Optimizing the use of the state of the art performance criteria

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presented by Thomas Streichert, Cologne

3 Models

The organizers of this symposium identified three models for defining analytical performance goals in laboratory medicine:

Model 1 - Based on the effect of analytical performance on clinical outcomes
Model 2 - Based on components of biological variation of the measurand
Model 3 - Based on state of the art

- Whereas the statement mentions limited use of model 1, it lists some benefits and disadvantages of model 2 and 3.
- To overcome some of the disadvantages, a working group of the German Society of Clinical Chemistry (DGKL) proposes a combination of model 2 and 3.

Consensus Statement 3.1, 1st EFLM Strategic Conference 2014

Problems with state-of-the-art concepts

- No scientific reasoning
- Often based on „old“ data which may be outdated
- Lack of transparency
- Lack of neutrality (dependency on industry)
- No relationship between what is achievable and on what is needed clinically

Problems with biological variation

- Large variability between studies (e.g. 2.1-22.9% for PSA)
- Often generated from relatively young and healthy subjects
- Dependent on time span studied (hours – years)
- Effect of measurand concentrations?
- Available for only about 80% of the measurands in routine laboratories

Due to the great diversity of literature reports, many authors consider biological variation not suited to set metrological requirements.

Söletormos et al. (1999, survey of 13 studies)

Model 2

Model 2 is based on **biological variation** of which three types have been described:

1. intra- (CV_W), interindividual variation (CV_G)
2. combined CV_B (combined CV_W and CV_G)
3. combined CV_{WA} (combined of CV_W and CV_A)

CV_B: biological variation
CV_W: within-subject biological variation
CV_G: between-subject biological variation
CV_A: analytical variation

We prefer the empirical biological variation CV_E derived of the reference interval as a surrogate for CV_B because laboratories

1. are obliged to have RI for all measurands.
2. must check their transferability (if taken from external sources).
3. can easily check their suitability under internal conditions (regarding population served and analytical procedures applied).

(according to ISO, CLSI, IFCC)

CV_E: empirical variation
RI: reference interval

Haeckel et al., Permissible limits for uncertainty of measurement in laboratory medicine. Clin Chem Lab Med, in print

Reference limits reflect the biological variation (including the analytical variation)

s_E = empirical standard deviation

In the case of a normal distribution (λ = 1):

$$s_E = (\text{upper RL} - \text{lower RL}) / 3.92$$

s_E: empirical standard deviation
RL: reference limit

A „true“ empirical normal distribution does not exist in laboratory medicine.

At small reference ranges (e.g. Na, Cl, hematological quantities), the distribution usually looks quasi „normal“, although λ can be either 0 or 1.

At relatively large reference ranges (e.g. TSH, TG, enzymes), a difference between λ=0 and the „true“ λ (e.g. determined via Box-Cox transformation) becomes obvious, but is of less medical relevance.

If λ is unknown, we recommend to assume a logarithmic distribution.

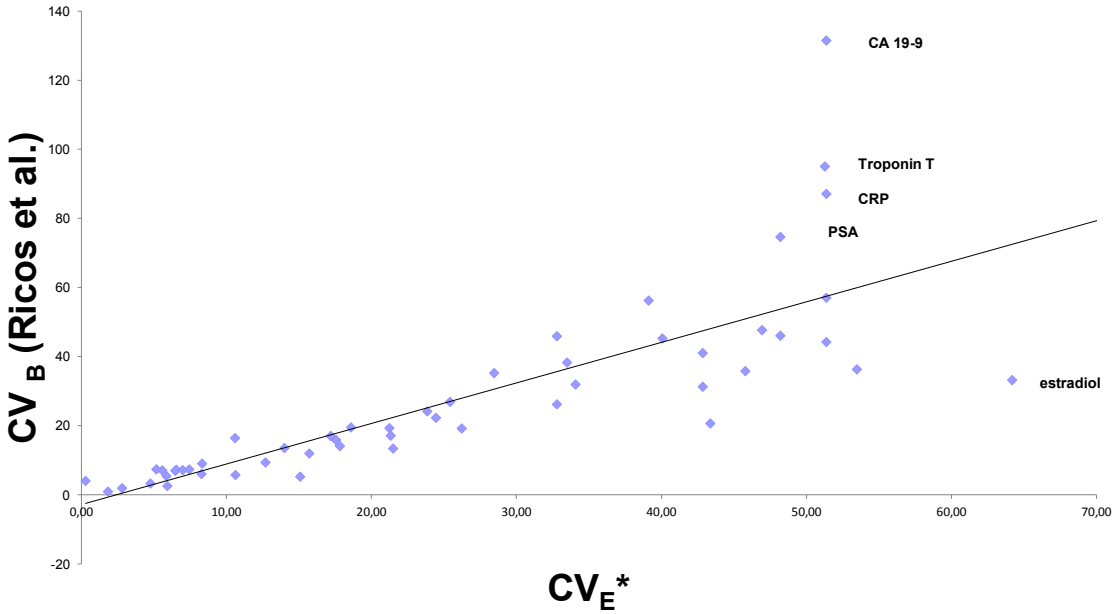
s_E and CV_E at skewed distribution

On the ln-scale:

$$s_{E,ln} = (lnRL_2 - lnRL_1)/3.92$$

$$CV_E^* = 100 \cdot (\exp s_{E,ln}^2 - 1)^{0.5}$$

CV_E^* : empirical (biological) coefficient of variation derived of $s_{E,ln}$
$s_{E,ln}$: empirical standard deviation on the ln-scale



PSA, intra-individual variation

Source	CV_W	CV_G
Ricos Table (www.westgard.com; 2014)	18.1	72.4
Söletormos et al. (1999, survey of 13 studies)	2.1-22.9	
Fraser (2001)	14.0	72.4
Dejter et a. (1988, n=30)	17.6	
Panteghini et al. (1992, n=5)	14.0	
Ornstein et al. (1997)	15.0	
Nixon et al. (1997)	7.3	
Schifman et al. (1987, n=10)	6.2	
Gurr, Haeckel (2008, n=4)	7.0	

$CV_E^* = 52.5$ $CV_B = 74.6$ (Ricos Table)

Facit: What is the correct CV_B? Lowering the CV_B would lead to a better correlation with CV_E^* of PSA.

The biological variation derived of the reference range, can be applied

1. to derive permissible analytical uncertainty.
2. to determine quantity quotients to standardize reporting laboratory results.

Biological variation concepts

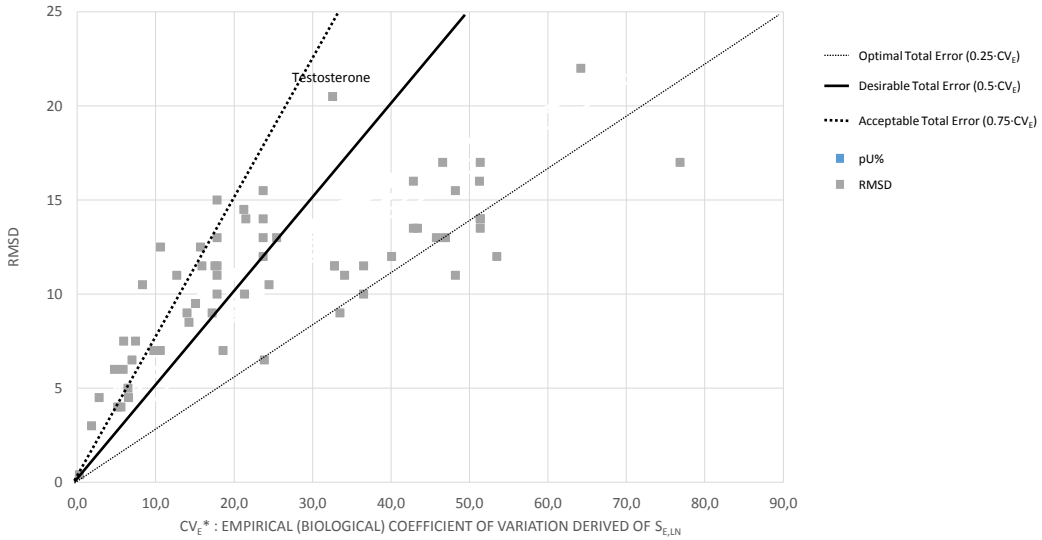
Harris, Cotlove: $pCV_A = 0.5 \cdot CV_B$

Fraser: 3 class model (0.25 / 0.5 / 0.75)

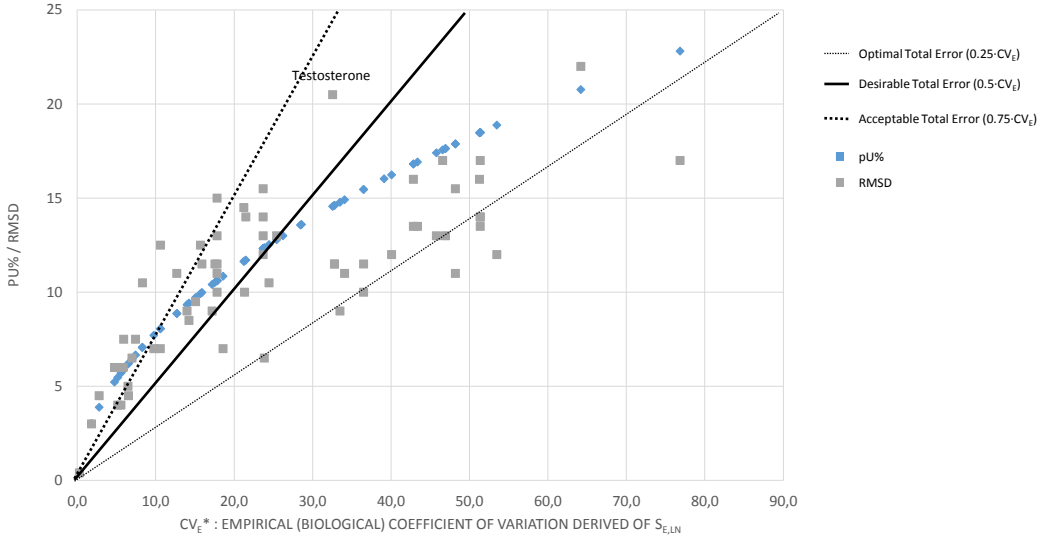
Haeckel, Wosniok: 5 class model

pCV_A : permissible analytical coefficient of variation
CV_B: biological coefficient of variation

Relation between CV_E* and RMSD values



Relation between CV_E* and pU% /RMSD values



New proposal based on a biological variation concept for analytical performance goals

$$pCV_A = (CV_E^* - 0.25)^{0.5}$$

pCV_A : permissible analytical coefficient of variation
CV_E* : empirical (biological) coefficient of variation derived of sE,ln

GUM[1)]: 3 Types of measurement uncertainty

1. Standard uncertainty u: imprecision (standard deviation)
2. Combined uncertainty u_c: $(u_1^2 + u_2^2 + u_3^2)^{0.5}$
3. Expanded uncertainty $U = k\, u_c$
   (if coverage factor k = 1.96, the level of confidence is 95%).

[1)] *Guide to the expression of uncertainty in measurement, supported by BIPM, IEC, IFCC, ISO, IUPAC, IUPAP, OIML, 1.edition 1993*

Permissible uncertainty (of measurement)

1.Permissible standard uncertainty (imprecision)

$$\mathbf{pCV_A = (CV_E^* - 0.25)^{0,5}}$$

CV_E^* : empirical (biological) coefficient of variation derived of sE,ln

2.Permissible bias

Permissible bias

$pB = 0.5\ pCV_A + u_B$

$u_B = t_{1-\alpha/2,n-1} \cdot ps_A/n^{0.5} \sim 0.5 \cdot pCV_A$

$pB = 0.5\ pCV_A + 0.5\ pCV_A = 0.7\ pCV_A$

$pB = 0.7 \cdot pCV_A$

Haeckel R, Wosniok W.; Clin Chem Lab Med. 2011

Permissible uncertainty (of measurement)

1.Permissible standard uncertainty (imprecision)

$pCV_A = (CV_E^* - 0.25)^{0,5}$

CV_E^* : empirical (biological) coefficient of variation derived of sE,ln

2.Permissible bias

$pB = 0.7 \cdot pCV_A$

Permissible uncertainty (of measurement)

1.Permissible standard uncertainty (imprecision)

$$\mathbf{pCV_A = (CV_E^* - 0.25)^{0,5}}$$

CV_E^* : empirical (biological) coefficient of variation derived of sE,ln

2.Permissible bias

$$\mathbf{pB = 0.7 \cdot pCV_A}$$

3.Permissible expanded uncertainty

pU% = 95% of the permissible imprecision + bias
(RMSD of RiliBÄK 2008, column 3 in Table B1a)

$$\mathbf{pU\% = 1.96 \cdot [(pCV_A)^2 + (0.7 \cdot pCV_A)^2]^{0,5} = 2.39 \cdot pCV_A}$$

Permissible limits for ring trials (EQAS)

Considering a 90% probability, the expanded uncertainty calculated is

$$\mathbf{pU_{EQAS}\% = 1.64 \cdot pU\% = 3.92 \cdot pCV_A}$$

and the 95% interval may be

$$\mathbf{pU_{EQAS}\% = 1.96 \cdot pU\% = 4.68 \cdot pCV_A}$$

The expanded uncertainty also leads to a curved relation with CV_E
(like pCV_A versus CV_E).

What means quantity quotient?

IQ = 100 means that the IQ is in the middle of the investigated population and

IQ = 70 – 130 is the reference interval (95% of the population)

This concept can be transferred to laboratory results if the biological variation (reference interval) is known.

Transformation of observed laboratory results in a quantity quotient (QQ):

a) In the case of a symmetrical distribution

$$QQ = 100 + 40\ (xi - mean)/(RL2 - RL1)\ [\lambda = 1]$$

b) In the case of a non-symmetrical distribution

$$QQ = 100 + 40 \cdot (\ln xi - M)/(\ln RL2 - \ln RL1) \quad [\lambda = 0]$$

Median $M = (\ln RL1 + \ln RL2)/2$

Report for serum creatinine

Serum of a 65 years old man was split and sent to four laboratories with different analytical procedures.

	Conventional result (RI) unit
Lab 1	140 (64-104) µmol/l
Lab 2	1.58 (0.72-1.18) mg/dl
Lab 3	1.60 (0.74-1.20) mg/dl
Lab 4	1.88 (1.02-1.48) mg/dl

Available Tools

The working group „Guide limits“ of the DGKL has developed easily to handle Excel (Microsoft) tools:

1. Estimation of reference intervals of intra-laboratory data pools
2. Estimation of the permissible uncertainty
3. Calculation of the quantity quotient

These tools are distributed gratuitously (e.g. website of the DGKL) and should be implemented by software companies in their information systems.

DGKL

Deutsche Vereinte Gesellschaft für Klinische Chemie und Laboratoriumsmedizin e.V.

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Reference Limit Estimator

Im klinisch-chemischen Laboratorium wird täglich eine große Anzahl von Messwerten ermittelt, bewertet und dokumentiert. Es existiert eine Datenbank, in der die Messergebnissen und andere relevante Informationen wie z. B das Datum der Probennahme, Alter und Geschlecht.

Im Allgemeinen ist für jede Messgröße der Anteil der pathologischen Werte im Vergleich zu Gesamtzahl aller Werte gering. In diesem Fall kann man mit bestimmten Modellannahmen und mit statistischen Methoden die Verteilung der Daten mit pathologischen Werten und die Verteilung der Daten mit nicht-pathologischen Werten zu trennen. Aus der Verteilung der nicht-pathologischen Werte lassen sich dann die Referenzgrenzen als das 2,5. und 97,5. Perzentile berechnen. Werden die Daten zuvor noch nach Alter oder Geschlecht gefiltert, können alters- und geschlechtsbezogene Referenzgrenzen ermittelt werden.

Der Vorteil zur konventionellen Methode, bei der ein zuvor ausgesuchtes Referenzkollektiv untersucht wird ist enorm: Die Daten sind bereits in den Datenbanken der Laboratorien vorhanden und das langwierige Auswählen und Untersuchen von Probanden eines Referenzkollektivs entfällt. Es ist außerdem aus Organisations-, Kosten- und Zeitgründen kaum möglich, eine so große Anzahl an Probanden zu finden, dass außer nach dem Geschlecht noch weitere Stratifizierungen (z. B. nach Alter) vorgenommen werden können. Zusätzlich sind häufig Zweifel an der Repräsentativität eines ausgesuchten Kollektivs angebracht. Ist die Messmethode nur schlecht standardisiert, so können die Referenzgrenzen, die in einem Labor mit Hilfe von Probanden ermittelt wurden, nicht von anderen Laboratorien übernommen werden. Werden dagegen die Messdaten aus der eigenen Datenbank des Laboratoriums verwendet, werden laborbezogene Referenzgrenzen ermittelt. Allgemein gültige Referenzgrenzen erhält man mit diesen Verfahren, wenn sich mehrere Laboratorien an der Ermittlung beteiligen und die Messprozedur einen hohen Standardisierungsgrad aufweist (1-6).

Der Anwender bedient das Programm über eine Excel-Oberfläche die mit Excel 2003 entwickelt wurde, sich aber auch mit den neueren Excel-Versionen verwenden lässt. Da die statistischen Berechnungen sehr umfangreich und teilweise komplex sind, wird die statistische Analyse mit dem Programm R und unter Verwendung einiger Zusatzmodule (packages) durchgeführt. Die statistischen Ergebnisse und graphischen Darstellungen werden dann wieder in die Excel-Oberfläche übertragen.

Downloads

Reference Limit Estimator (Programm als ZIP-File, Version 20141017)

Reference Limit Estimator (PDF-Handbuch)

Zulässige Messunsicherheit

Die Arbeitsgruppe Richtwerte der DGKL hat ein Konzept entwickelt, um die zulässige Messunsicherheit (zulässige Impräzision und zulässiger Bias) aus dem Referenzintervall abzuleiten. Dieses Konzept und die zugrunde liegenden Algorithmen wurden in Clin Chem Lab Med 2015 (Permissible limits of uncertainty in laboratory medicine) beschrieben. Das Excel-Programm errechnet automatisch die zulässige Messunsicherheit (permissible coefficient of variation, pCVA) und die zulässigen Grenzen der Abweichung des Einzelwertes gemäß den RiliBÄK 2008 (Δmax). Die Tabelle enthält fast alle Messgrößen der RiliBÄK 2008.

Excel-Datei Zulässige Messunsicherheit

Excel File Permissible Uncertainty

Leitung/Kontakt: Prof. Dr. Eberhard Gurr

http://www.dgkl.de/PA106975_DE_VAR100

	Permissible imprecision (pCV_A) and combined uncertainty (pU%) for a particular measurand (x_i).									
									RiliBÄK 2008	RiliBÄK 2008
Quantity	Upper RL[1]	Lower RL[1]	x_i	Unit	Remark[2]	$pCV_A(x_i)$	$pU\%^4$ (x_i)	pU_{EQAS} %	RMSD[6]	EQAS
Plasma, serum, whole blood										
Activated PTT	26	36	31	s		2,82	6,73	13,2	10,5	18,0
Albumin	35	53	44	g/l	> 60 years	3,18	7,60	14,9	12,5	20,0
Alcaline phosphatase	30	80	55	U/l	women	4,78	11,41	22,4	13,0	21,0
Aldosteron	180	790	485	pmol/l	standing	5,78	13,81	27,1		
Alpha-Fetoprotein (44)	0,9	6	3,45	µg/l		6,55	15,66	30,7	17,0	24,0
AST/GOT	10	35	22,5	U/l	women	5,34	12,77	25,0	11,5	21,0
ALT/GPT	10	35	22,5	U/l	women	5,34	12,77	25,0	11,5	21,0
Bilirubine, total	3,4	18,8	11,1	µmol/l		6,21	14,83	29,1	13,0	22,0
Ca 19-9	6	40	23	KU/l		6,55	15,66	30,7	14,0	27,0
Calcium	2,2	2,65	2,425	mmol/l		2,12	5,06	9,9	6,0	10,0
Calcium,ionized	1,15	1,45	1,3	mmol/l		2,37	5,67	11,1	7,5	15,0
Carbamazepin	4	10	7	mg/l		4,63	11,06	21,7	12,0	20,0
CEA	0,75	5	2,875	µg/l		6,55	15,66	30,7	14,0	
Chloride	95	106	100,5	mmol/l		1,59	3,81	7,5	4,5	8,0
Cholesterol (45)	3,90	5,90	4,9	mmol/l		3,18	7,59	14,9	7,0	13,0
Cholinesterase	3,93	10,8	7,365	U/l	women	4,84	11,57	22,7		
Cortisol	138	690	414	nmol/l	8 o´clock	6,02	14,39	28,2	16,0	30,0
Creatinine	49	97	73	µmol/l	men	4,04	9,66	18,9	11,5	20,0
Creatinkinase	25	150	87,5	U/l	women	6,36	15,19	29,8	11,0	20,0
C-reaktives Protein	0,75	5	2,875	mg/l		6,55	15,66	30,7	13,5	20,0
Digoxin	0,8	2	1,4	mg/l		4,63	11,06	21,7	14.0	30,0
Digitoxin	10	25	17,5	mg/l		4,63	11,06	21,7	15,5	30,0
Erythrocytes	31,4	41,2	36,3			2,57	6,14	12,0		
Estradiol,17-beta	110	1100	605	pmol/l	Follicle phase	7,32	17,50	34,3	22,0	35,0
Ferritin	22	112	67	µg/l	w, 20-50 years	6,05	14,47	28,4	13,5	25,0
Glucose	3,9	6,4	5,15	mmol/l	venous plasma	3,47	8,28	16,2	11,0	15,0
Glucose	70	115,0	92,5	mg/dl	venous plasma	3,47	8,29	16,3		
γ-Glutamyltransferase	9	36	22,5	U/l	women	5,60	13,39	26,2	11,5	21,0
Hämoglobin	125	153	139	g/l	women	2,21	5,28	10,3	4,0	6,0
Haemoglobin A1c [7]	3,4	4,7	4,05	%		2,81	6,72	13,2		
Haemoglobin A1c [7]	14	28	21	mmol/mol		4,07	9,72	19,1	10,0	18,0

Examples of a QQ report already realized by a software company

S	Kürzel	Wert	K	±	Grafik EQ
XP	Na P	146		+	
DX	K P	4.0			
XP	Cl P	120		+	
DX	Ca P	2.30			

Ana 1(Na P) (EQ: 103) VW(TNR: 24.05.11/1639): 144 (EQ: 116) RG: 136-145 mmol/l

Summary

- The empirical (biological) variation (CV_E^*) derived from the reference range is suggested as a surrogate for the biological variation.
- Reference limits are available to all measurands and, most probably, the laboratories have more experience with these data, because they have to validate them before their introduction in the diagnostic service, and then to verify them periodically according to good laboratory practice.
- CV_E^* values can be used to derive permissible uncertainty by algorithms which may reconcile the presently competing biological variation model and the state-of-the-art model.

Thank you!