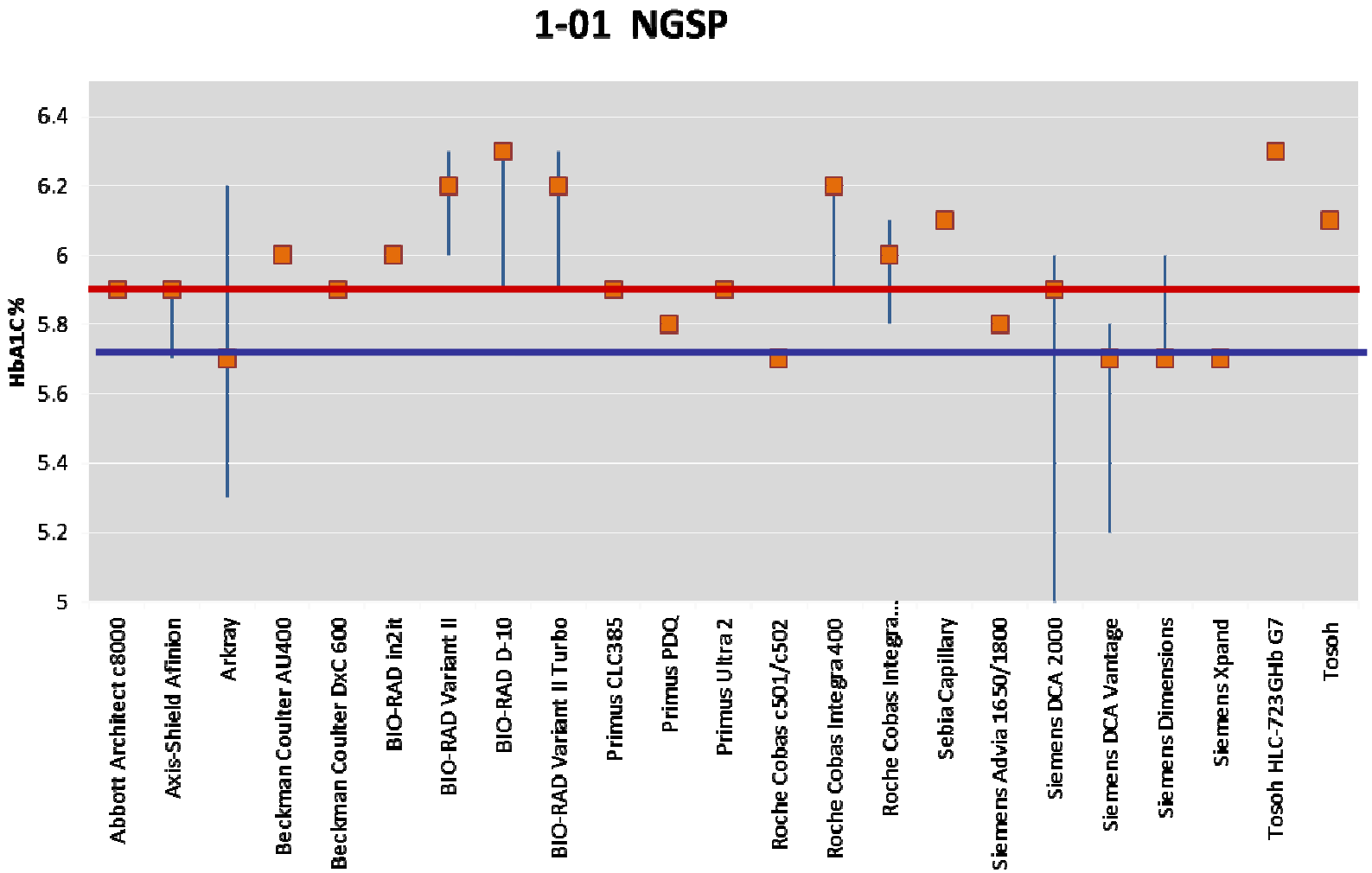




ALT - Australia



HbA1c – Whole blood - 2012



Median
5.9 %
(41 mmol/mol)

Ref.
5.7%
(39 mmol/mol)

RCPAQAP
RCPA Quality Assurance Programs

European Reference Laboratory for Glycohaemoglobin

ERL

Address for correspondence
Dr. C. W. Weykamp
Queen Beatrix Hospital
Beatrix Park 1
7101 BN Winterswijk
The Netherlands
Telephone: + 31 543 54 47 74
Fax: + 31 543 52 42 85
e-mail: c.w.weykamp@sdbwinterswijk.nl

Winterswijk, 5 March 2012

Please find below the IFCC and NGSP (DCCT) certified value assignment of your HbA1c samples. Values have been assigned in triplicate with two IFCC Secondary Reference Measurement Procedures, IFCC calibrated. NGSP values are derived from the IFCC values using the Master Equation.

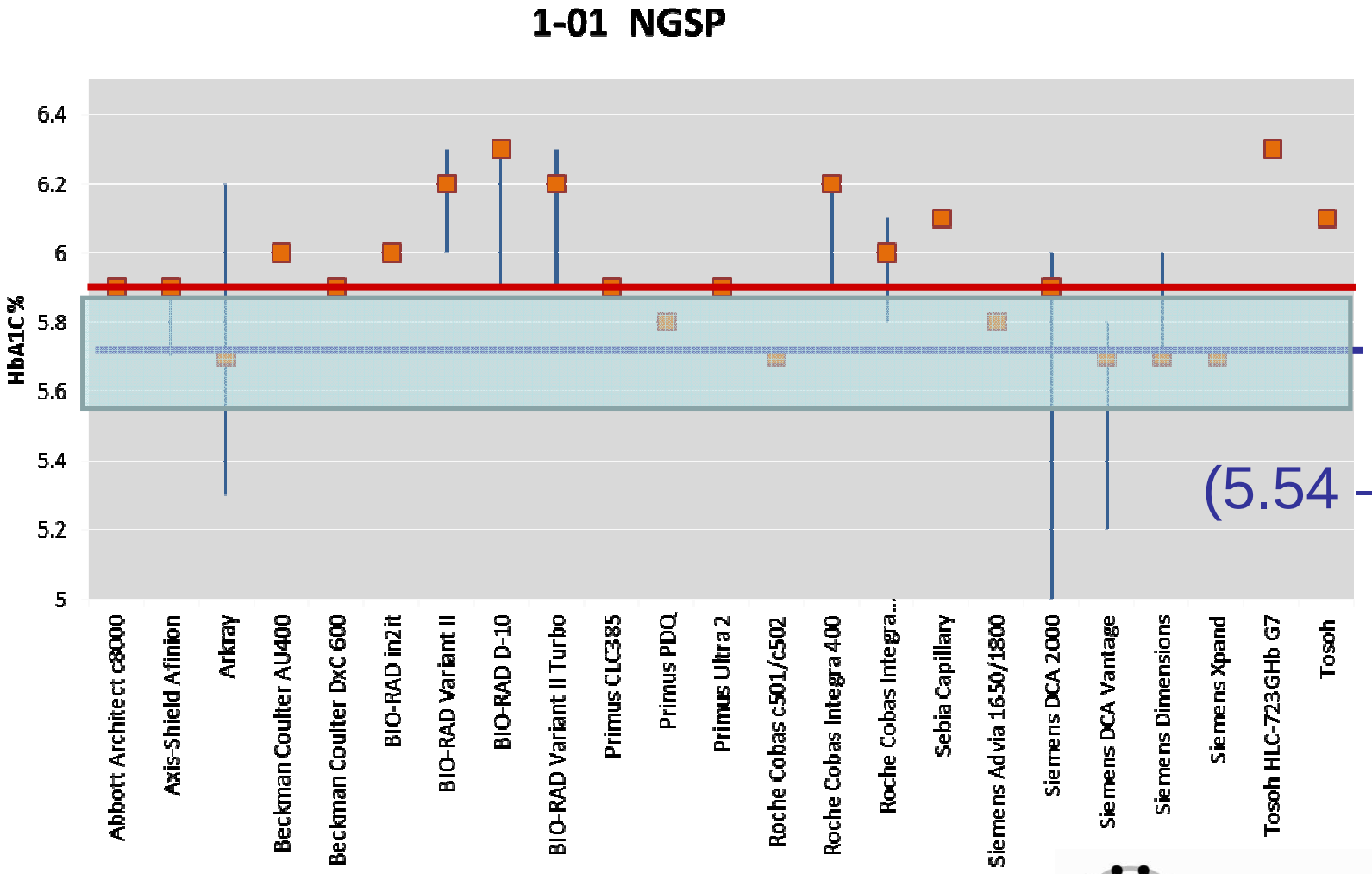
Sample ID	**Assigned IFCC value** mmol/mol	**Unc** (k=2)	**Assigned NGSP value** %	**Unc** %
Sample 1-01	**38.8**	1.8	**5.70**	0.16
Sample 1-02	**88.7**	3.0	**10.27**	0.27

Dr. Ir. R. J. Slingerland
chair

Dr. C. W. Weykamp
coordinator

Dr. P. van der Vaart
assessor

HbA1c – Whole blood - 2012



Median
5.9 %

Ref.
5.7%
(5.54 – 5.86)

RCPAQAP
RCPA Quality Assurance Programs

HbA1c – Whole Blood

- Working Party formed
  - Pathologists, Diabetologists, Scientists, QAP staff

- Aim to use data for:
  - Establishing performance criteria
  - Assessing suitability of methods for use
  - Providing feedback to labs
  - Providing confidence to users

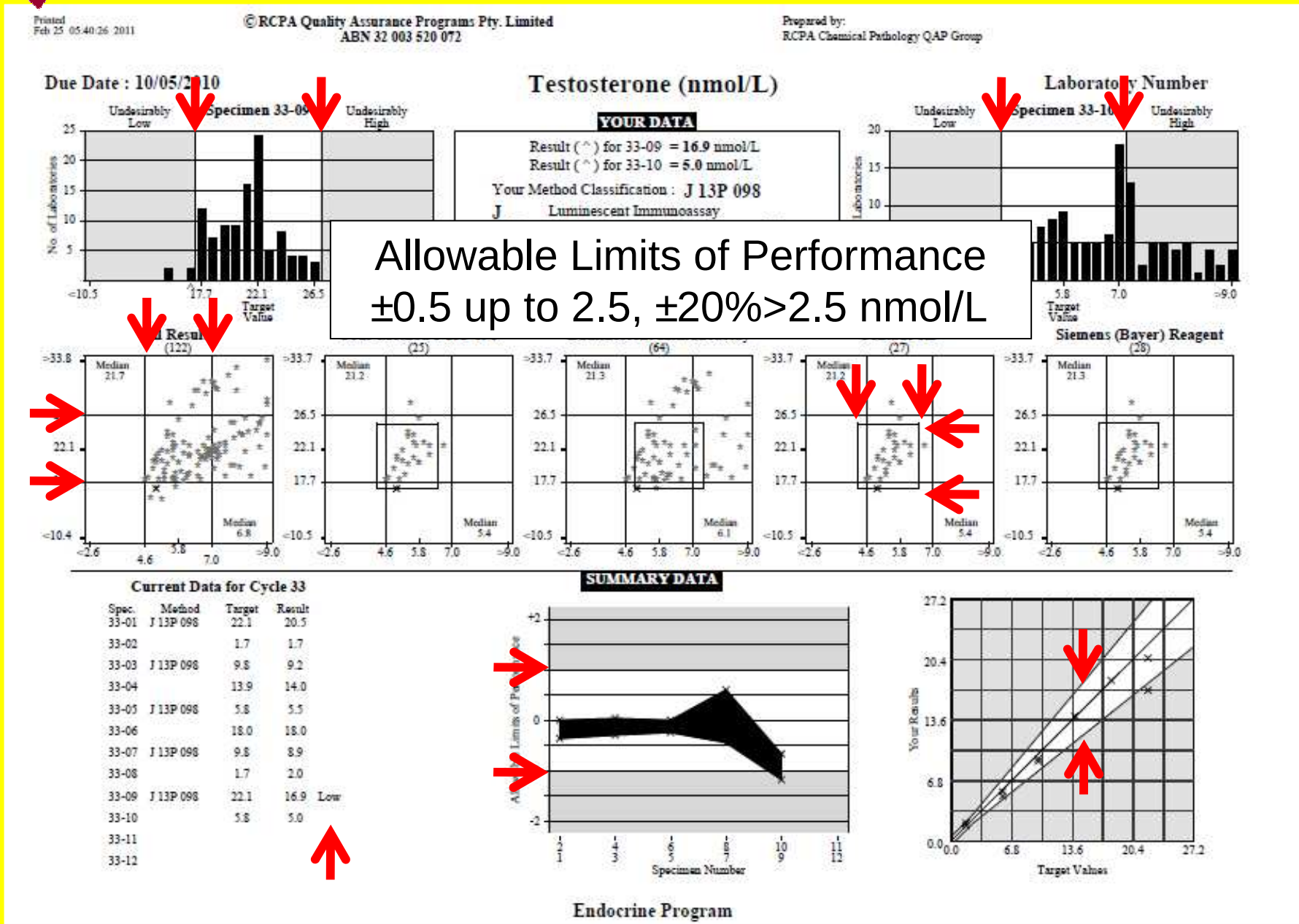
RCPAQAP
RCPA Quality Assurance Programs

QAP - Allowable Limit of Performance

- “Quality Standard” for assessing QAP results
- Based on Clinical decision making
- Highest level of Stockholm criteria (usually biological variation)

RCPAQAP
RCPA Quality Assurance Programs

RCPA QAP Interim Report



Meaning of ALP

Analyte	New ALP					
	±	To	Then %	Comment	Level	Basis
Conj Bili	3	15	20%	Same	Optimal	Imprecision
Calcium	0.10	2.50	4%	Same	Minimal	Imprecision
Chloride	3	100	3%	Same	Minimal	Total Error
Cholesterol	0.3	5	6%	Looser	Desirable	Imprecision
CK-MB	3	15	20%	Looser	Desirable	Imprecision
Creat Kinase	15	125	12%	Tighter	Optimal	Imprecision
Creatinine	8	100	8%	Tighter	Minimal	Imprecision

Basis

"Total Error" – Can share reference interval

"Imprecision" – Can Monitor

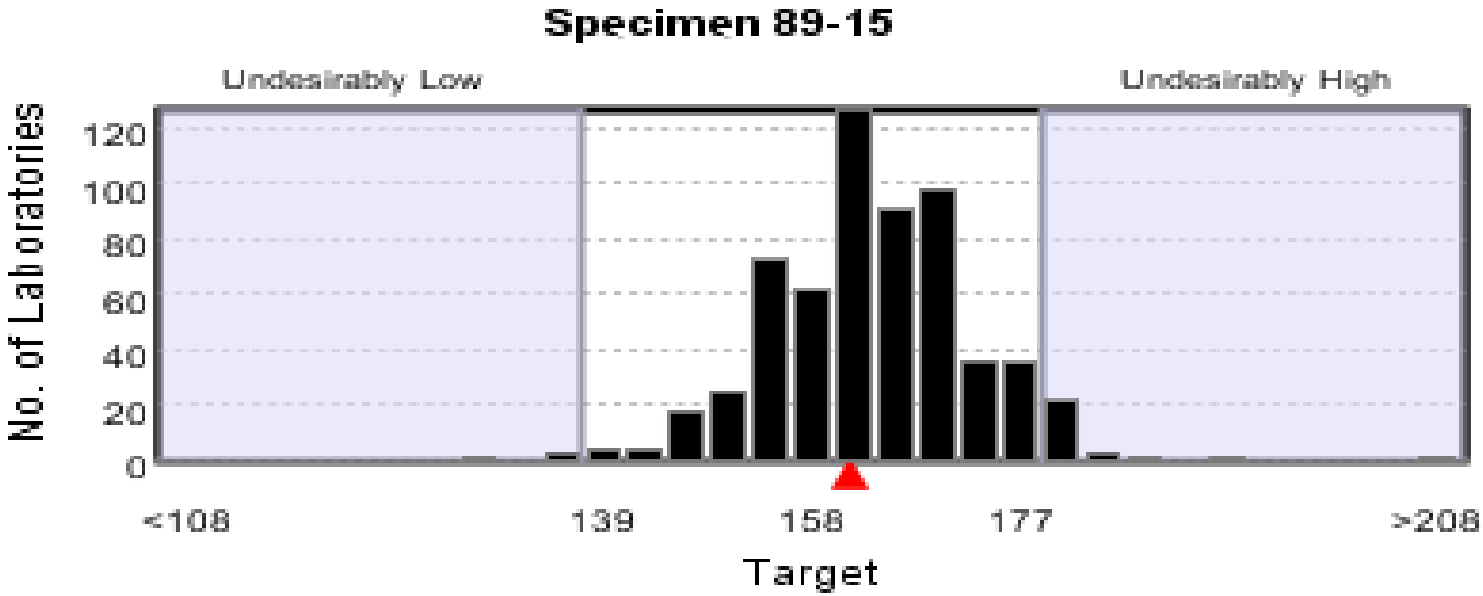
Level

"Optimal" – no need to improve

"Desirable" – satisfactory

"Minimal" – just satisfactory

CK - 2012



- All labs (nearly) within limits
- **Optimal Precision limits**
- Can monitor patients from lab to lab
- Can share reference intervals

QAP – Other uses

Reporting units for therapeutic drug monitoring: a correctable source of potential clinical error

Graham R D Jones

MJA 2007; 186: 420–421

Drug	Mass Units	Mass units (%)	SI units	SI units (%)	MIMS
Methotrexate	mg/L	0%	umol/L	100%	10^{-6} M, 10^{-7} M, 10^{-8}M
Lithium	mg/dL	0%	mmol/L	100%	mmol/L
Digoxin	µg/L	28%	nmol/L	72%	ng/mL (nmol/L)[a]
Phenytoin	mg/L	31%	µmol/L	69%	ng/mL (nmol/L)[a]
Carbamazepine	mg/L	31%	µmol/L	69%	ng/mL (nmol/L)[a]
Valproate	mg/L	33%	µmol/L	67%	ng/mL (nmol/L)[a]
Theophylline	mg/L	35%	µmol/L	65%	ng/mL (nmol/L)[a]
Phenobarbitone	mg/L	33%	µmol/L	67%	ng/mL (nmol/L)[a]
Salicylate	mg/L	45%	mmol/L	55%	ug/mL, ng/mL[b]
Paracetamol	mg/L	39%	µmol/L	61%	ug/mL[c]
Quinidine	mg/L	40%	umol/L	60%	mg/L (umol/L)
Lignocaine	mg/L	50%	umol/L	50%	umol/L (umol/L)
Amiodarone	mg/L	64%	umol/L	36%	ug/mL
Vancomycin	mg/L	96%	µmol/L	4%	mg/L
Gentamicin	mg/L	97%	µmol/L	3%	ug/mL
Amikacin	mg/L	100%	umol/L	0%	ug/mL
Tobramycin	mg/L	100%	umol/L	0%	ug/mL

AACB ASM 2006 - poster

Response

- Working Party
  - RCPA, AACB, ASCEPT, RACP
- Considered all factors
  - Current practice, current guidelines, textbooks and websites, international practice, clinical use, laboratory effects
  - Patient safety is highest priority
- Distributed document widely for comment
- Re-drafted
- Approved by parent bodies Published …

Clinical focus

Mass or molar? Recommendations for reporting concentrations of therapeutic drugs

MJA 198 (6) · 1 April 2013

- mass units should be used for reporting therapeutic drug concentrations in Australia and New Zealand; and
- the litre (L) should be used as the denominator when expressing concentration. Examples of these units are mg/L and µg/L.

Exceptions to these principles include:

- drugs for which there is current uniformity of reporting and supporting information using molar units, notably lithium (mmol/L) and methotrexate (µmol/L);
- drugs that are also present as endogenous substances, where the units used routinely should continue to be used. This applies to many substances, including minerals (eg, iron; µmol/L), vitamins (eg, vitamin D; nmol/L) and hormones (eg, thyroxine; pmol/L).

Numbers are the easy part?

Printed Jul 28 10:34:32 2010

Prepared by:
RCPA Chemical Pathology QAP Group

Due Date : 12/07/2010 **Case 11-05**

Patient Report Comments

Laboratory Number

A Suggested Comment

Cortisol is not suppressed after 1 mg dexamethasone in contrast to the results 2 weeks earlier. This could be due to a lack of compliance in this test or specimen mix up in either the previous or this test. Serum dexamethasone measurement could clarify compliance and specimen identity. Rare possibility of cyclical Cushing's could be considered. Recommend assessment of midnight salivary cortisol or 24 hour UFC.

Patient ID 65 year old female

Patient Location Medical Outpatients (Diabetes Unit)

Clinical Notes on Request Form

Type 2 diabetes; to exclude Cushing's syndrome

Case Details

Dexamethasone Suppression of Cortisol

Day	Time (h)	Cortisol (nmol/L)	Ref Int
1	0900	414	(160-650)
1	2300	1.0mg oral dexamethasone given	
2	0900	329	(<50)

Your Comments

Dexamethasone (DXM) suppression tests have high false positive rates. Nonsuppression is associated with many factors including variation in levels after oral ingestion, co-administration of drugs which accelerate DXM metabolism, depression, alcohol excess and so on. At least one other test of hypothalamic pituitary axis is required such as 24 hour UFC, morning plasma ACTH or measurement of cortisol diurnal rhythm.

Would you phone this result? NO

Rationale and References

Poorly controlled diabetes mellitus can be associated with mild hypercortisolism and abnormal dexamethasone suppressibility. However, a clearly suppressed test a fortnight previously with a clearly unsuppressed result now should prompt consideration of non compliance with dexamethasone in the second test or sample mix-up in either the first or the second test. Increased metabolism of dexamethasone by ethanol abuse or glitazone therapy initiated in the interim is unlikely in view of the short interval. Other causes of a false positive DST such as obesity, depression and oestrogen therapy are not considered for the same reason. Further testing with midnight salivary cortisol or with 24 hour UFC would be useful if pre-test probability of Cushing's syndrome is high.

References:

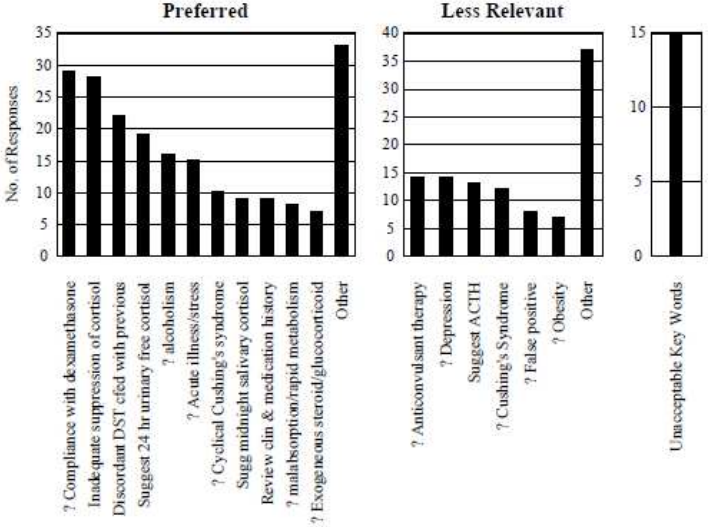
J Clin Endocrinol Metab. May 2008, 93(5):1526-40.
JAMA 1993;269:2232-8.
Am J Med 1986;80:83-8

Additional Information

2 weeks earlier

Dexamethasone Suppression of Cortisol

Day	Time (h)	Cortisol (nmol/L)	Ref Int
1	0900	358	(160-650)
1	2300	1.0mg oral dexamethasone given	
2	0900	<35	(<50)



Your Key Words

? False positive	Less Rel
? malabsorption/rapid metabolism	Pref
? Depression	Less Rel
? alcoholism	Pref
Suggest 24 hr urinary free cortisol	Pref
Suggest ACTH	Less Rel
Suggest late evening cortisol	Less Rel
Drug induced rapid liver metabolism	Pref

Response Summary

Total 50

Telephoning Results

Yes 11 No 34

Key Word Summary

Number of key words 47

No. of Key Words Used Per Response

	Pref	Less Rel	Unacc
Sugg Comment	8		
Your Comment	4	4	
Median Response	4	3	1

Personal Observations…

- If labs can do it differently, they will
- Unless EQA can show labs are the same, assume they are not
- If EQA shows lab differences, it will not fix itself
- Action requires people talking, setting standards and doing
- Action can be local, national or international

Funding

- Pathology is funded for **laboratories** to provide results
- There is little funding for **organisations** to make the results and reports the same
- The process is slow ….

JCTLM

JCTLM Database
Laboratory medicine and *in vitro* diagnostics

pathologyharmony.co.uk
working to harmonise standards in UK pathology

CIRME

towards pathology harmonisation

Conclusions

- EQA is vital to ensure comparability of results
- (Ideally confirming everything is OK)
- If problems found, **action is required**
  - If not us, who? If not now, when?
- Mauro Panteghini
  - "5th Pillar of traceabilty"