Total error in the uncertainty era: which role?

Wytze P. Oosterhuis, MD, PhD

11th International Scientific Meeting

MEASUREMENT UNCERTAINTY IN MEDICAL LABORATORIES: FRIEND OR FOE?

MILANO, ITALY

November 30th, 2017

Stockholm/Milan criteria 2014

Consensus Statement

Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

Model 1. Clinical outcomes

Model 2. Biological variation ←

Model 3. State-of-the-art

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Task & Finish Group Total Error

Terms of Reference:
Proposal:
-how to use the total error concept
-how to possible combine performance specifications for bias and imprecision.

Deliverable:
A manuscript dealing with this topic.

Task & Finish Group Total Error

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DE GRUYTER

Clin Chem Lab Med 2017; aop

Opinion Paper

Wytze P. Oosterhuis*, Hassan Bayat, David Armbruster, Abdurrahman Coskun, Kathleen P. Freeman, Anders Kallner, David Koch, Finlay Mackenzie, Gabriel Migliarino, Matthias Orth, Sverre Sandberg, Marit S. Sylte, Sten Westgard and Elvar Theodorsson

The use of error and uncertainty methods in the medical laboratory

https://doi.org/10.1515/cclm-2017-0341
Received April 19, 2017; accepted July 4, 2017

Criteria for Judging Precision and Accuracy in Method Development and Evaluation

James O. Westgard, R. Neill Carey, and Svante Wold[1]

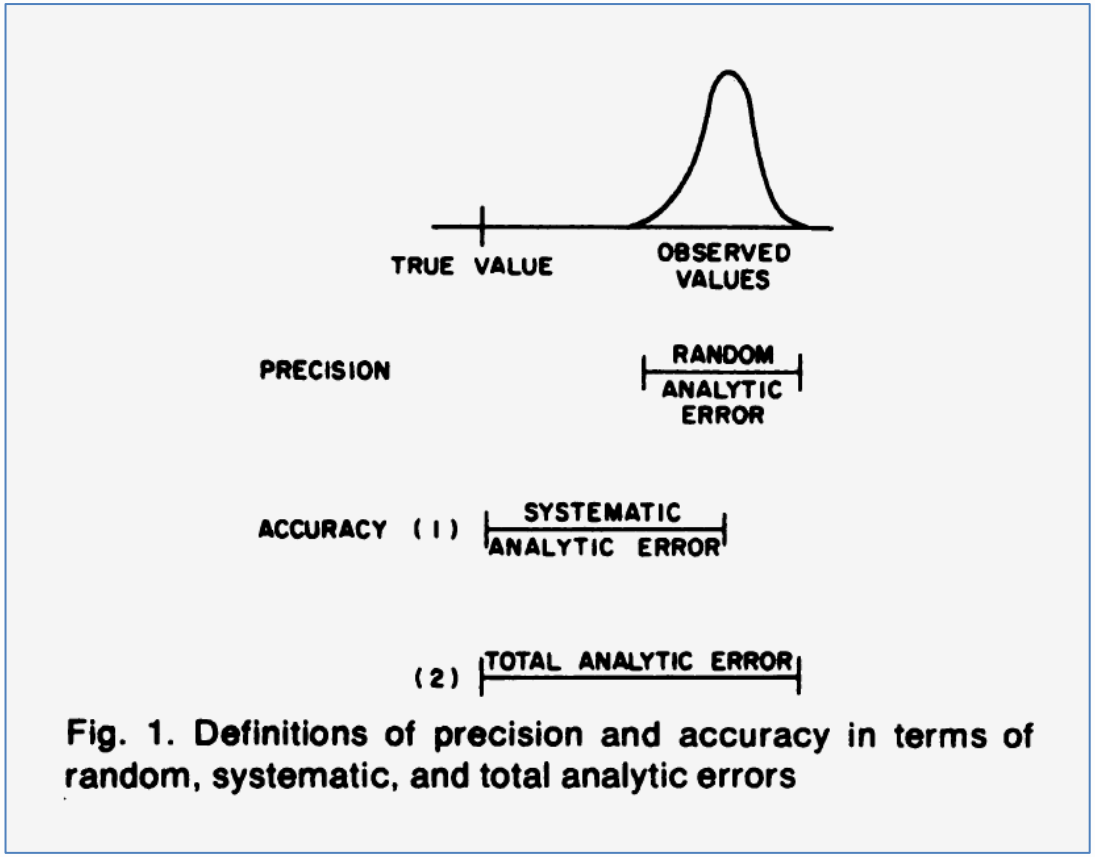

Fig. 1. Definitions of precision and accuracy in terms of random, systematic, and total analytic errors

$$TE = bias + z \times SD_a$$

Clin Chem 1974;20:825

Quality goals in external quality assessment are best based on biology

C. G. FRASER & P. HYLTOFT PETERSEN

$$TE_a = 1.65(0.5CV_I) + 0.25(CV_I^2 + CV_G^2)^{½}$$

Scan J Clin Lab Invest 1993; 53 suppl. 212: 8-9.

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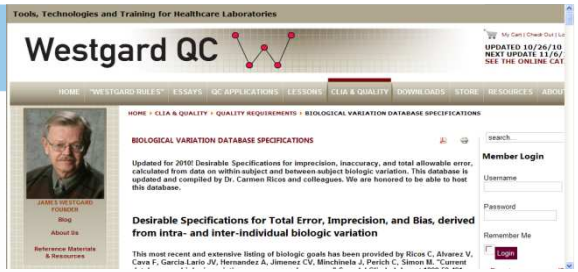
Example CK: TE_a



	collagen (s-CTx)					
U-	C-Telopeptide of type I collagen/creatinine, 1st morning	32.8	48.0	16.4	14.5	41.6
U-	C-Telopeptide type I collagen/creatinine, 2nd morning	23.4	---	11.7	---	---
S-	Creatine kinase (CK)	22.8	40.0	11.4	11.5	30.3
S-	Creatine kinase MB, %	6.9	48.2	3.45	12.17	17.87
S-	Creatine kinase MB, activity	19.7	24.3	9.9	7.8	24.1

$CV_{I(within)}$ = **22.8%**

$CV_{G(between)}$ = **40.0%**

Imprecision = 0.5 x CV_I = **11.4%**

Bias = 0.25 $\sqrt{(CV_I^2 + CV_G^2)}$ = **11.5%**

$TE_{allowable}$ = Bias + 1.65 x imprecision = 11.5% + 1.65 x 11.4% = **30.3%**

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Linear model:

$TE_a = 1.65(½CV_I) + 0.25(CV_I^2 + CV_G^2)^{½}$ = constant

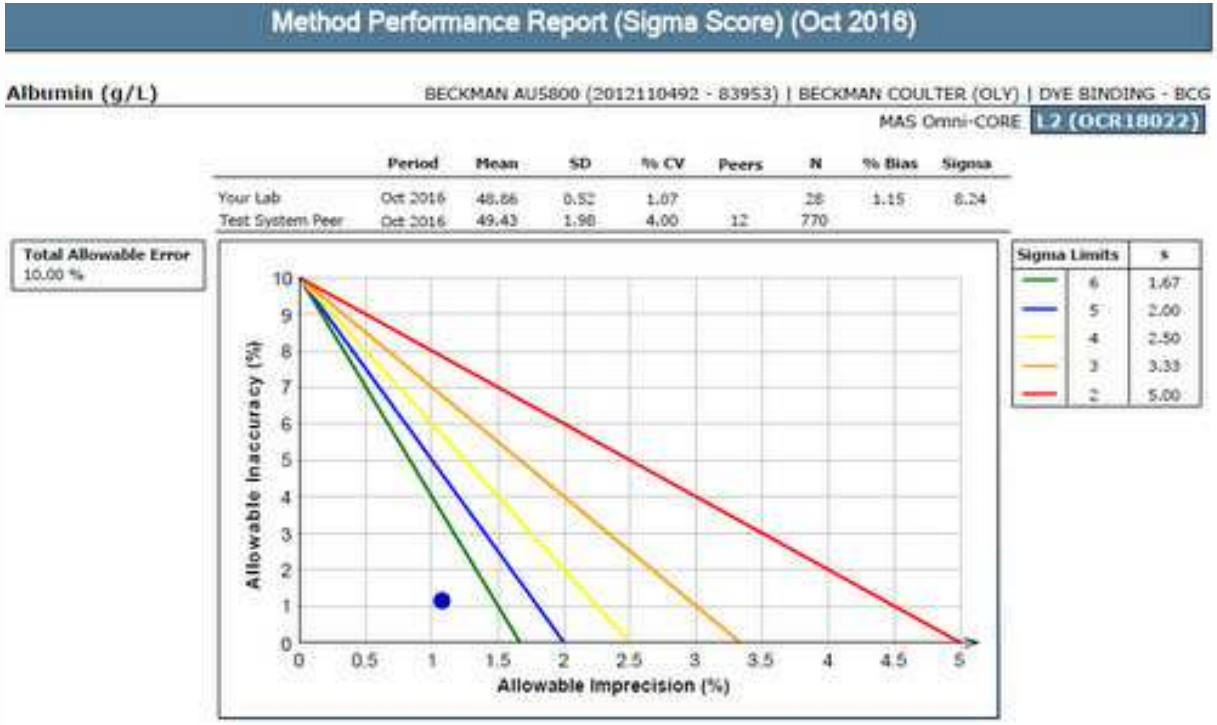
$TE_a \geq zCV_a + bias$

$bias \leq -zCV_a + TE_a$

$y=ax + b$

$Sigma = (TE_a\text{-}bias)/CV_a$

$= z$



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Desirable routine analytical goals for quantities assayed in serum

Stöckl et al. Eur J Clin Chem 1995; 33: 157

"A stricking feature is the fact that all of the individuel approaches described recommend numbers for analytical standard deviation near or equal to 0.5 times the biological standard deviation"

Imprecision <0.5CV_b → analytical variation <12% total variation

$$TE_a = 1.65(0.5CV_I) + 0.25(CV_I^2 + CV_G^2)^{½}$$

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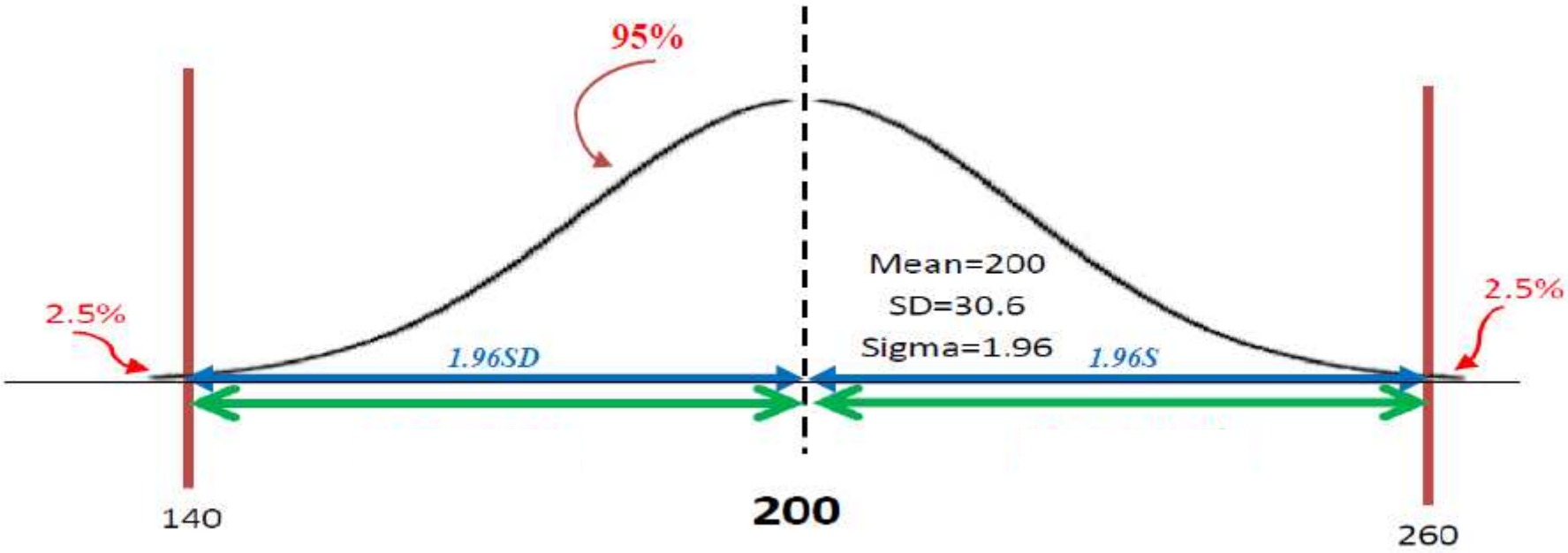
Scand J Clin Lab Invest 1988; 48: 757–764

Analytical goals for the acceptance of common reference intervals for laboratories throughout a geographical area

E. M. S. GOWANS,*† P. HYLTOFT PETERSEN,† O. BLAABJERG† & M. HØRDER†

*Department of Biochemical Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, and †Department of Clinical Chemistry, Odense University Hospital, Odense C, Denmark



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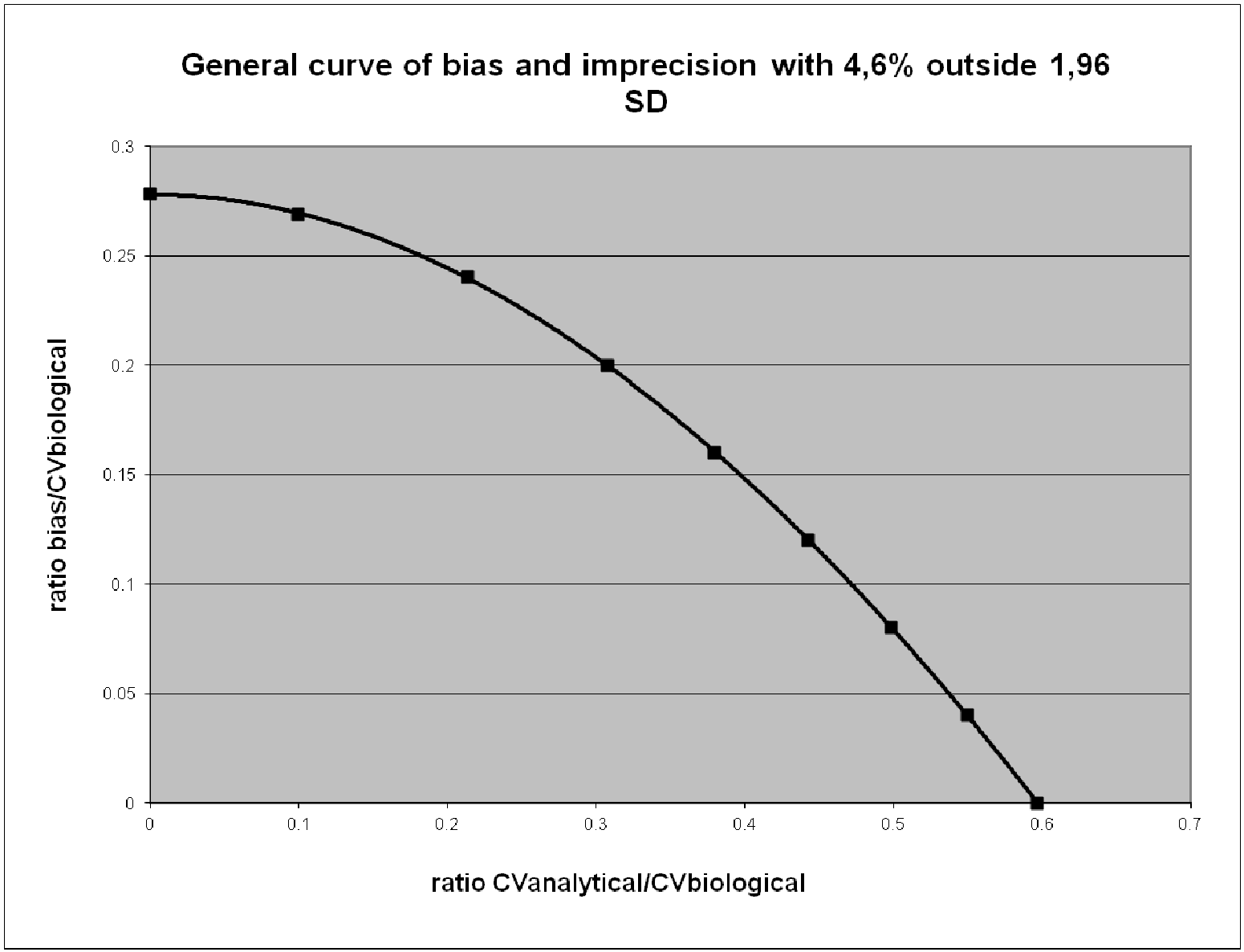
General curve of bias and imprecision with 4,6% outside 1,96 SD
ratio bias/CVbiological
0.3
0.25
0.2
0.15
0.1
0.05
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
ratio CVanalytical/CVbiological

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The estimate for bias:

SD_a <0.58SD_{biol} (with bias=0)
Bias <0.27SD_{biol} (with SD_a=0)

$$TE_a = 1.65(0.5CV_i) + 0.25(CV_i^2 + CV_g^2)^{½}$$

Gowans et al. Scan J Clin Lab Invest 1988; 48: 757

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Problems:

Conventional model is flawed:

$TE_A = 0.25CV_B + 1.65(0.5CV_I)$

Summing of mutual exclusive terms.

Gross Overestimation of Total Allowable Error Based on Biological Variation

To the Editor:

Clinical Chemistry 57:9 (2011)

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Other problem: mixing of models for monitoring and diagnosis:

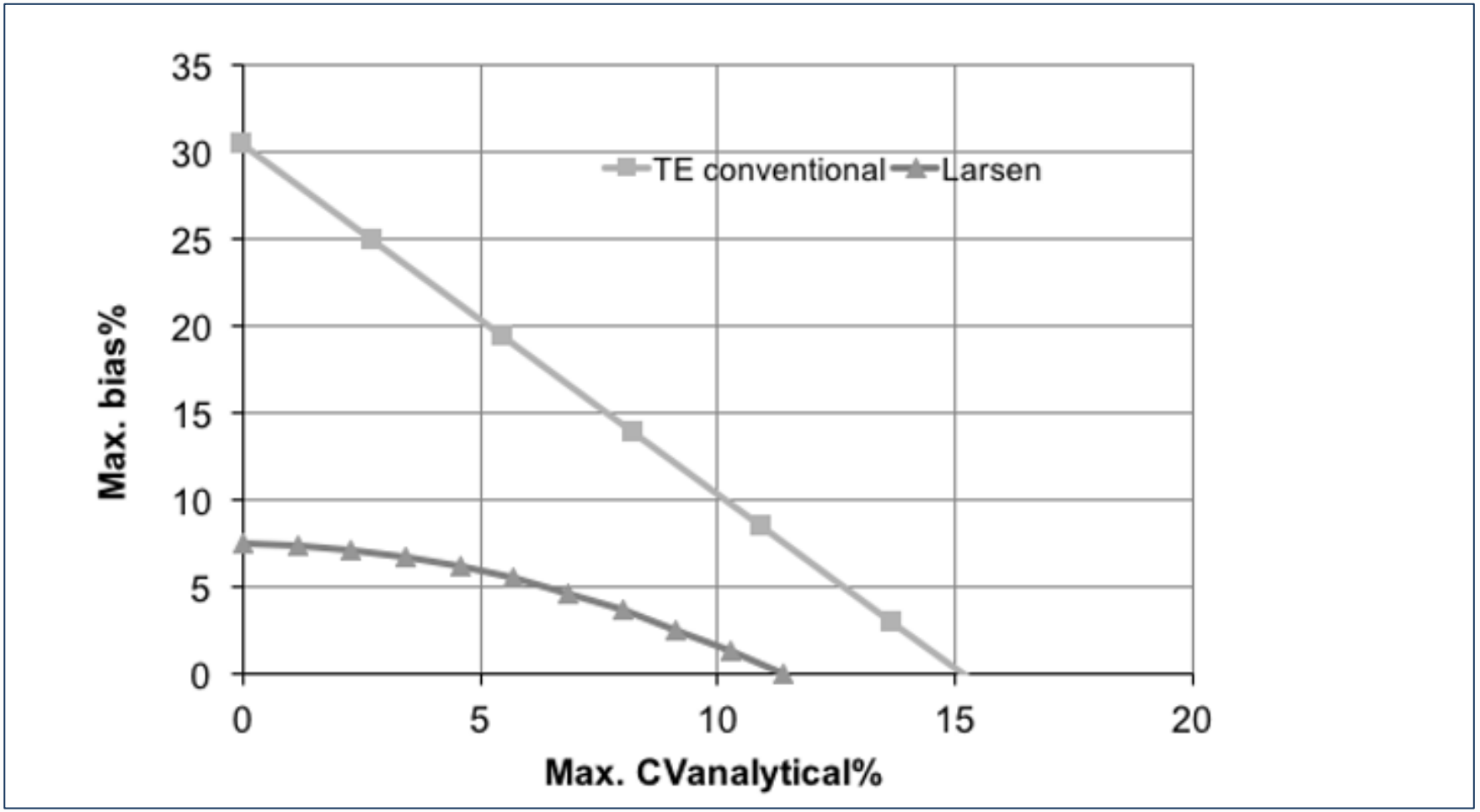
<u>Diagnosis</u>

Maximum imprecision CV_A	$< 0.5(CV_I^2+CV_G^2)^{1/2}$
Maximum bias	$< 0.25(CV_I^2+CV_G^2)^{1/2}$

<u>Monitoring</u>

Maximum imprecision CV_A	$< 0.5CV_I$
Maximum bias	$< 0.25(CV_I^2+CV_G^2)^{1/2}$?

Models for permissible bias and impecision, CK



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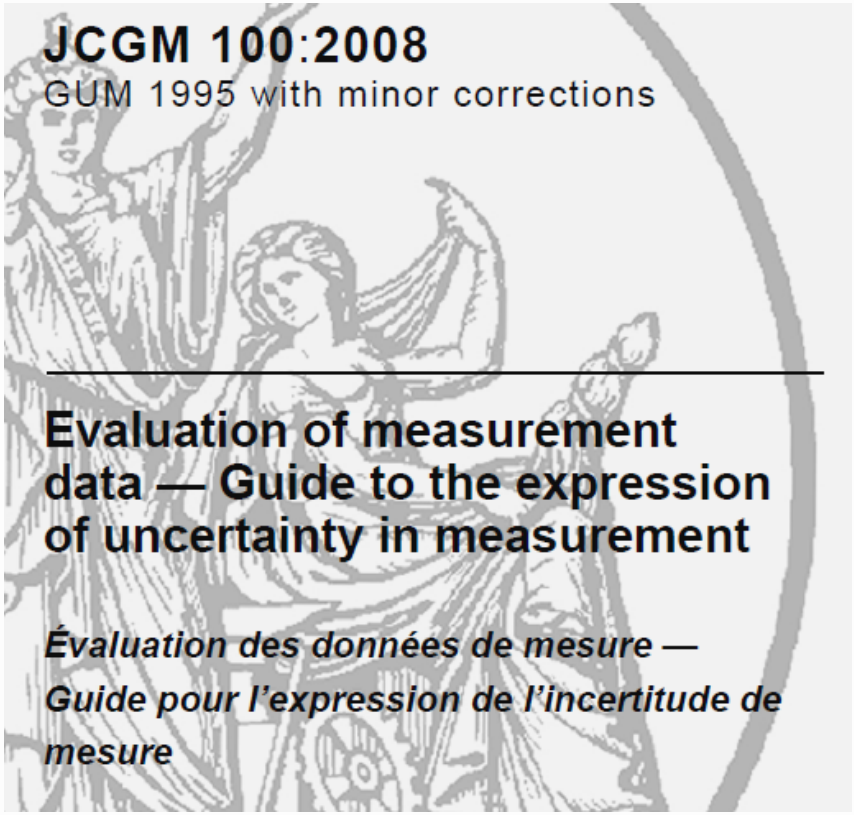

Measurement uncertainty

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GUM Guideline to the expression of uncertainty in measurement:

- “true value”does not exist/cannot be known or considered irrelevant

- Take all sources of uncertainty into account

- Correction of bias, include uncertainty of correction

ISO 15189:2012:

"The laboratory shall determine measurement uncertainty for each measurement procedure in the examination phases used to report measured quantity values on patients' samples.

The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty."

Uncertainty model

Bottom-up: complex mathematical model

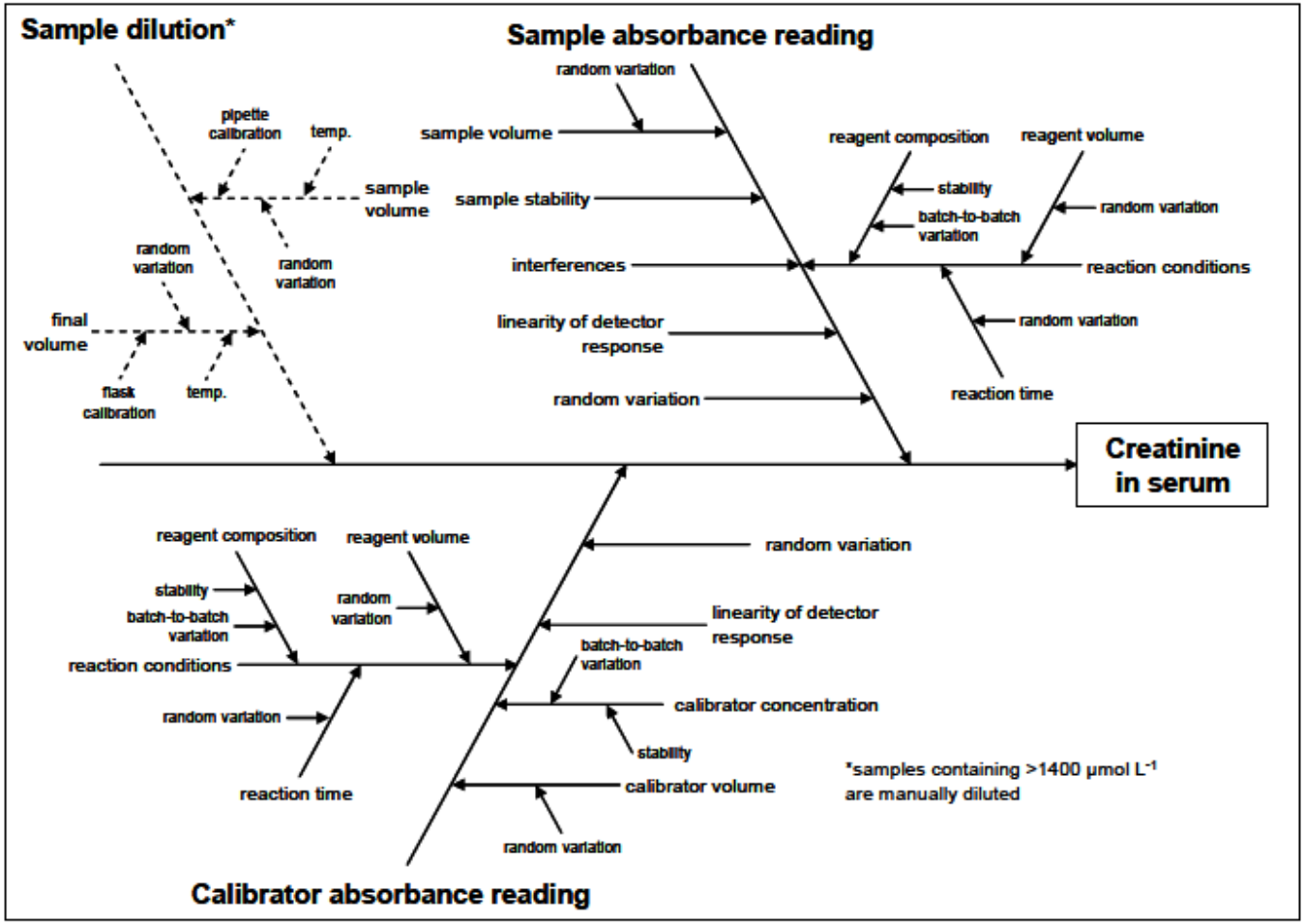
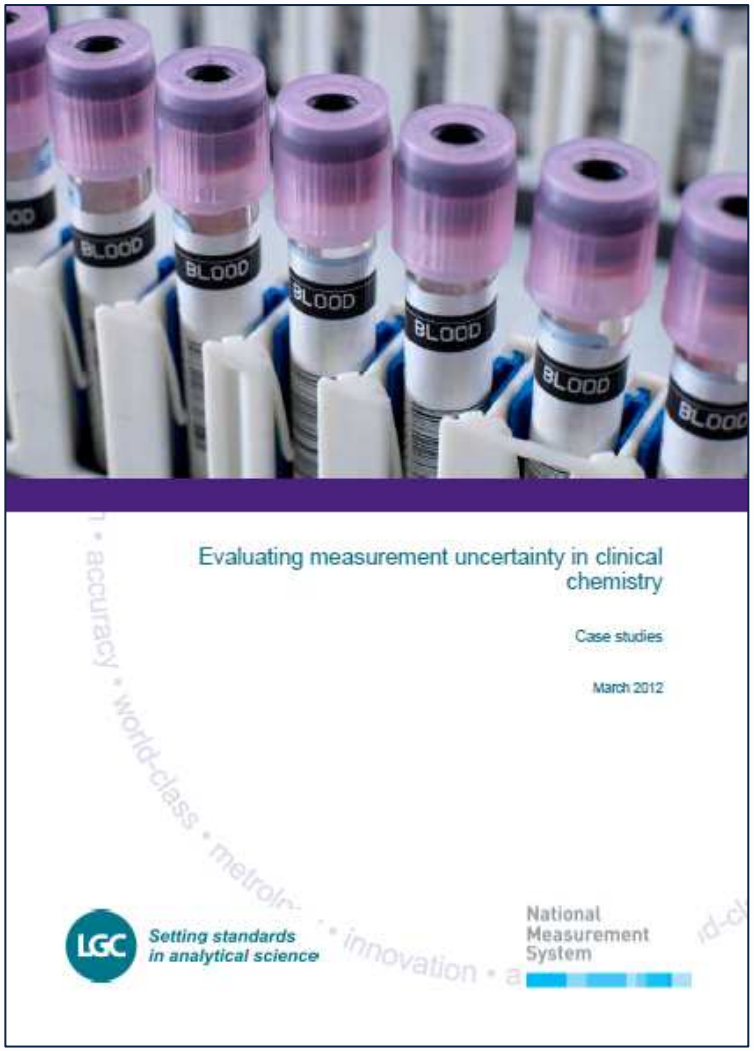


Figure 3: Cause and effect diagram identifying possible sources of uncertainty associated with the determination of creatinine in serum.

Uncertainty model

Top-down: based on quality control results



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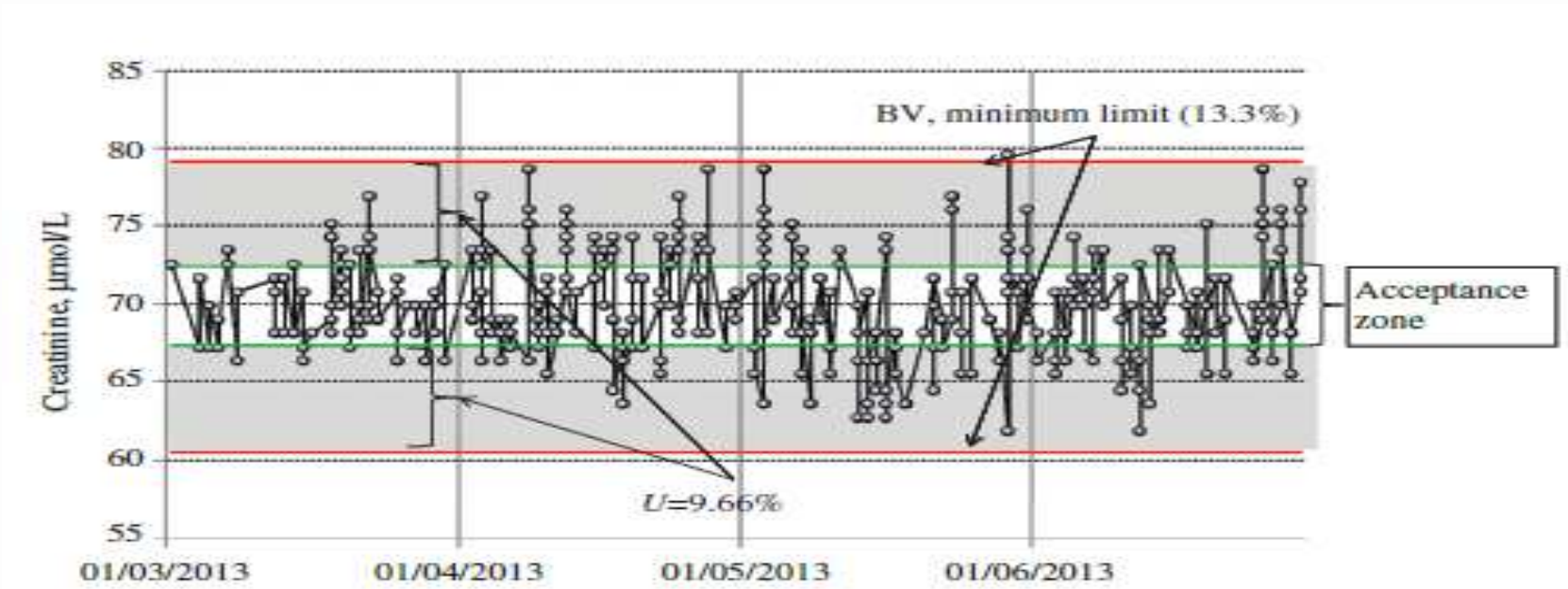

Figure 6: Low level creatinine quality control chart. Same as Figure 5B.

The time frame will have an important effect on the estimation of bias.

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Total error and uncertainty: Friends or foes?

E. Rozet, R.D. Marini, E. Ziemons, W. Dewé, S. Rudaz,
B. Boulanger, Ph. Hubert

Modeling measurement: error and uncertainty

Luca Mari [1*] *and Alessandro Giordani* [2]

[1] Università Cattaneo - LIUC, Castellanza (VA), Italy
[2] Università Cattolica, Milano, Italy

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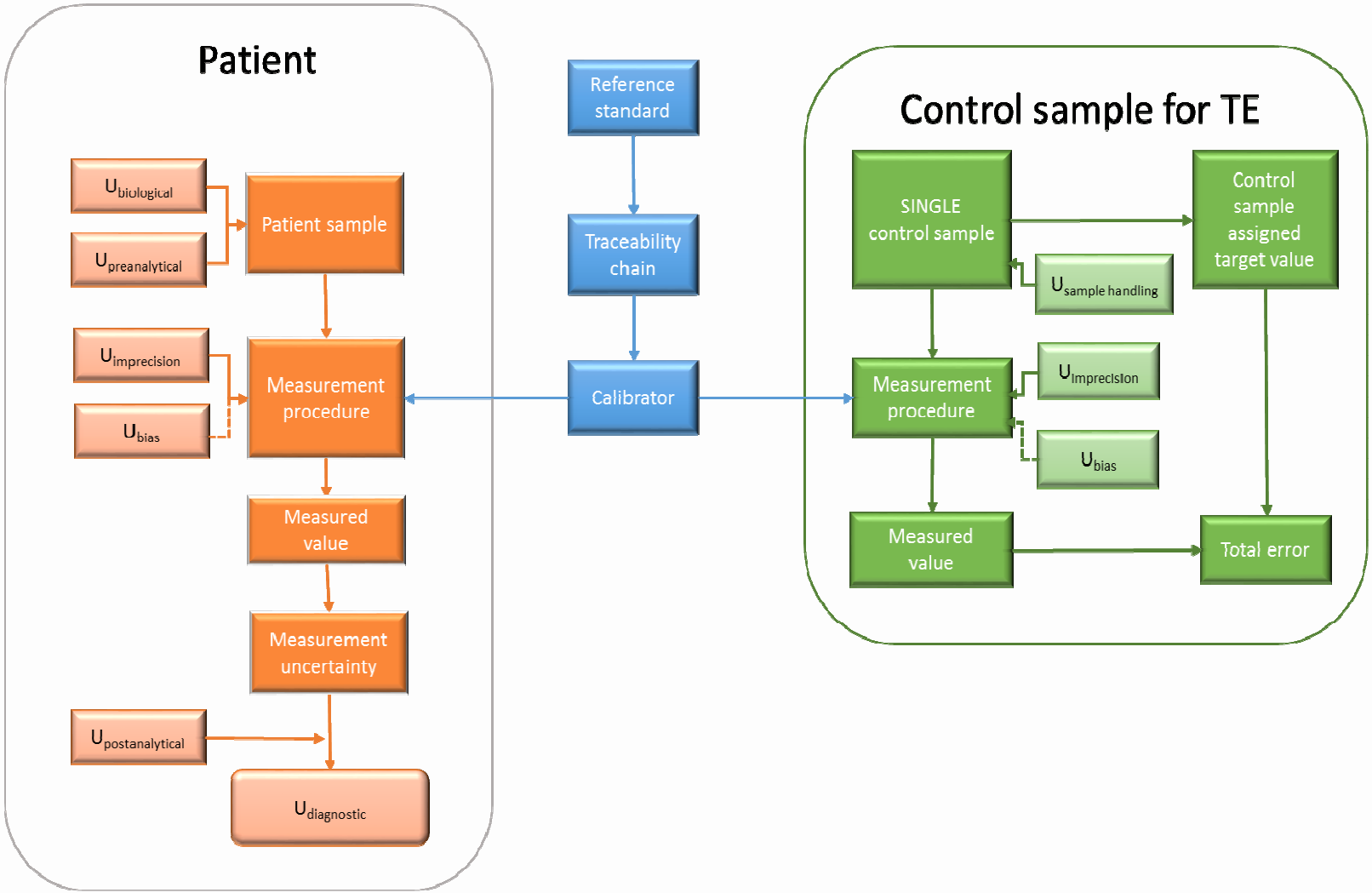
Patient
$U_{biological}$
$U_{preanalytical}$
Patient sample
$U_{imprecision}$
U_{bias}
Measurement procedure
Measured value
Measurement uncertainty
$U_{postanalytical}$
$U_{diagnostic}$
Reference standard
Traceability chain
Calibrator
Control sample for TE
SINGLE control sample
Control sample assigned target value
$U_{sample\ handling}$
Measurement procedure
$U_{Imprecision}$
U_{bias}
Measured value
Total error

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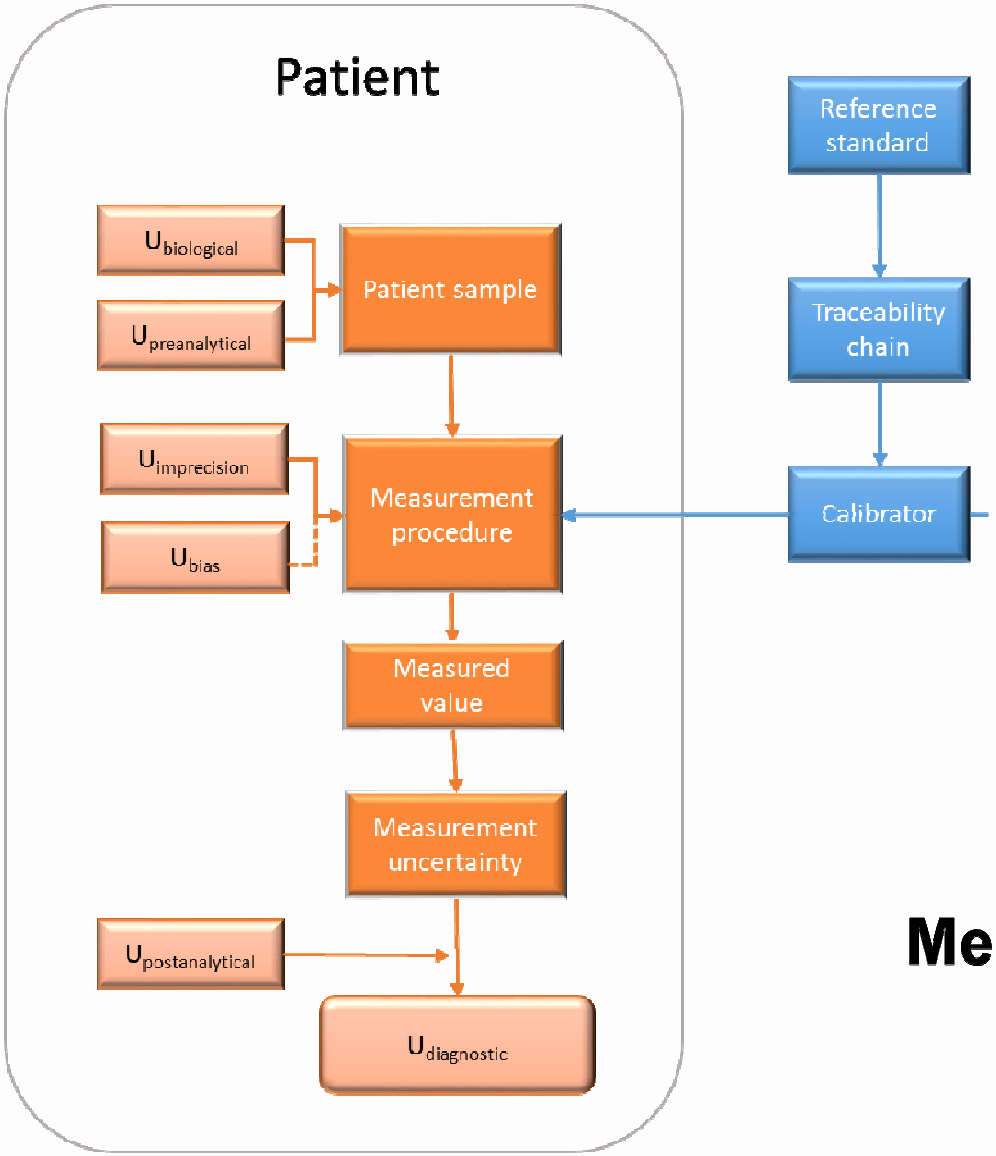

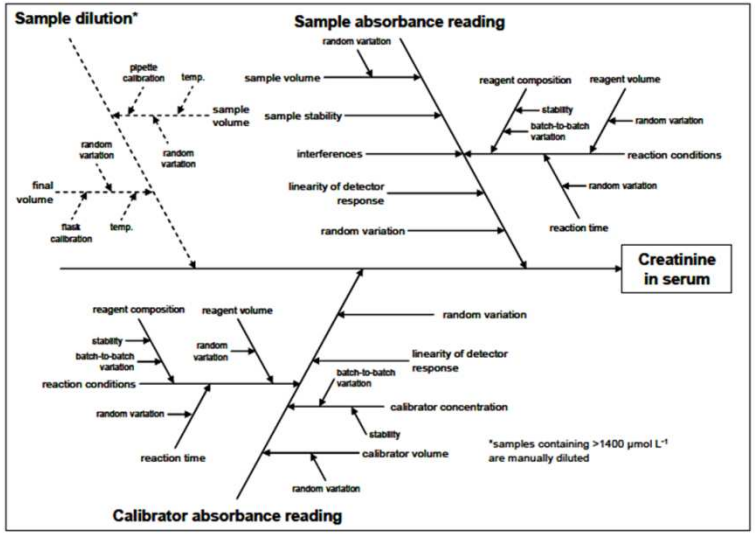

Figure 3: Cause and effect diagram identifying possible sources of uncertainty associated with the determination of creatinine in serum.

Measurement uncertainty

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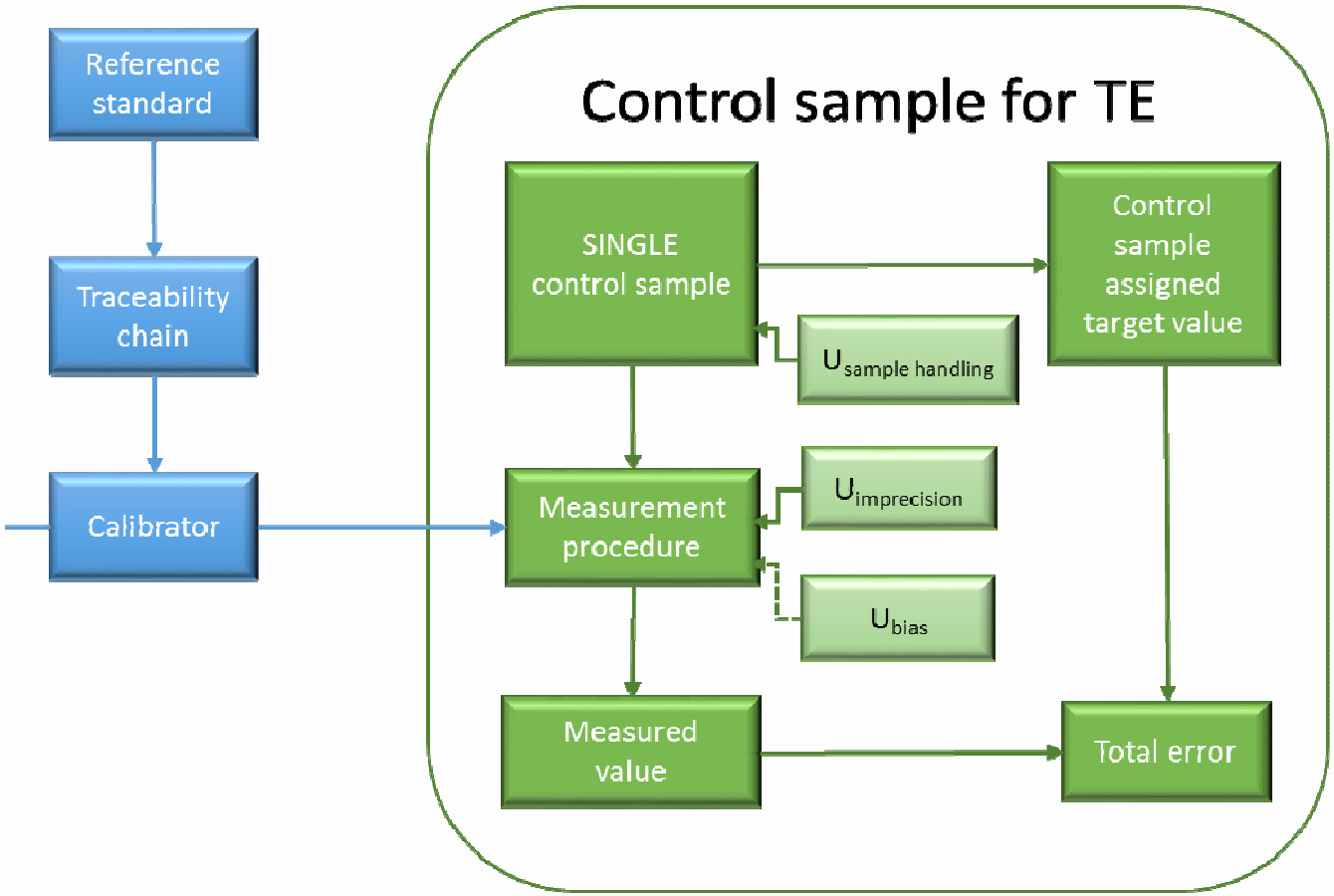
Total error



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Problems:

- TE model flawed
- How to combine random and systematic errors?
- Include uncertainty of bias?
- How to calculate allowable TE and MU?
- How to define quality limits?

Terms of Reference TE Task&Finish group:

Proposal:

- how to use the total error concept
- how to possible combine performance specifications for bias and imprecision.

Jan S. Krouwer*

The problem with total error models in establishing performance specifications and a simple remedy

Wytze P. Oosterhuis* and Sverre Sandberg

Proposal for the modification of the conventional model for establishing performance specifications

Quality control review: implementing a scientifically based quality control system

James O Westgard and Sten A Westgard

Rainer Haeckel*, Werner Wosniok, Ebrhard Gurr and Burkhard Peil

Permissible limits for uncertainty of measurement in laboratory medicine

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Review Article

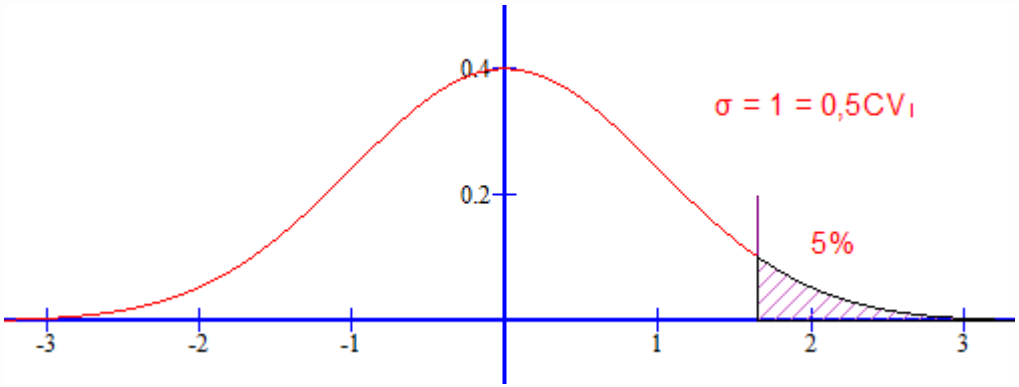
Analytical performance specifications in clinical chemistry: the holy grail?

Wytze P. Oosterhuis

Submitted Sep 01, 2017. Accepted for publication Sep 04, 2017.
doi: 10.21037/jlpm.2017.09.02
View this article at: http://dx.doi.org/10.21037/jlpm.2017.09.02

Performance specification: $CV_A < 0{,}5CV_I$

- Performance specification as maximum variation
- For QC (sigma) we need a performance limit



Sigma = $1{,}65(0{,}5CV_I)/CV_A$
= 1,65

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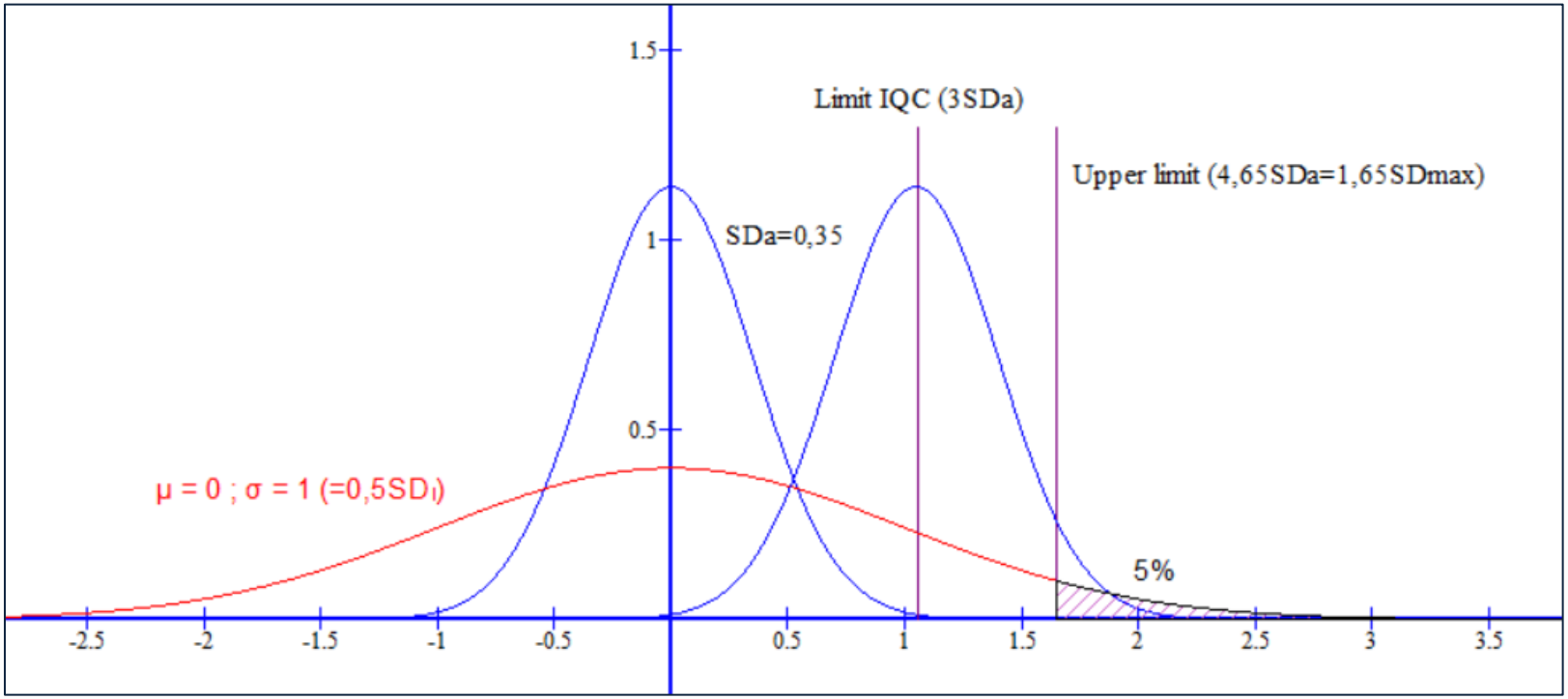
pTE = 1.65(0.5CVi)



0.5CVi = 1.65 SD

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Not logical:

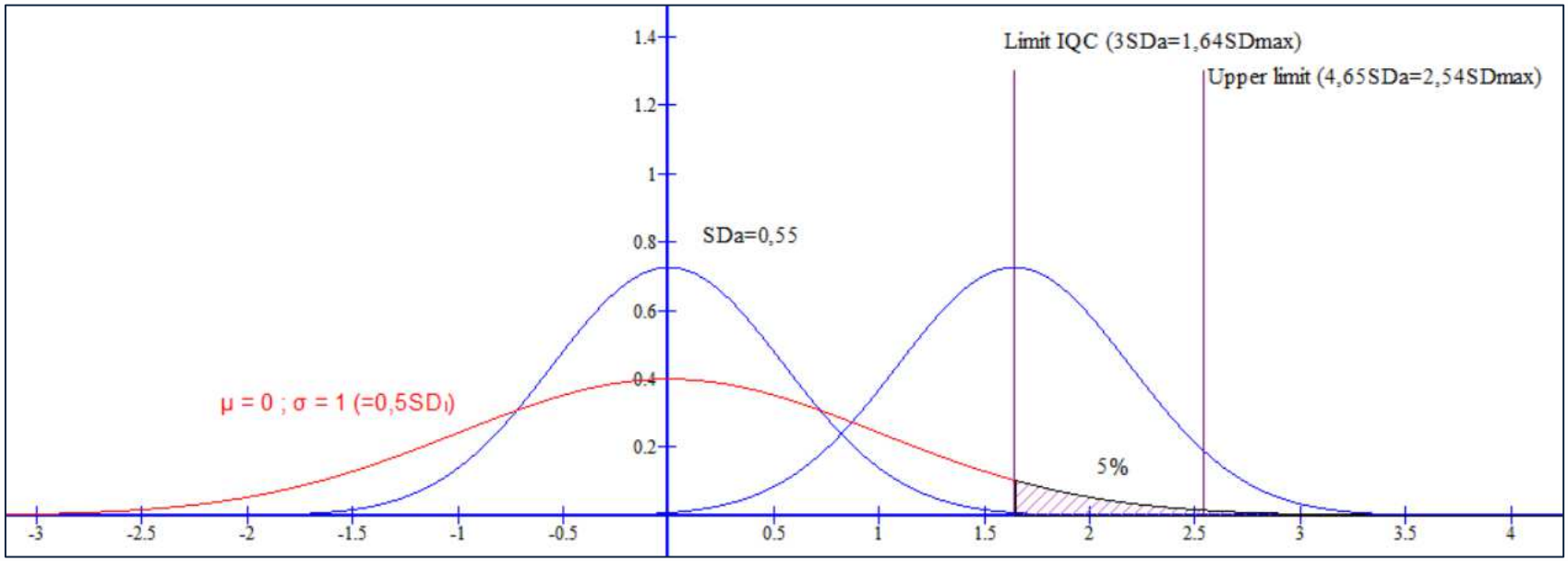
1) Sigma metric: performance limit based on z=1.65 is arbitrary.

2) Sigma metric of 1.65 is low: $CV_a=0.5CV_i$ cannot be maintained by QC.

3) Contrast with Six Sigma model: performance limit, but at the same time 5% outside limit is acceptible.

How to translate a maximum CV_a to a performance limit and sigma metric?

pTE = 2.5(0.5CVi)



0.5CVi = 2.5 sigma

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Quality control and measurement in industry

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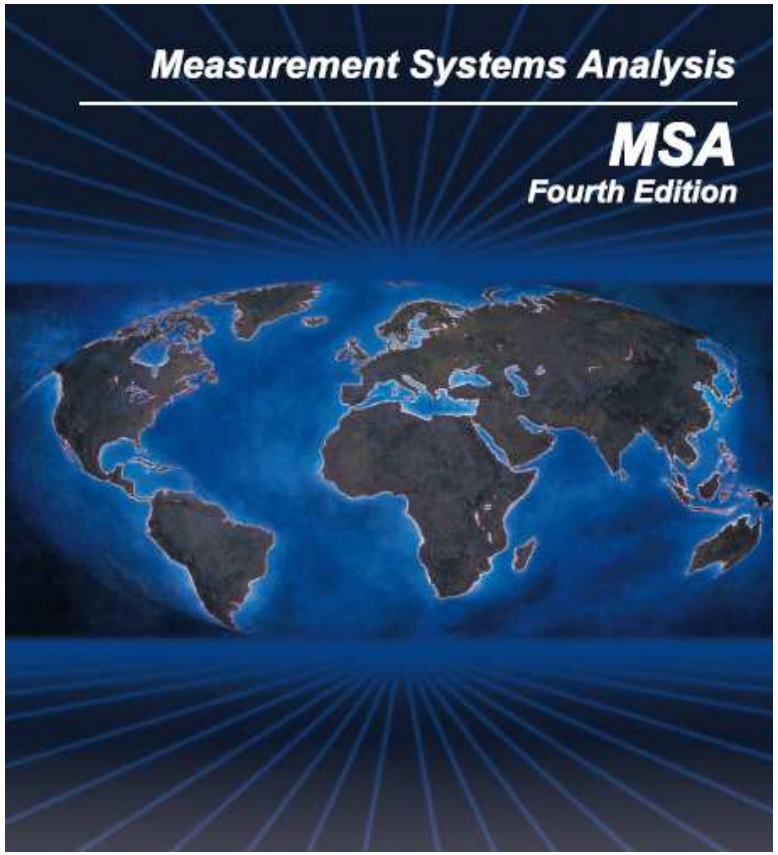

Measurement Systems Analysis Reference Manual, Fourth edition, Chrysler Group LLC, Ford Motor Company, General Motors Corporation (Automotive Industry Action Group, AIAG), Detroit-Michigan, USA, June 2010.

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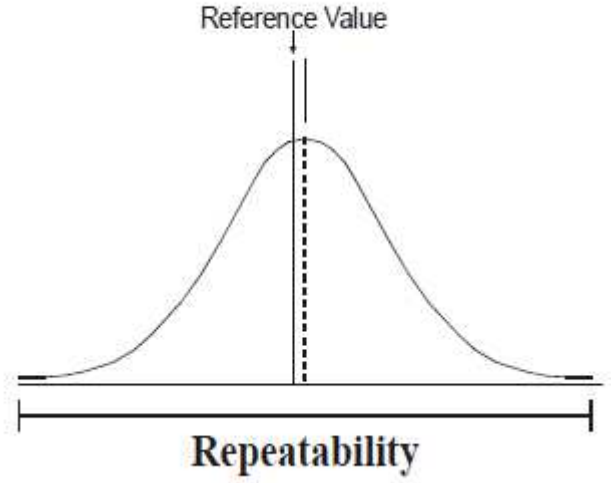
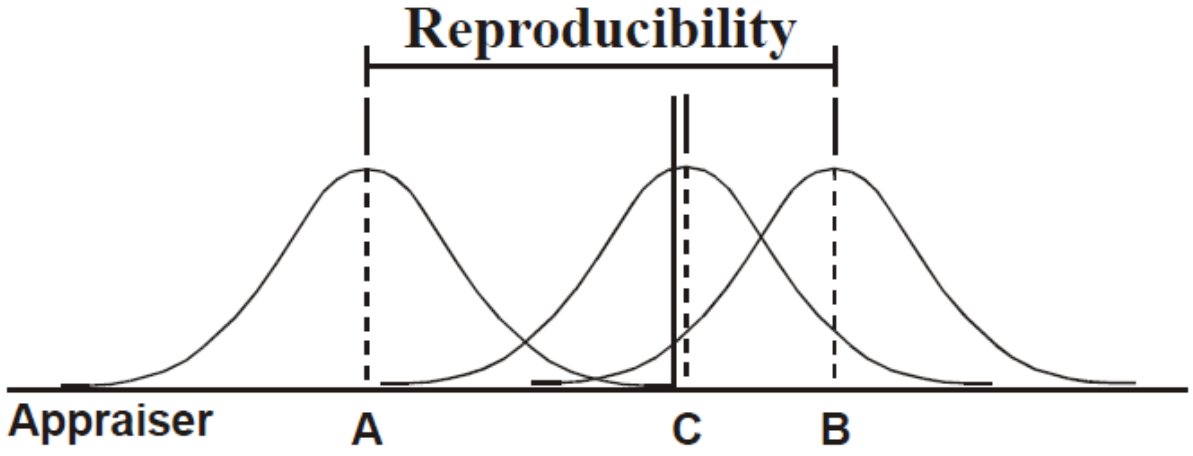
“Gage R&R”

$$\sigma^2_{GRR} = \sigma^2_{reproducibility} + \sigma^2_{repeatability}$$



Repeatability = imprecision

Reproducibility =
batch-to-batch variation
between-run variation
between instrument bias



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$$\Delta_{max} = \sqrt{k^2 * s_{ep}^2 + \delta_{ep}^2}\ ,$$

wobei

k = 3, Erweiterungfaktor für die Berechnung der laboratoriumsinternen Fehlergrenze

s_{ep}, empirische Standardabweichung der zur Berechnung herangezogenen Kontrollprobenmessungen in der Ermittlungsperiode (*ep*)

δ_{ep}, systematische Messabweichung der zur Berechnung herangezogenen Kontrollprobenmessungen in der Ermittlungsperiode (*ep*)

RiliBäk

Richtlinie der Bundesärztekammer

zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen

“NDC: Number of Distinct Categories”

$$\text{NDC} = \sqrt{2}\left(\frac{\sigma_{part}}{\sigma_{measurement}}\right)$$

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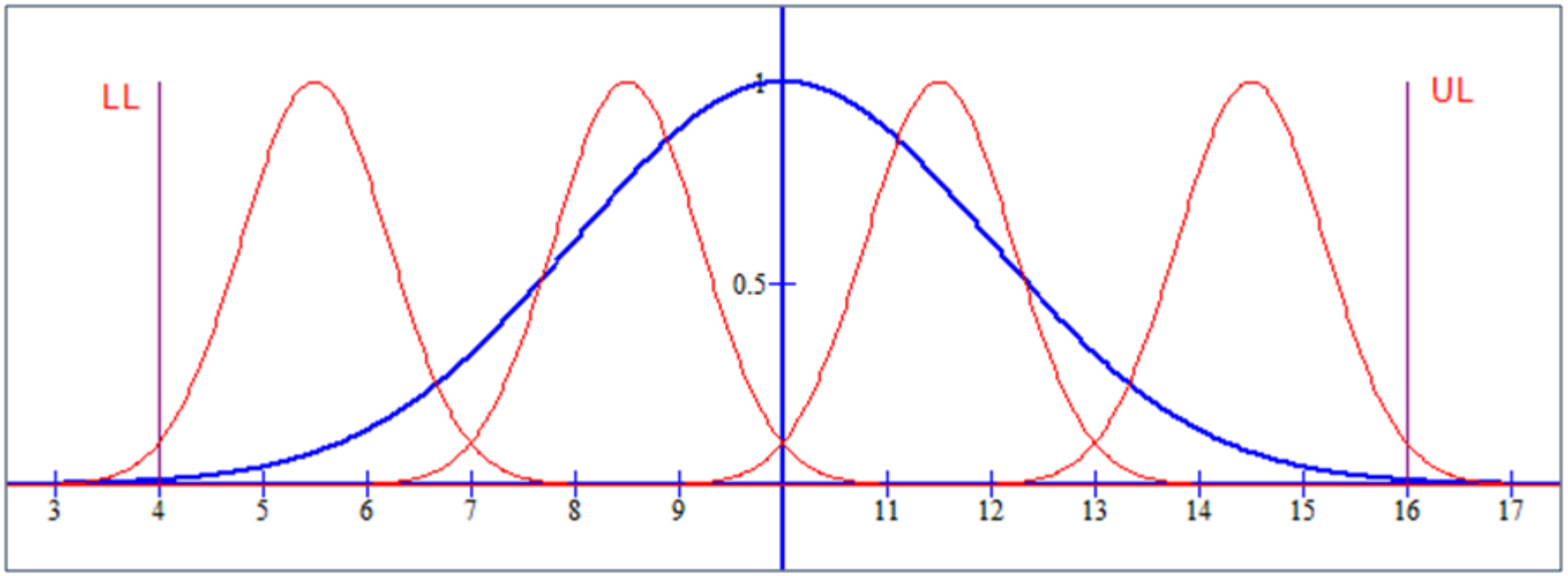
NDC: Number of distinct categories ≥ 4



Variation of product

Variation of measurement

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NDC: Number of distinct categories

Gage R&R	Decision	NDC	Comments
Under 10%	Generally considered to be an acceptable measurement system	>14	Recommended, especially useful when trying to sort or classify parts or when tightened process control is required.
10% to 30%	May be acceptable for some applications	4-14	Decision should be based upon, for example, importance of application measurement, cost of measurement device, cost of rework or repair. Should be approved by customer.
Over 30%	Considered to be unacceptable	<4	Every effort should be made to improve the measurement system. This condition may be addressed by the use of an appropriate measurement strategy; for example, using the average result of several readings of the same part characteristic in order to reduce final measurement variation.

Clinical chemistry: $CV_I/CV_A \leq 0{,}5 = 50\%$

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Test	CV_a*	$CV_{intra\text{-}individual}$	CV_{group}	pTE#	Sigma (TE)	NDC
Creatinine	1.22%	5.95%	14.7%	8.9%	7.3	6.9
Sodium	1.11%	0.6%	0.7%	0.73%	0.66	0.76
Potassium	1.36%	4.6%	5.6%	5.6%	4.1	4.9
Glucose	0.70%	5.6%	7.5%	6.96%	9.9	11.3
Iron	1.77%	26.5%	23.2%	30.7%	17.3	21.2
Albumen	2.60%	3.2%	4.75%	4.07%	1.6	1.7
TSH	1.25%	19.3%	24.6%	38.2%	30.6	21.8

Conclusions:

-TE and MU models both have their place

-Consensus on an improved error model is needed

-We could be inspired by ideas outside clinical chemistry

End