Define performance goals in standardization:

Is fitness for medical purpose the key?

7th CIRME International Scientific Meeting
Metrological traceability and assay standardization
Stresa, May 24th, 2013

Dietmar Stöckl
Dietmar@stt-consulting.com

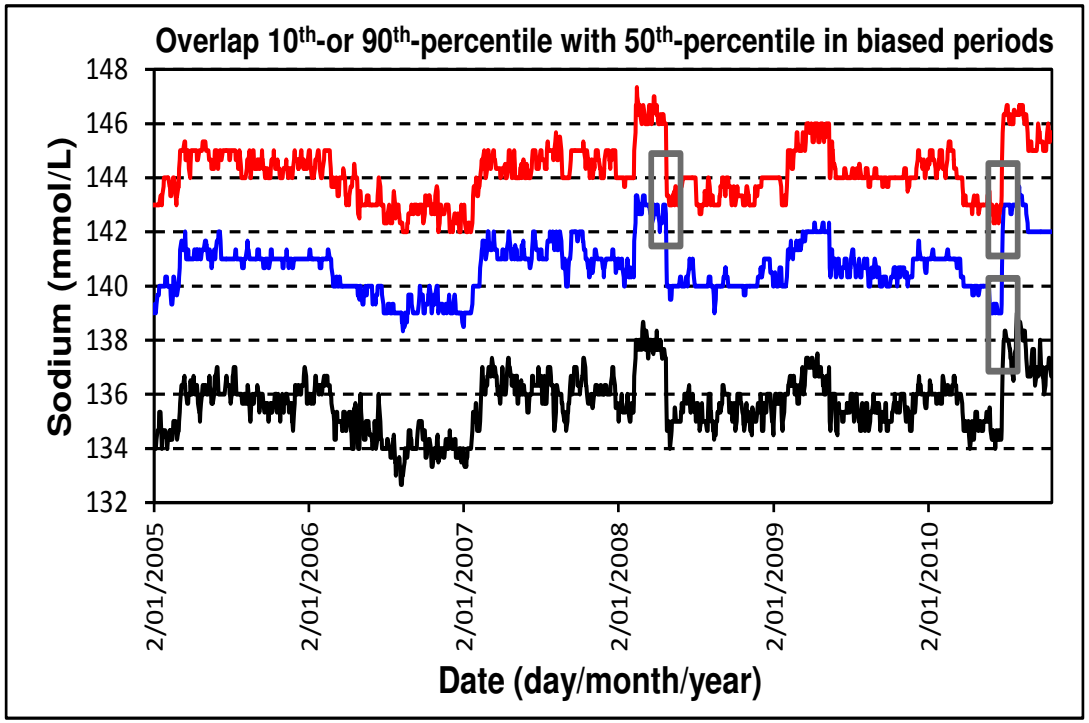
STT
Consulting

Observation

Effect of assay instability on surrogate medical decision

Hyponatremia in a laboratory population (<135 mmol/L):

Triplication "low" versus "high" periods!



Is this assay fit for medical purpose?

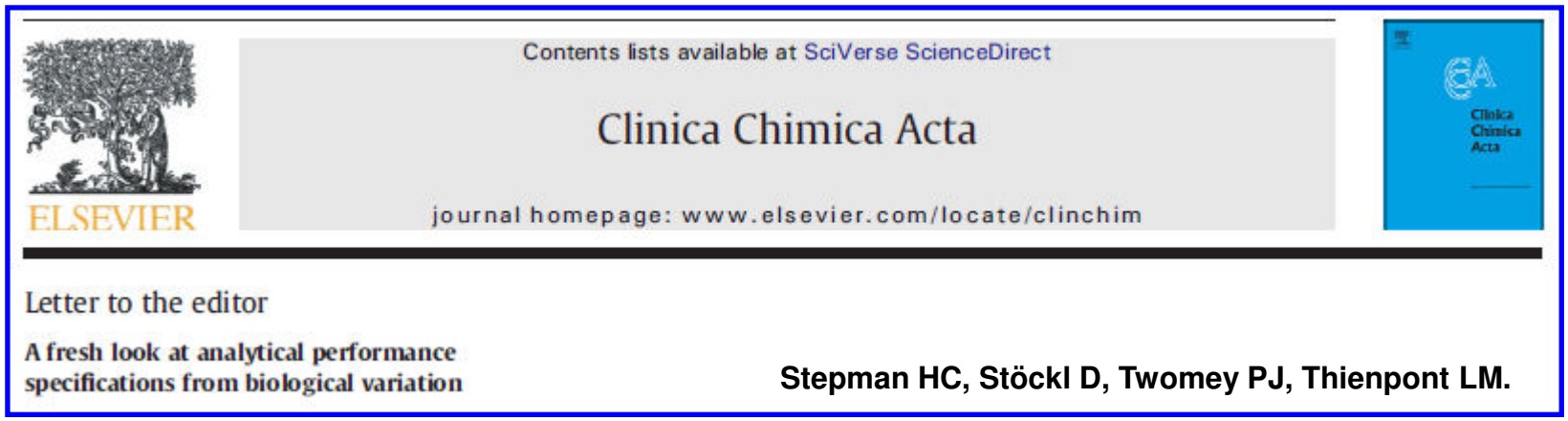
What is acceptable?

>ASAP concept

Long-term stability of clinical laboratory data – sodium as benchmark. Stepman HC, Stöckl D, Stove V, Fiers T, Couck P, Gorus F, Thienpont LM. Poster at AACC 2011.

The ASAP# Concept

#As Simple As Possible



Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

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

ELSEVIER

Letter to the editor

A fresh look at analytical performance specifications from biological variation

Stepman HC, Stöckl D, Twomey PJ, Thienpont LM.

Stepman HC, Stöckl D, Twomey PJ, Thienpont LM.
A fresh look at analytical performance specifications from biological variation. Clin Chim Acta 2013;421:191-2.

The ASAP Concept

Elements

Biological variation

Normal distribution

1-sided statistics

Unimodal disease concept (“increasing risk”)

Definition of a cut-off

Increase of *surrogate* false positives (FP)/false negatives (FN) due to analytical imprecision or bias in a *laboratory population*

The ASAP Concept

Basic assumption for defining FP#

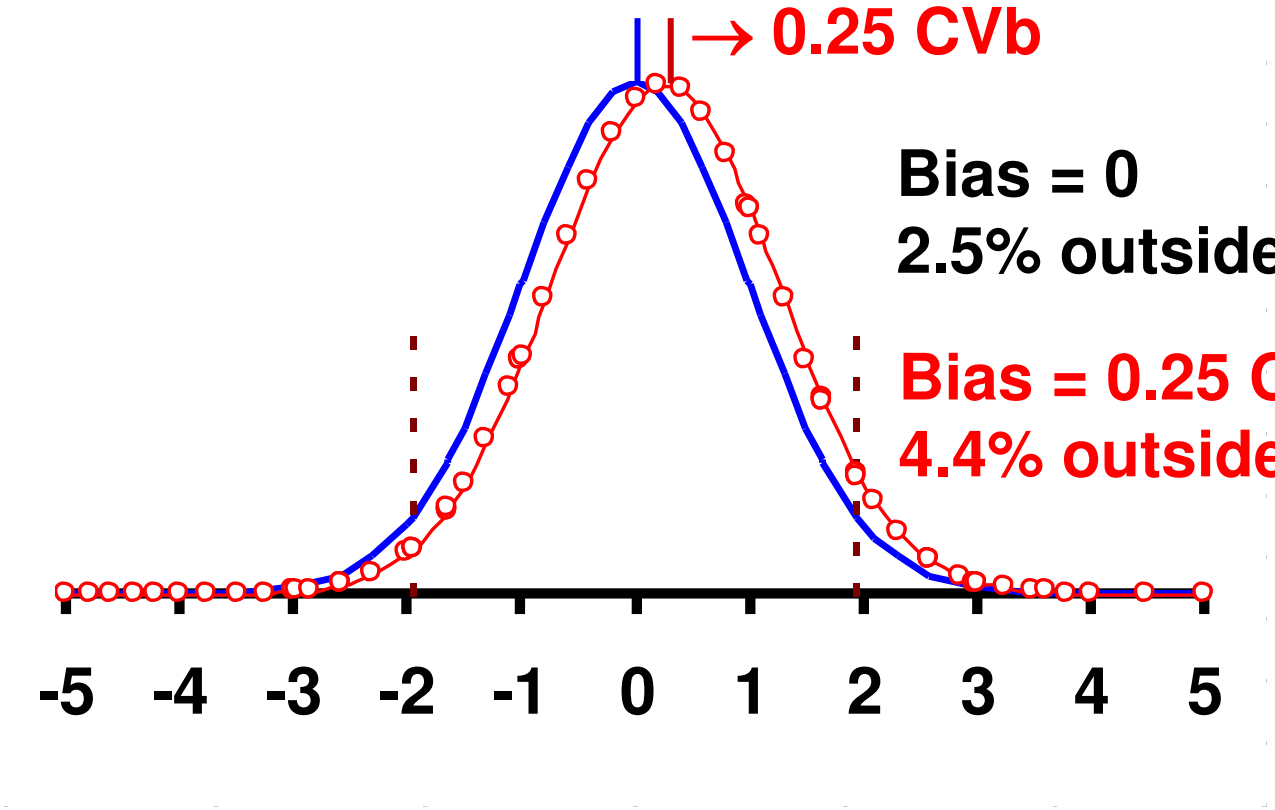
For a unimodal distribution, once an arbitrary cut-off level has been adopted, all persons above that would be regarded as "diseased" (= true positives, TP), and there would be no false positives (FP).

Cutoffs can be ~1.96 σ, ~1 σ (cholesterol), or others.

#Principles and practice of screening for disease. JMG Wilson, G. Junger, Eds. World Health Organization, Geneva 1968, p. 26;
http://whqlibdoc.who.int/php/ WHO_PHP_34.pdf

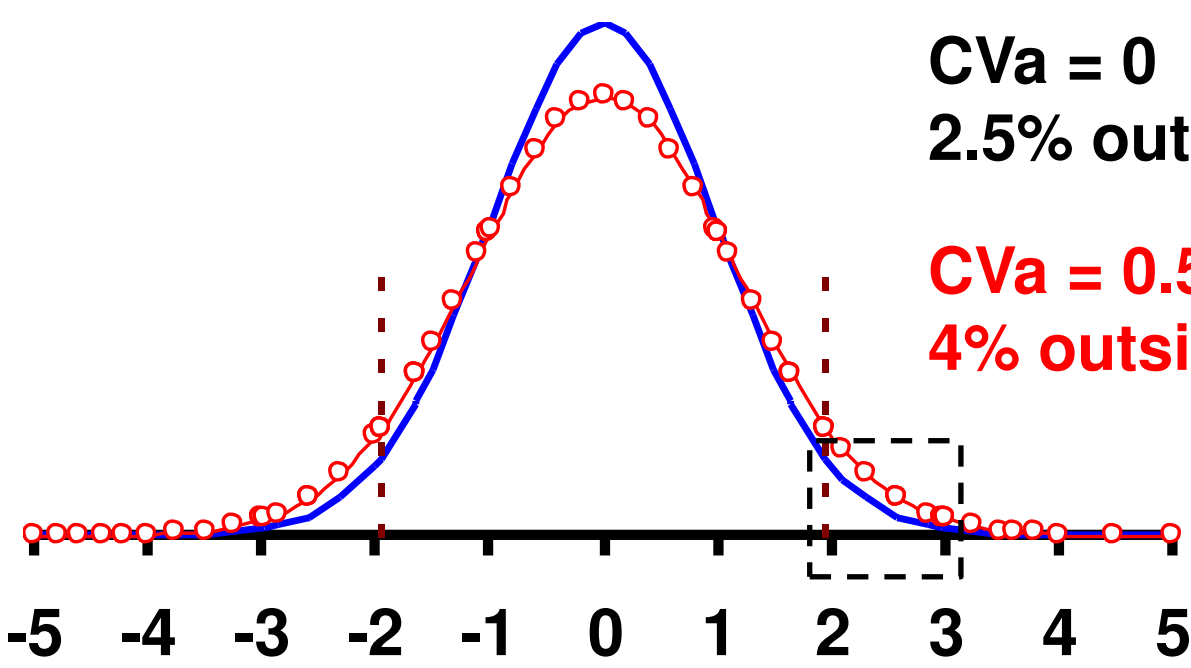
Effect of bias

Bias = 0.25 CVb [cut-off 1.96 σ]: 75% FP



Effect of imprecision

CVa = 0.5 CVb [cut-off 1.96 σ]:
59% FP + 27% FN = 86% false decisions

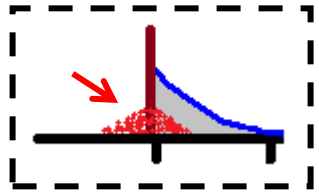


CVa = 0
2.5% outside (TP)

CVa = 0.5 CVb
4% outside = 59% FP

Imprecision
False negatives!

CVa = 0.5 CVb
0.67% inside = 27% FN



The ASAP Concept

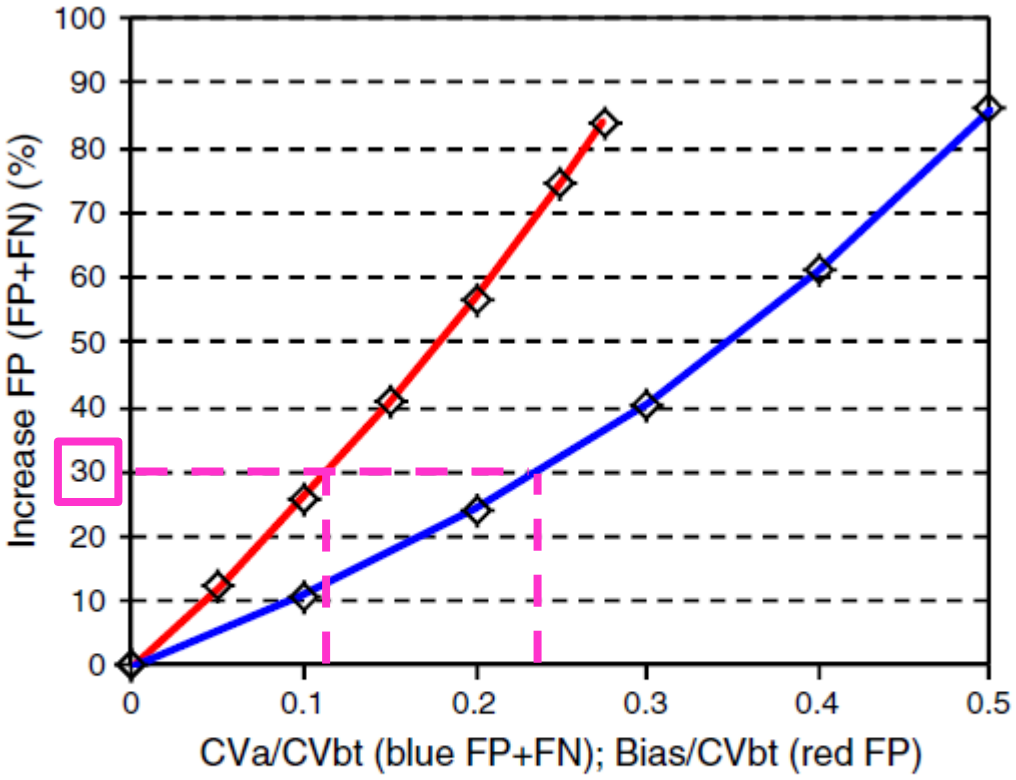


Fig. 1. %-FP plus %-FN for the ratio CVa/CVb (blue) and %-FP for the ratio bias/CVb (red) beyond the 1.96 σ decision points for Gaussian distributed data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Bias has most effect on false decisions

What is acceptable?

The ASAP Concept

30% Increase of false decisions

Laboratory fractions

Bias <0.125 CVb

Imprecision <0.25 CVb

(corresponds to optimum numbers of the variance propagation concept)

Manufacturer fractions:
50% of laboratory to allow for decent IQC

Bias <0.06 CVb

Imprecision <0.125 CVb

ASAP in Practice

Manufacturer values, 134 mainstream analytes

(limit values in red: limit CV 10% and limit bias 5% @ #130)

				Manu Specs	
		Biological Variation		CVa (%)	Bias (%)
Measurand (134-126)	CVw	CVg	**CVbt**	0.13*CVbt	0.06*CVbt
S- Thyr. Perox. Antib.	11	147	**147**	**10**	**5**
S- CA 19.9 antigen	16	102	**103**	**10**	**5**
S- C-Reactive protein	42	76	**87**	**10**	**5**
S- Lipoprotein (a)	8.5	86	**86**	**10**	**5**
S- Thyrogl. Antib.	8.5	82	**82**	**10**	**5**
S- Folate	24	73	**77**	9.6	4.8
S- PSA	18	72	**75**	8.3	4.7
S- Troponin I	14	63	**65**	8.1	4.0
S- Creatine kinase MB	18	61	**64**	8.0	3.7

http://www.westgard.com/biodatabase1.htm

ASAP in Practice

Manufacturer values, 134 mainstream analytes

				Manu Specs	
		Biological Variation		CVa (%)	Bias (%)
Measurand (114 to 106)	CVw	CVg	**CVbt**	0.13*CVbt	0.06*CVbt
S- Androstendione	11	51	**52**	6.5	3.3
S- Tumor Necr. Factor-α	43	29	**52**	6.5	3.2
S- Cortisol	21	46	**50**	6.3	3.1
S- Aldosterone	29	40	**50**	6.2	3.1
S- Tissue polyp.ant. TPA	29	40	**50**	6.2	3.1
S- ALT	24	42	**48**	6.0	3.0
S- Immunoglobulin M	5.9	47	**48**	6.0	3.0
S- α-Fetoprotein	12	46	**48**	5.9	3.0
S- Myeloperoxidase	36	30	**47**	5.9	2.9

ASAP in Practice

Manufacturer values, 134 mainstream analytes

				Manu Specs	
		Biological Variation		CVa (%)	Bias (%)
Measurand (80 to 72)	CVw	CVg	**CVbt**	0.13*CVbt	0.06*CVbt
B- Lactate	27	17	**32**	4.0	2.0
S- Luteinizing hormone	15	28	**31**	3.9	2.0
S- Creatine kinase MB	20	24	**31**	3.9	2.0
S- TSH	19	25	**31**	3.9	2.0
S- α-Amylase	8.7	28	**30**	3.7	1.9
S- DHEAS	4.2	29	**30**	3.7	1.8
S- Alk. Phosph., liver	10	27	**29**	3.6	1.8
S- Lutein	20	21	**29**	3.6	1.8
S- IGF-1	9.4	27	**29**	3.6	1.8

ASAP in Practice

Manufacturer values, 134 mainstream analytes

				Manu Specs	
		Biological Variation		CVa (%)	Bias (%)
Measurand (50 - 42)	CVw	CVg	**CVbt**	0.13*CVbt	0.06*CVbt
P- Factor VIII	4.8	19	**20**	2.5	1.2
S- Procollagen 1 N-term.	6.8	18	**20**	2.5	1.2
S- FT3	7.9	18	**19**	2.4	1.2
S- T3	8.7	17	**19**	2.4	1.2
S- γ-Globulins	15	12	**19**	2.4	1.2
P- Fibrinogen	11	16	**19**	2.4	1.2
S- α2-Macroglobulin	3.4	19	**19**	2.4	1.2
S- Immunoglobulins I	4.8	18	**19**	2.3	1.2
S- α1-Antitrypsin	5.9	16	**17**	2.2	1.1

ASAP in Practice

Manufacturer values, 134 mainstream analytes

				Manu Specs	
		Biological Variation		CVa (%)	Bias (%)
Measurand (9 - 1)	CVw	CVg	**CVbt**	0.13*CVbt	0.06*CVbt
S- Transferrin	3.0	4.3	**5.2**	0.7	0.3
S- Albumin	3.1	4.2	**5.2**	0.7	0.3
S- Protein, total	2.7	4.0	**4.8**	0.6	0.3
B- pH [H+]	3.5	2.0	**4.0**	0.5	0.3
S- Calcium	1.9	2.8	**3.4**	0.4	0.2
S- Water	3.1	0.1	**3.1**	0.4	0.2
S- Chloride	1.2	1.5	**1.9**	0.2	0.1
S- Osmolality	1.3	1.2	**1.8**	0.2	0.1
S- Sodium	0.7	1.0	**1.2**	0.2	0.1

ASAP Paradigm

Fitness for purpose [standardization]

The [Bias] goal is "zero"#

Supported by personal communication

- **Manufacturer**
- **Physician**

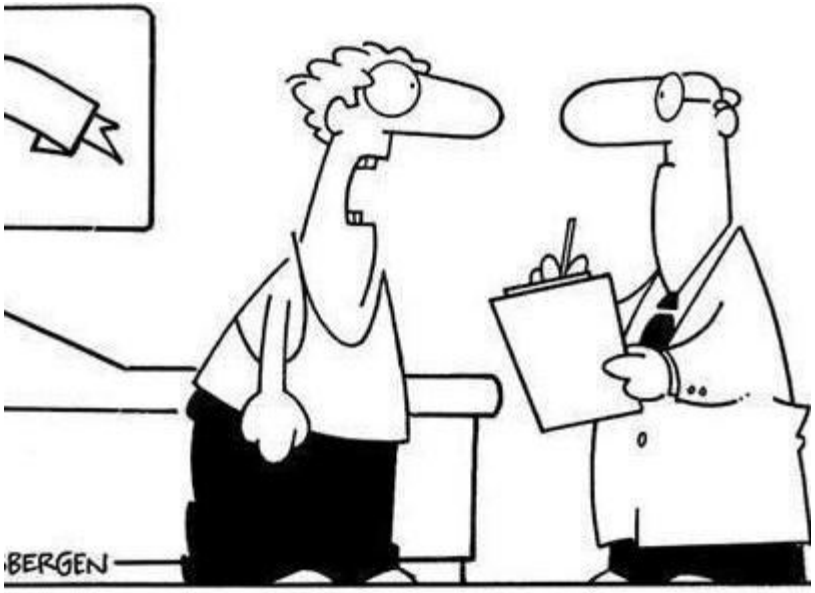
#High biological variation
- Bias limit 5%

Freedom

The [Bias] goal is “zero”

Freedom not to worry about goals anymore

Relax, concentrate on current quality



**“I’m learning how to relax, doctor —
but I want to relax *better* and *faster!*
*I want to be on the cutting edge of relaxation!”***

Current quality

In our favour: excellent systems!

Multichannel analyzers have basic analytical characteristics all tests profit of!

Analyte	CVw (%)	CVa,wr (%)
Cholesterol	5.4	<1.5
Glucose	5.7	<1.5
Phosphate	8.5	<1.5
Uric acid	9.0	<1.5
Triglycerides	21	<1.5

Current quality

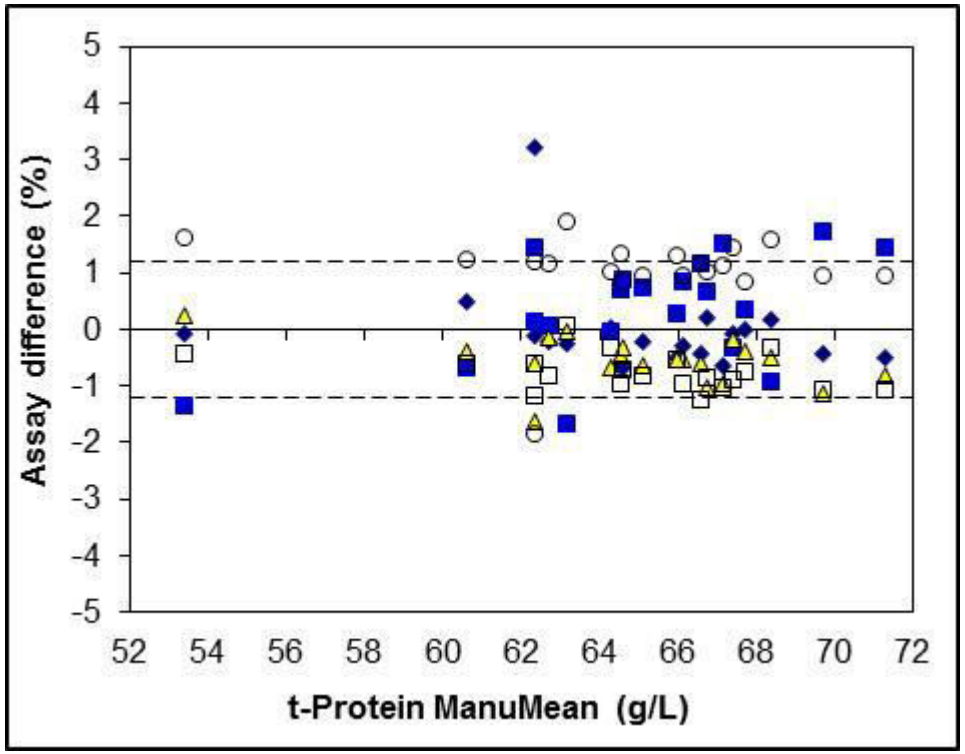
Excellent within-run precision and between laboratory comparability for many serum analytes

Uric acid method comparison (µmol/L)

Sample	Lab A	Lab B	%-Diff		Sample	Lab A	Lab B	%-Diff
1	276	275	0.4		11	311	311	0.0
2	205	205	0.0		12	437	430	**1.6**
3	277	277	0.0		13	231	230	0.4
4	317	315	0.6		14	347	346	0.3
5	281	280	0.4		15	215	214	0.5
6	271	270	0.4		16	263	262	0.4
7	498	494	0.8		17	311	310	0.3
8	284	283	0.4		18	321	321	0.0
9	365	360	1.4		19	276	276	0.0
10	370	369	0.3		20	358	356	0.6
					Average	**314**	**313**	**0.5**

Current quality

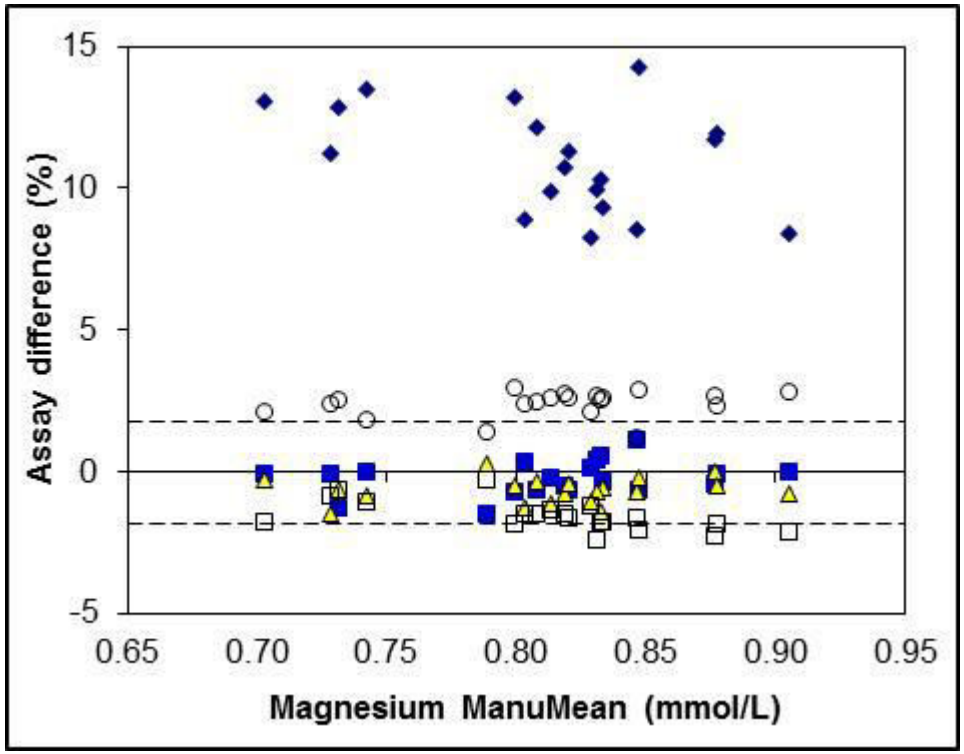
Excellent standardization status for several analytes



Calcium, magnesium, albumin, and **total protein** measurement in serum as assessed with 20 fresh-frozen single-donation sera. [5 manufacturers] Van Houcke SK, Rustad P, Stepman HC, Kristensen GB, Stöckl D, Røraas TH, Sandberg S, Thienpont LM. Clin Chem 2012;58:1597-9.

Current quality

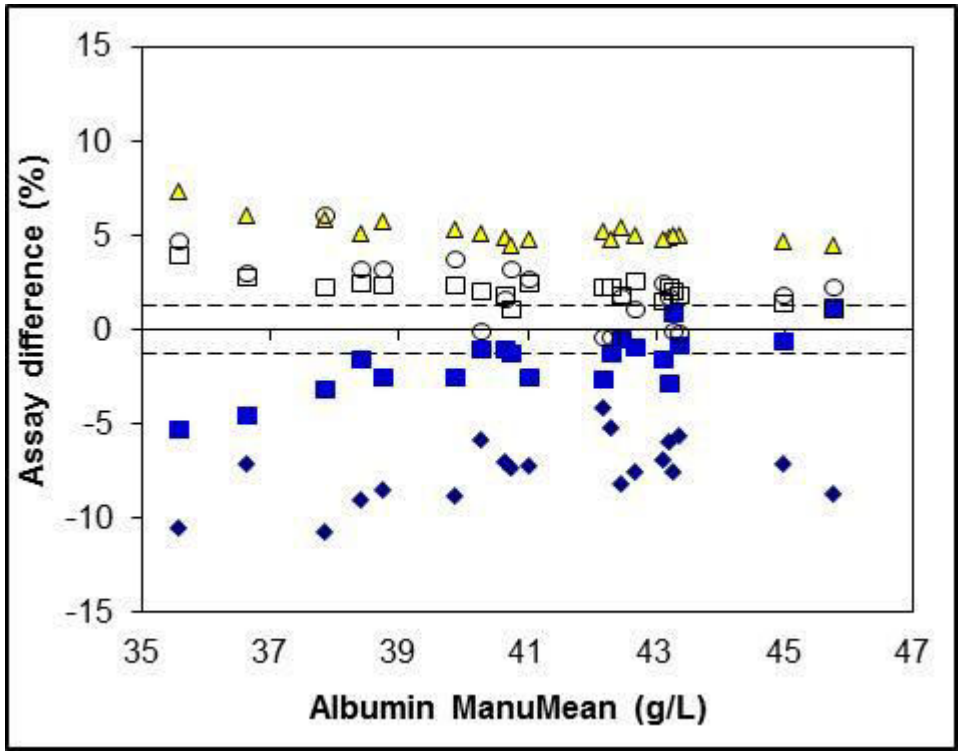
Standardization downsides!



Calcium, **magnesium**, albumin, and total protein measurement in serum as assessed with 20 fresh-frozen single-donation sera.
Van Houcke SK, Rustad P, Stepman HC, Kristensen GB, Stöckl D, Røraas TH, Sandberg S, Thienpont LM. Clin Chem 2012;58:1597-9.

Current quality

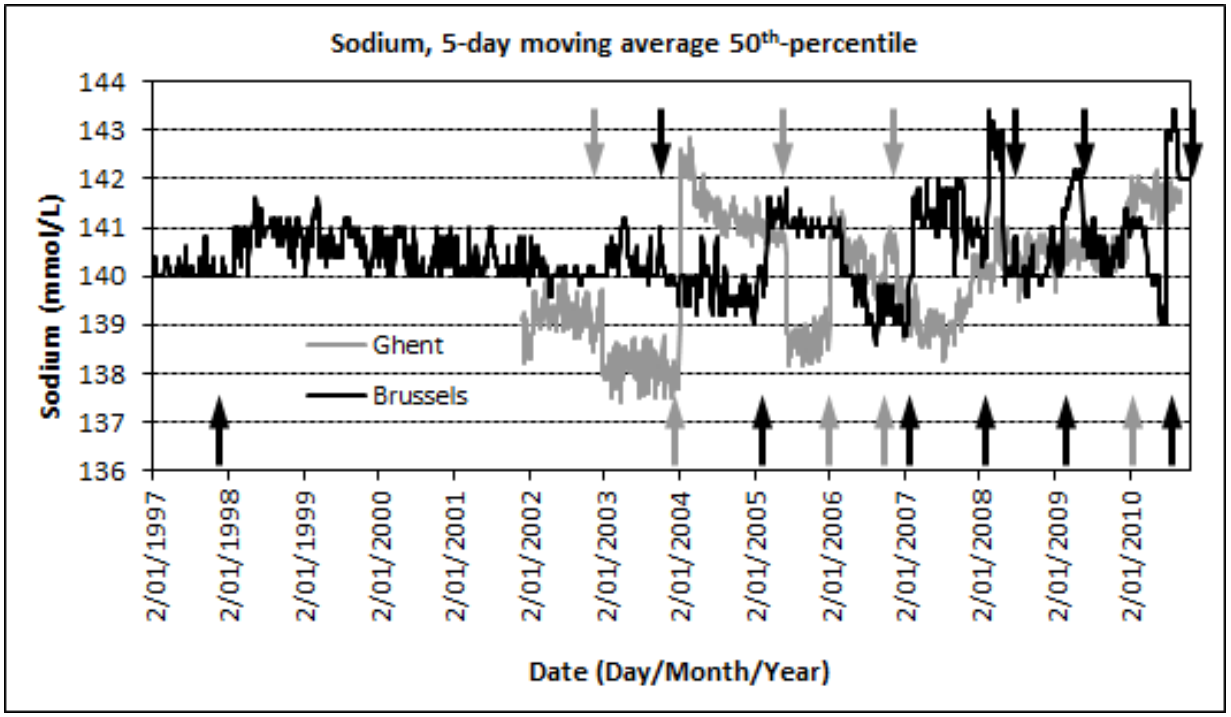
Standardization downsides!



Calcium, magnesium, **albumin**, and total protein measurement in serum as assessed with 20 fresh-frozen single-donation sera.
Van Houcke SK, Rustad P, Stepman HC, Kristensen GB, Stöckl D, Røraas TH, Sandberg S, Thienpont LM. Clin Chem 2012;58:1597-9.

Current quality

Stability upsides! YES, lot variation is important for traceability!

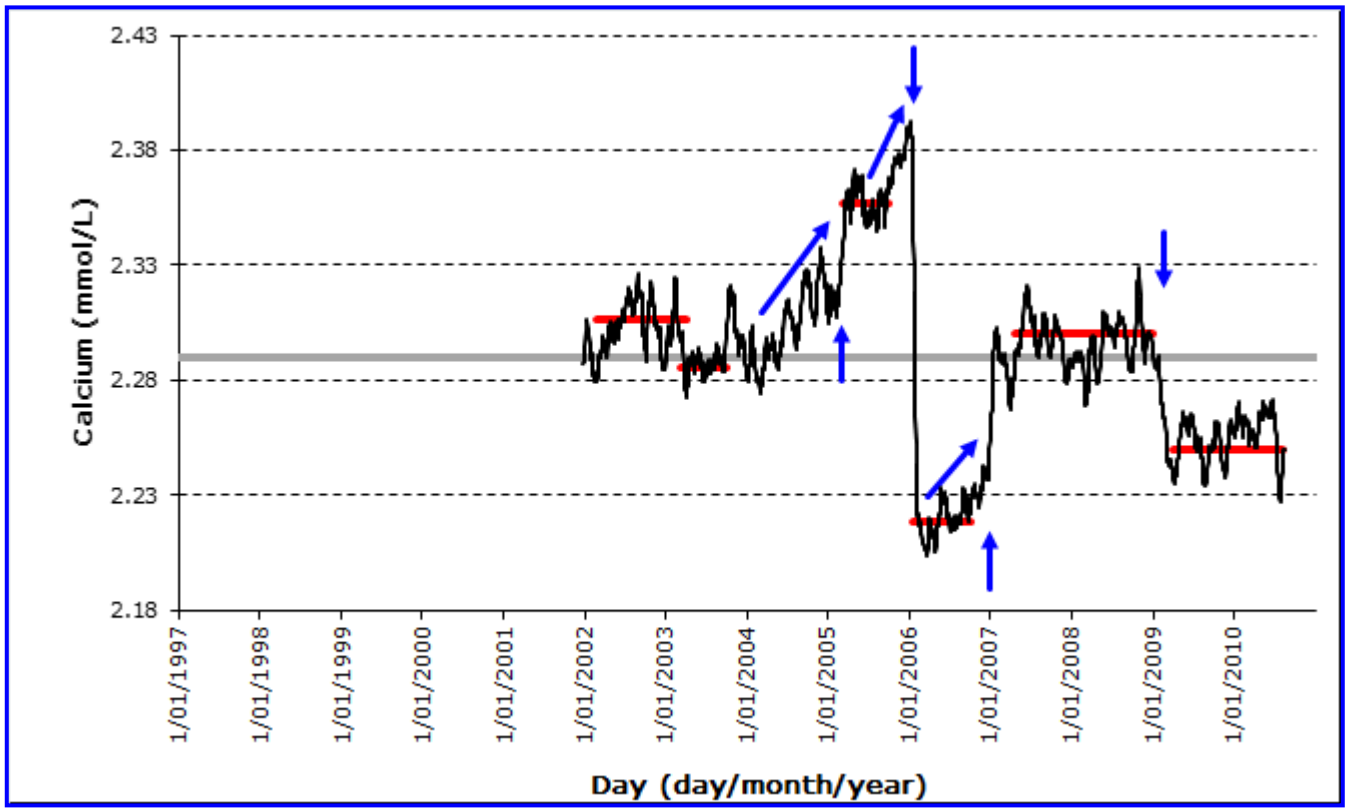


Brussels: *S*-Sodium "mmol stability" >8 years!

Long-term stability of clinical laboratory data: **sodium** as benchmark. Stepman HC, Stöckl D, Stove V, Fiers T, Couck P, Gorus F, Thienpont LM. Clin Chem 2011;57:1616-7

Current quality

Stability downsides! [Calcium]



Long-term stability of laboratory tests and practical implications for quality management. Van Houcke SK, Stepman HC, Thienpont LM, Fiers T, Stove V, Couck P, Anckaert E, Gorus F. Clin Chem Lab Med 2013 [Epub ahead of print].

Where is the fitness for medical purpose?

ASAP Paradigm

Fitness for purpose [standardization]

The [Bias] goal is "zero"

Medical ["reverse"] Paradigm

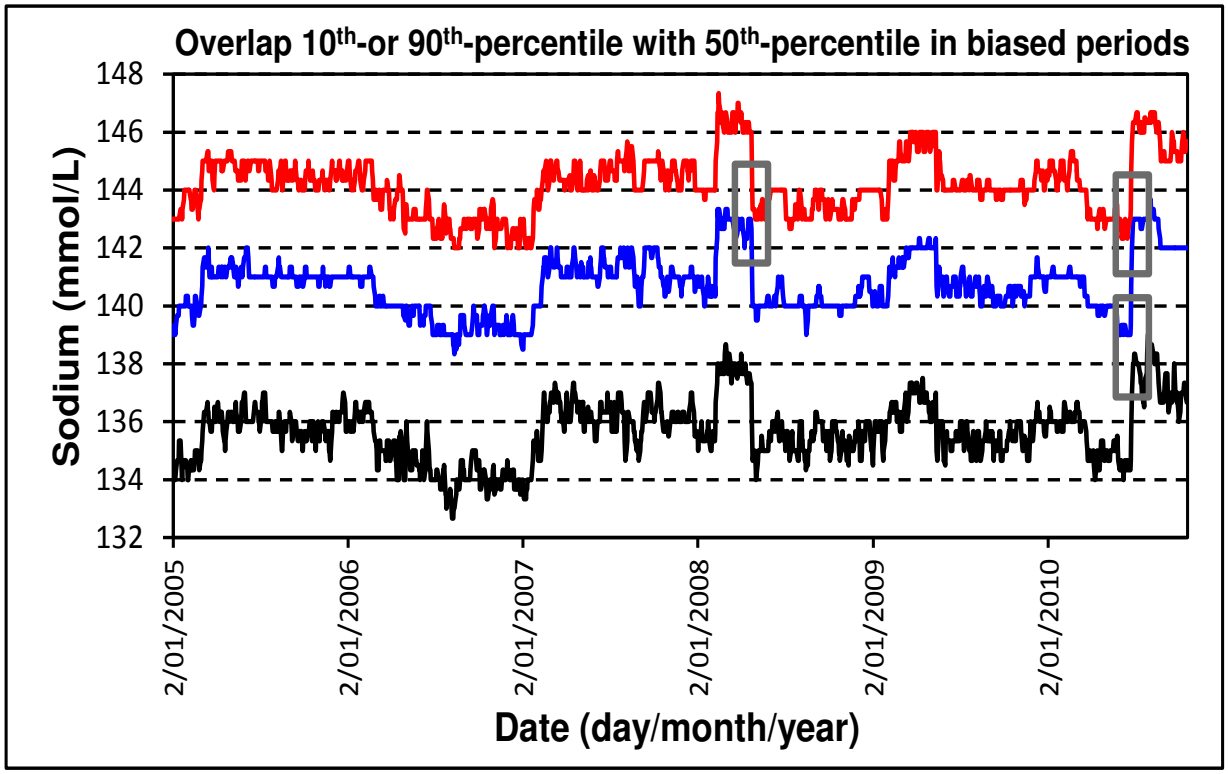
All tests ordered by experienced physicians are fit for medical purpose!

(otherwise, they would not order them!)

Experienced physicians tailor the medical purpose to the fitness of the analytical test!

Remember?

Triplication of hyponatremia in "low" versus "high" periods!



YES, this assay was fit for medical purpose!
Physicians accounted for the instabilities!

Conclusion

The concept

Fitness for medical purpose

Will NOT help us in setting traceability goals!

The traceability goal is “zero” bias

Concentrate on current quality!