Sigma Metrics
for
Coagulation Analyzer

ชวดี นพรัตน์
นักเทคนิคการแพทย์ชำนาญการพิเศษ
คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์
13 ก.ย. 2561

Coagulation laboratory

Pre-pre-analytical process

Pre-analytical process

- Specimen collection
- Specimen transport
- Specimen processing
- Specimen storage

Analytical process

- Analyzer
- Quality control (IQC/EQA/PT)
- Procedure (WI)
- Staff competency

Post-analytical process

- Clinical correlation and interpretation
- Result report and approval
- Transmission of result

Quality system in coagulation laboratory

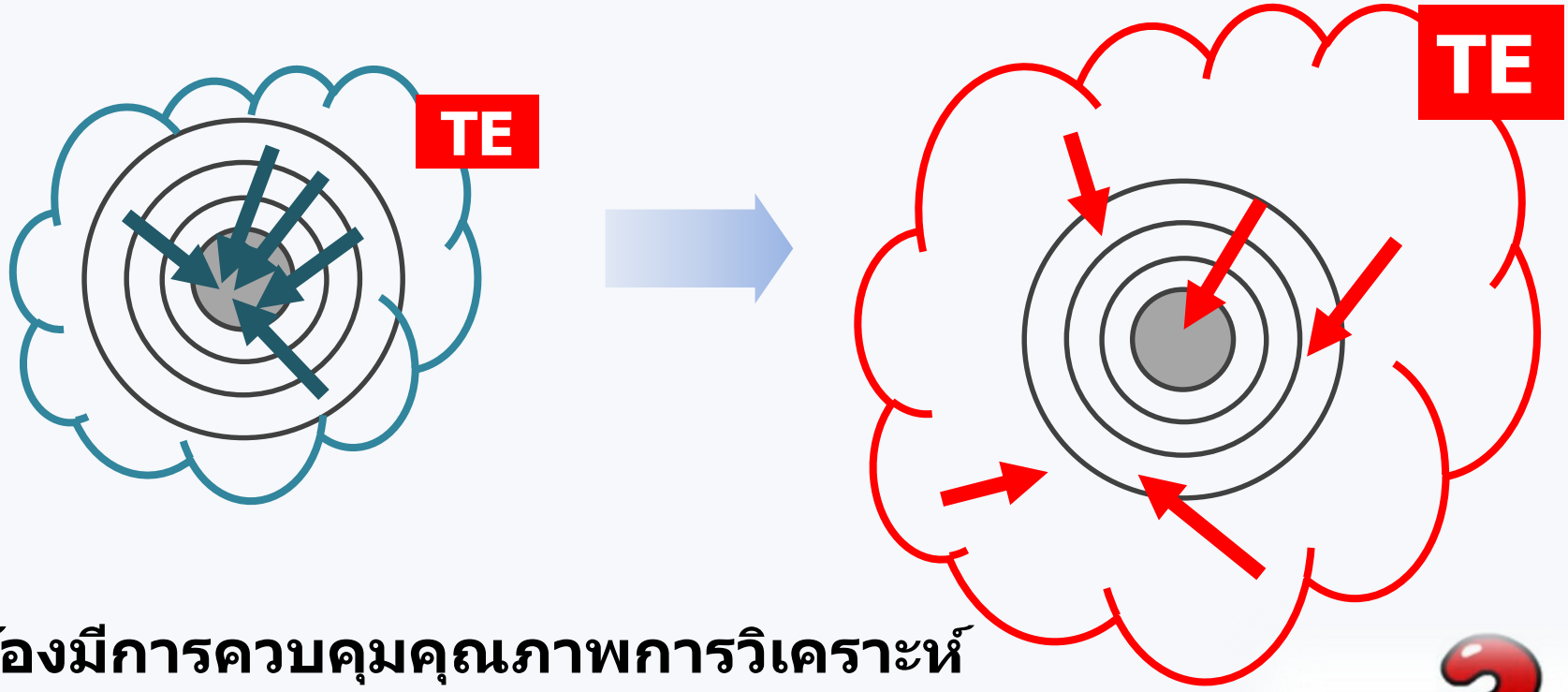
อยากได้ เครื่องมือ/น้ำยา/วิธีการทดสอบ
ที่มีประสิทธิภาพสูงๆ

Method verification

การทดสอบเพื่อที่จะประกันว่าวิธีการวิเคราะห์/เครื่องมือ ที่จะนำมาใช้ในห้องปฏิบัติการมีความถูกต้อง แม่นยำ เป็นไปตามคุณสมบัติที่กล่าวไว้

รายงานผลการทดสอบประสิทธิภาพการทำงาน เครื่องตรวจวัดการแข็งตัวของเลือดอัตโนมัติ CS-1600 และ CS-2500

...นำมาใช้งานจริง
ควบคุมไม่ให้เกิดความผิดพลาดได้อย่างไร?



ต้องมีการควบคุมคุณภาพการวิเคราะห์

- การควบคุมคุณภาพภายใน (internal quality control, IQC)
- การตรวจสอบคุณภาพจากภายนอก (external quality assessment, EQA)
- Peer group; IQC interlaboratory online (Bio-rad, Riquas…)

ทำอย่างไร? จึงจะมั่นใจว่า ผลการทดสอบของเราถูกต้อง แม่นยำ เชื่อถือได้ตลอดเวลา

- ต้องมีระบบคุณภาพ
- ต้องมีการควบคุมคุณภาพการวิเคราะห์ตลอดกระบวนการ
- **ต้องมีการประเมินผลและปรับปรุงให้ดีขึ้นอย่างสม่ำเสมอ (Quality improvement)**

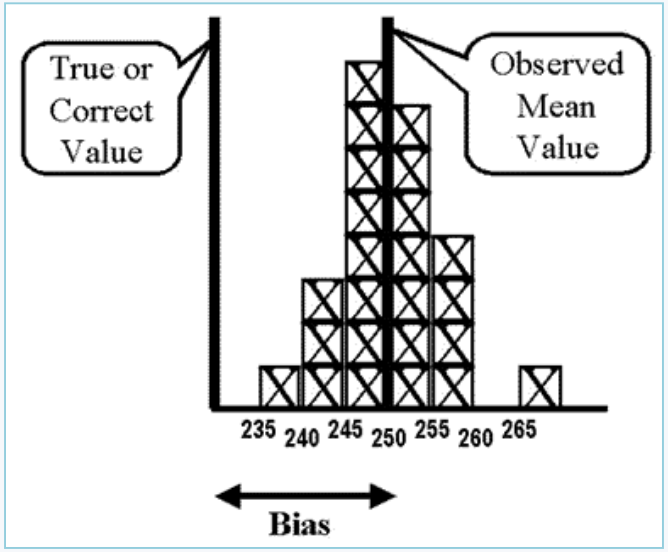
ประเมินความสามารถของวิธีวิเคราะห์
Method performance

Sigma metrics

Sigma metrics for coagulation analyzer

1. Inaccuracy => %Bias
2. Imprecision => %CV
3. Total Error => TEa
4. Sigma-metrics
5. Method decision chart
6. QC planning

1. Inaccuracy, bias



Bias= Measured value - True value

Inaccuracy/Bias Estimation

1. Peer group from IQC
2. EQA (External quality assurance) or PT (Proficiency testing) data
3. Method comparison

การหาค่า Inaccuracy/Bias โดยใช้ค่า Peer group IQC

Peer group : a group of people, usually of similar age, background, and social status, with whom a person associates and who are likely to influence the person's beliefs and behavior

ข้อมูล IQC ที่ใช้ control lot เดียวกัน, วิธีการทดสอบเหมือนกัน , เครื่องรุ่นเดียวกัน, same system

$$\% \text{ Bias} = \frac{(\text{Lab result} - \text{Group mean})}{\text{Group mean}} \times 100$$

การหาค่า Inaccuracy/Bias โดยใช้ค่า Peer group IQC

SNCS-CBC

JULY 2018 MONTHLY REPORT REPORT ID:eQAP215-DL

LAB NO. 6382510246 LOT NO . QC-81341101 * , QC-81341102 *

			YOUR LAB				GROUP TOTAL (YOUR METHOD)					
ITEM.	Control Lot		MEAN	SD	CV	N	MEAN	TOTAL-SD	INTER-SD	INTRA-SD	LABS	SDI
WBC	QC-81341101	*	2.964	0.0581	1.96	20	3.013	0.0710	0.0419	0.0573	1302 L	-0.693
	QC-81341102	*	6.819	0.0772	1.13	20	6.860	0.1296	0.0895	0.0937	1488 L	-0.315
	QC-81341103	*	16.650	0.1848	1.10	20	16.711	0.3390	0.2292	0.2497	1525 L	-0.181
RBC	QC-81341101	*	2.224	0.0304	1.36	20	2.244	0.0318	0.0238	0.0211	1302 L	-0.642
	QC-81341102	*	4.274	0.0343	0.80	20	4.325	0.0509	0.0386	0.0331	1488 L	-1.003
	QC-81341103	*	5.133	0.0465	0.90	20	5.177	0.0704	0.0525	0.0469	1525 L	-0.627

Item	QC-lot	Your lab Mean	Group Mean	Bias	%bias
WBC	QC-81341101	**2.964**	**3.013**	(2.964–3.013)/3.013 = -0.016	**- 1.6**

การหาค่า Inaccuracy/Bias โดยใช้ EQA/PT data

EQA is defined as a system for objectively checking the laboratory's performance using an external agency or facility

PT are interlaboratory comparisons that are organized regularly to assess the performance of analytical laboratories and the competence of the analytical personnel

$$\% \text{ Bias} = \frac{(\text{Lab result} - \text{Group mean})}{\text{Group mean}} \times 100$$

การหาค่า Inaccuracy/Bias โดยใช้ EQA/PT data

Thailand National External Quality Assessment Scheme For Blood Coagulation

Survery Number :	52	Machine :	CS2000i, CS2100i
Participant Number :	114	% Sodium Citrate :	3.2
PT Reagent :	Thromborel S	Source of Reference Range :	Normal healthy volunteer
APTT Reagent :	Actin FS	Source of Denominator :	Geometric mean from fresh normal plasma

PT / INR Results

Participant in your group :	260	Your normal range	Lower limit : 9.90
Reference lab in your group :	191		Upper limit : 12.30

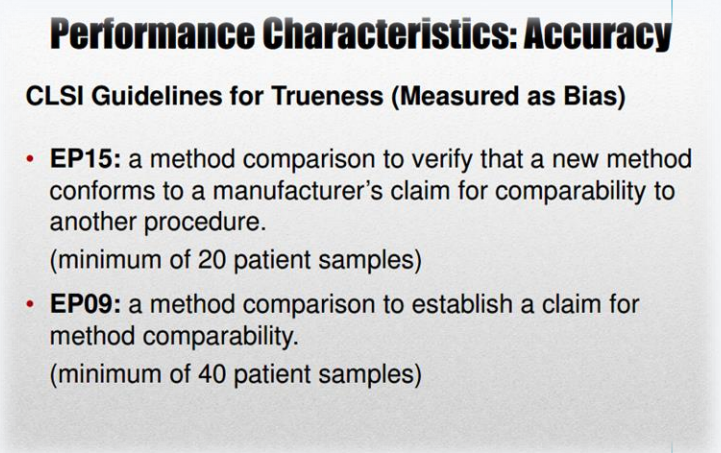
	01/18	02/18	03/18
Your previous % deviation	-1.72	-2.19	19.68
	04/18	**05/18**	**06/18**
Your result of PT (sec.)	36.4	41.8	13.2
Your PT ratio	3.28	3.77	1.19
Median of PT ratio	-	-	1.12
Your INR	3.4	3.92	-
Median of INR	3.35	3.97	-
Your % deviation	1.49	-1.26	6.25
Your assessment against	Reagent	Reagent	Reagent
Your performance (Consensus)	Within	Within	Within
Your interpretation	Abnormal	Abnormal	Borderline
Overall interpretation (%)			
Normal	.00	.00	63.47
Borderline	1.03	.77	22.02

INR

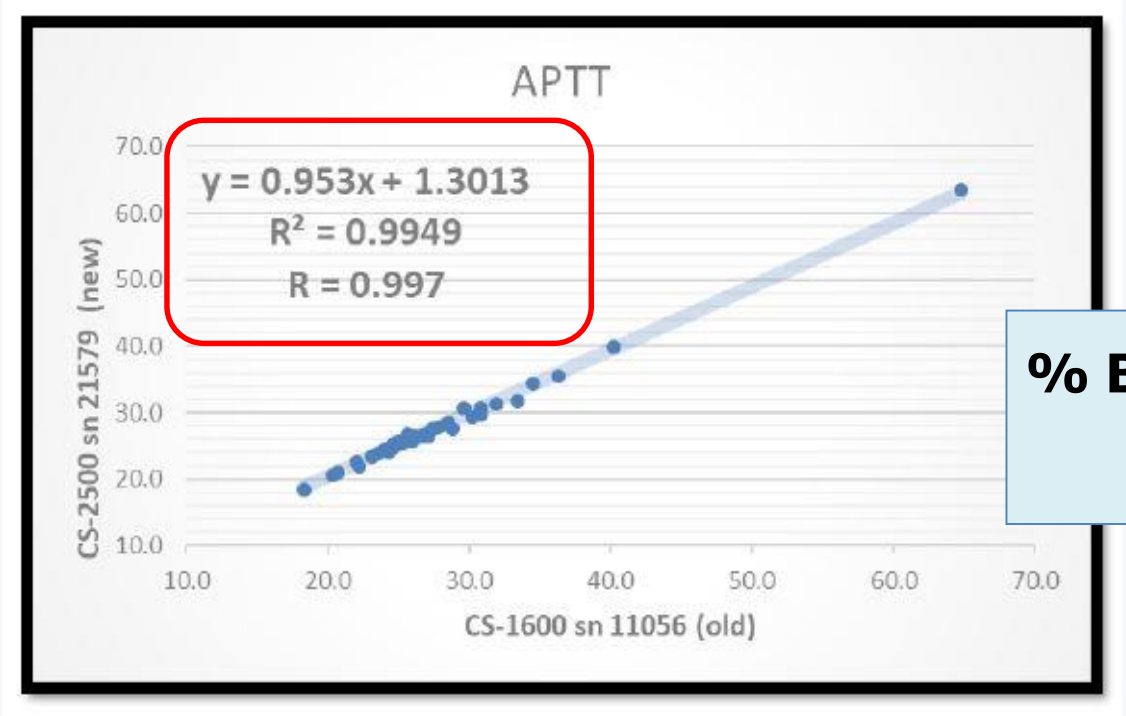
$$\% \text{ Bias} = \frac{(3.4 - 3.35) \times 100}{3.35} = 1.49$$

การหาค่า Inaccuracy/Bias โดยใช้ Method comparison

- Comparative method
  - reference method
  - provisional method
- Number of patient sample
  - minimum of 40, 20 (EP15,CLSI)
  - cover measuring range
- Single/duplicate measurements
- Time period
  - minimum of 5 days, within 2 hrs.



การหาค่า Inaccuracy/Bias โดยใช้ Method comparison



$$\% \text{ Bias} = \frac{(Yc - Xc)}{Xc} \times 100$$

Xc = medical decision value *(เช่นกำหนดที่ระดับ 50%activity)* = 30.0 sec

Yc = (0.953 x 30) + 1.3013 = 29.9

$$\text{Bias} = \frac{(Yc - Xc)}{Xc} \times 100 = \frac{(29.9 - 30)}{30} \times 100 = -0.33\%$$

2. Imprecision, %CV

Repeatability, intra-assay precision ,

within-run, within-day precision

within-day, short –term precision

- Intermediate precision, between-day

precision, intra-laboratory

- Reproducibility, inter-laboratory,

long-term precision

Replication Experiment

control material, pooled serum

- pooled fresh patient serum
- 2-3 levels, low, normal, high
- at/near medical decision level
- minimum n =20

Performance Characteristics: Precision

CLSI Guidelines for Precision

- **EP15:** a five-day procedure to verify that imprecision meets the claims of a measurement procedure
  (EP15 is most frequently used by clinical laboratories for method evaluation.)
- **EP05:** a 20-day procedure to establish the imprecision for a measurement procedure

EP 05: Traditional Replication Test

- within-run precision/within-day imprecision

  n = 20 within-run, within-day, 1 day

  short –term imprecision, CV_{wr}

- between-day imprecision

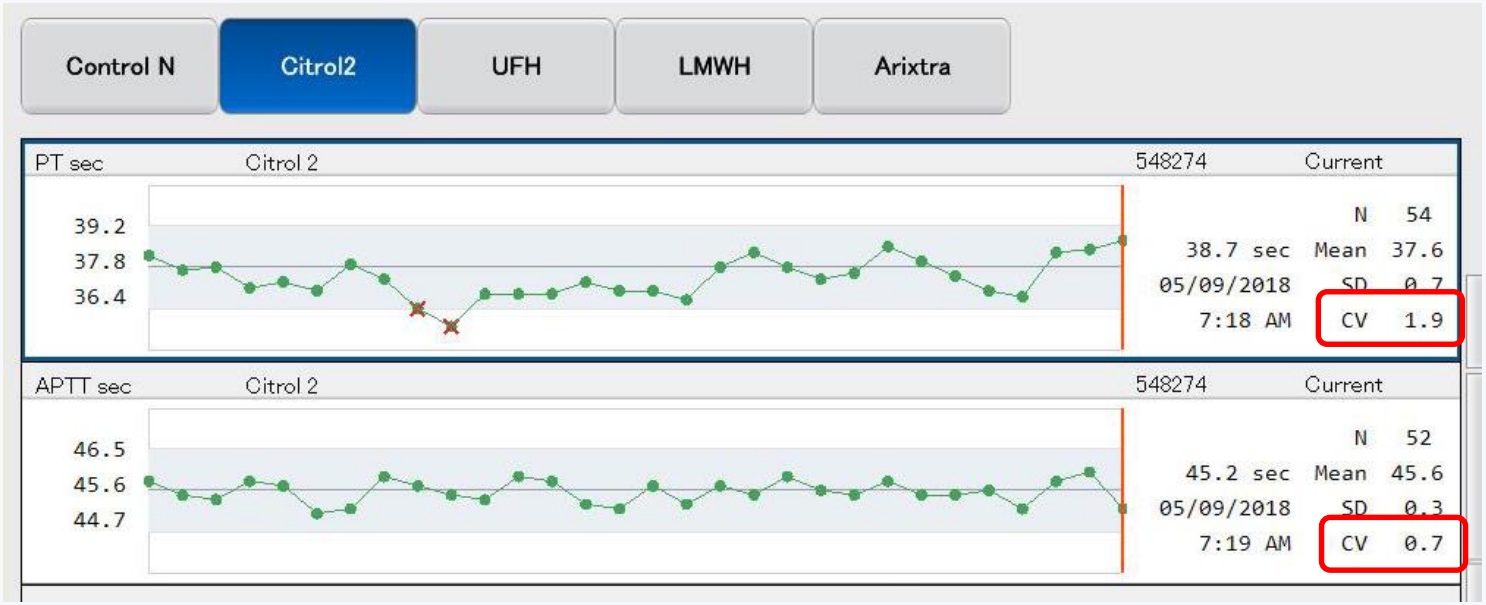
  n = ≥ 20 , 20 days or more

  long term imprecision, CV_{br}

- Total imprecision

  $$\mathbf{CV_{total} \quad \sqrt{(CV_{wr})^2 + (CV_{br})^2}}$$

Between-day imprecision (CV_{br})



EP 15-A2: 3 replicate over 5 days for method verification

- หาค่า %CV_{wr} และ %CV_{total} ได้ในการทดสอบชุดเดียวกัน
- ลดค่าใช้จ่าย ระยะเวลาสั้น
- เหมาะสำหรับการทำ method/reagent verification

Control PCCM1 lot 186373					
Day	Rep1	Rep2	Rep3	Day mean	Day variance
1	201	202	203	202.00	1.0000
2	204	204	202	203.33	1.3333
3	210	205	206	207.00	7.0000
4	201	206	204	203.67	6.3333
5	200	206	203	203.00	9.0000
	all mean =	203.80		B= variance of Day mean	A=average of Day variance
	n = replicate = 3				

A	SD^2_{wr} = average of day variance	4.9333
B	SD^2_{br} = variance of day mean	3.5889
C	SD_{total} = sqrt of SD^2_{br} + SD^2_{wr}*(n-1/n)	2.6226
D	% CV_{wr} = (SD_{wr}/all mean)*100	1.09
E	% CVt = (SD_{total}/all mean)*100	1.29

Criteria for acception

- **Within-run imprecision : $\%CV_{wr} \leq 0.25\ TE_a$**
- **Between-run imprecision : $\%CV_{br} \leq 0.33\ TE_a$**
- **Total imprecision : $\%CV_{total} \leq 0.33\ TE_a$**
- **Bias < B_a**
- **Bias < TE_a**

Total error = SE+RE = %Bias + %CV

TE < TEa

TE_a : Allowable Total Error
ความผิดพลาดที่ยอมรับได้

3. Allowable Total Error (TEa)

An analytical quality requirement that sets a limit for both the imprecision (random error) and inaccuracy (systematic error or bias) that are tolerable in a single measurement or single test result to insure clinical usefulness.

- Medical Requirement (NCEP,American Diabetic Association, NKEP)
- Biological Variation
- Regulatory Requirements (CLIA 88)
- Reference Interval
- Published data
  - Peer group survey result
  - Process SD

Strategies for selecting TEa

Rank	Strategy	Subclasses
1.	Impact on specific clinical decision making	Quality specifications in specific clinical situations
2.	Impact on general clinical decision making	A. Based on biological variation B. Based on medical opinions
3.	Professional recommendations	A. International expert groups B. Expert individuals
4.	EQAS recommendations	A. Regulatory requirement (CLIA88) B. EQAS
5.	Published data on state of the art	A. Published by PT/EQAS B. Published individual method (SD)

Stockholm Consensus 1999

TEa based on Regulatory requirement

CLIA 88 (clinical laboratory improvement)amendments

WESTGARD QC

Hematology	
Test or Analyte	Acceptable Performance
Cell identification	90% or greater consensus on identification
White cell differentiation	Target ± 3 SD based on percentage of different types of white cells
Erythrocyte count	Target ± 6%
Hematocrit	Target ± 6%
Hemoglobin	Target ± 7%
Leukocyte count	Target ± 15%
Platelet count	Target ± 25%
Fibrinogen	Target ± 20%
Partial thromboplastin time	Target ± 15%
Prothrombin time	Target ± 15%

TEa based on general clinical situations
Biological variation

Biological Variation

ความแปรปรวนทางชีวภาพของแต่ละบุคคล

- อายุ
- เพศ
- เชื้อชาติ
- กรรมพันธุ์
- สภาพแวดล้อม
  - TE_a = Allowable Bias + 1.65*(Allowable Imprecision)
    - Allowable Imprecision is based on within person BV
    - Allowable Bias is based on within person and between person BV

➢ http://www.qcnet.com/Portals/0/PDFs/BVValues1Final.pdf

TEa based on biological variation

TEa = 1.65 (imprecision) + bias (5% confidence)

Performance Goal	**Precision**	**Bias**	**TEa**
Minimum	0.75 CVi	$0.375\sqrt{CVi^2 + CVg^2}$	$1.65(0.75\ CVi) + 0.375\sqrt{CVi^2 + CVg^2}$
Desirable	0.5 CVi	$0.25\sqrt{CVi^2 + CVg^2}$	$1.65(0.5\ CVi)\ 0.25\sqrt{CVi^2 + CVg^2}$
Optimum	0.25 CVi	$0.125\sqrt{CVi^2 + CVg^2}$	$1.65(0.25\ CVi) + 0.125\sqrt{CVi^2 + CVg^2}$

TEa based on biological variation

	Analyte	Number of Papers	Biological Variation		Desirable specification		
			CV_I	CVg	I(%)	B(%)	TE (%)
S-	Acid phosphatase tartrate-resistant (TR-ACP)	2	8.0	13.3	4.0	3.9	10.5
S-	Acid phosphatase prostatic activity (PAP)	1	33.8	---	16.9	---	---
P-	Activated partial thromboplastine time	3	2.7	8.6	1.4	2.3	4.5
P-	Adiponectin	1	18.8	51.2	9.4	13.6	29.1
S-	Adenosine deaminase (ADA)	1	11.7	25.5	5.9	7.0	16.7
U-	Protein, output, 24h	2	35.5	23.7	17.8	10.7	40.0
P-	Prothrombin time	2	4.0	6.8	2.0	2.0	5.3
U-	Pyridinoline	1	19.4	23.6	9.7	7.6	23.6
B-	Pyruvate	1	15.2	13.0	7.6	5.0	17.5

CV_I = within-subject biologic variation
CV_G = between-subject biologic variation
I = desirable specification for imprecision
B = desirable specification for inaccuracy
TE = desirable specification for allowable total error

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

TEa based on Professional recommendations

- Various groups of experts have published quality specifications for specific sets of analytes.
- The National Cholesterol Education Panel in the US has published recommendations for the precision, accuracy and total allowable error for lipids.
- The American Diabetes Association has documented quality specifications for self-monitoring blood glucose, etc.

From: Allowable Total Error. https://youtu.be/CQGBPzKXKgI

TEa calculation

TEa format	Analytes	Example	Calculation
%	Cholesterol	10%	As is
Absolute value	Calcium	± 1.0 mg/dL	TEa/(Target value)* 100
Range	Sodium	138 – 146 mmol/L	[(Upper – Lower)/range] * 100
SD	TSH	Target value ± 3SD	[(Target value ± 3SD)/target value]*100

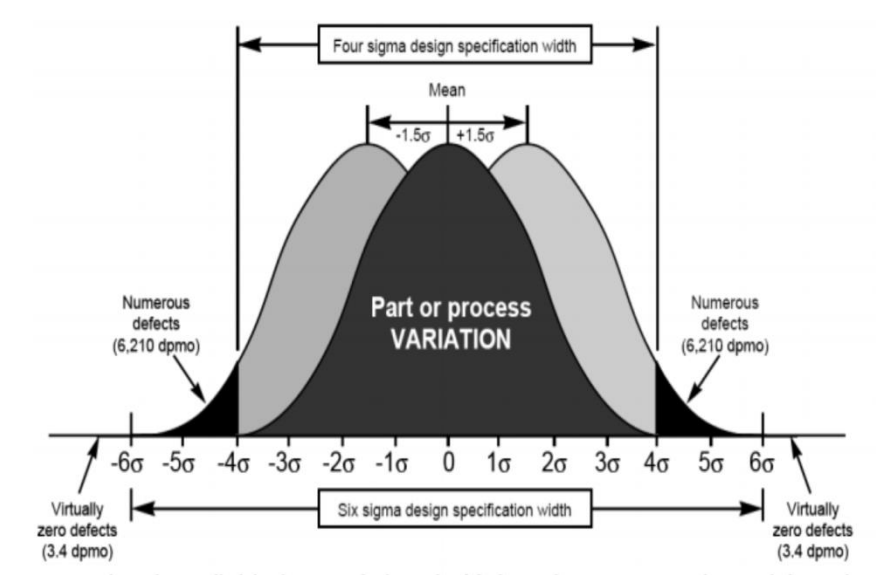
Consideration on TEa selection

- Consideration should be given to what quality specifications are used.
- Biological variation based quality specifications are very defensible and should be the logical selection.
- CLIA'88 Proficiency specifications should always be the minimum.

From: Allowable Total Error. https://youtu.be/CQGBPzKXKgI

4. Sigma metrics

Sigma: σ (Greek letter) => Standard Deviation (statistics)



เทคนิค/เครื่องมือ ที่ใช้ในการปรับปรุงกระบวนการ

"not a standard or certificate!"

- removing the causes of defects and minimizing variability
- Motorola set a goal of "six sigma"
- => free of defects (3.4 defective features per million opportunities)

Two Approaches for Measuring Process Performance

Measuring outcome

Inspect outcomes
นับ defects

Error rate

Calculate defect per million(DPM)

Convert DPM to Sigma metrics

Measuring variation

Measure variation of process

inaccuracy (%bias)
imprecision (%CV)

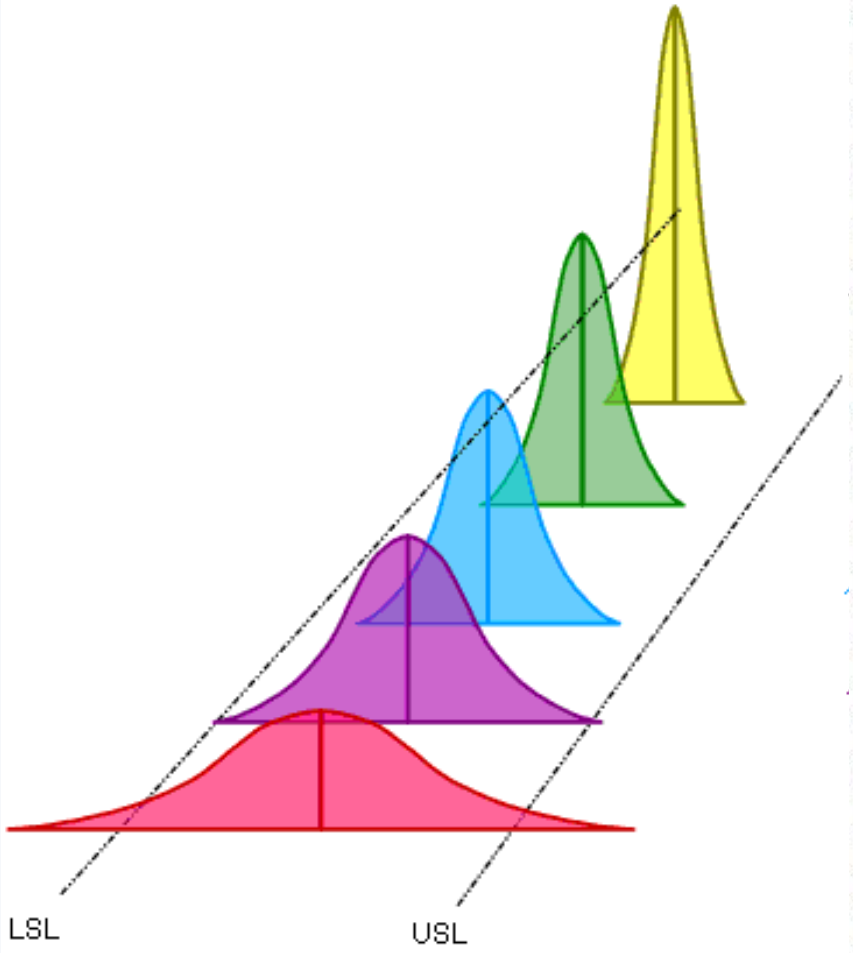
Calculate SD and process capability

Convert capability to Sigma metrics

From: http://www.westgard.com/lesson66.htm

Six sigma =>measuring outcome

Sigma No.	Defects per million
1.5σ	500,000
2.0σ	308,300
2.5σ	158,650
3.0σ	67,000
3.5σ	22,700
4.0σ	6,210
4.5σ	1,350
5.0σ	233
5.5σ	32
6.0σ	3.4

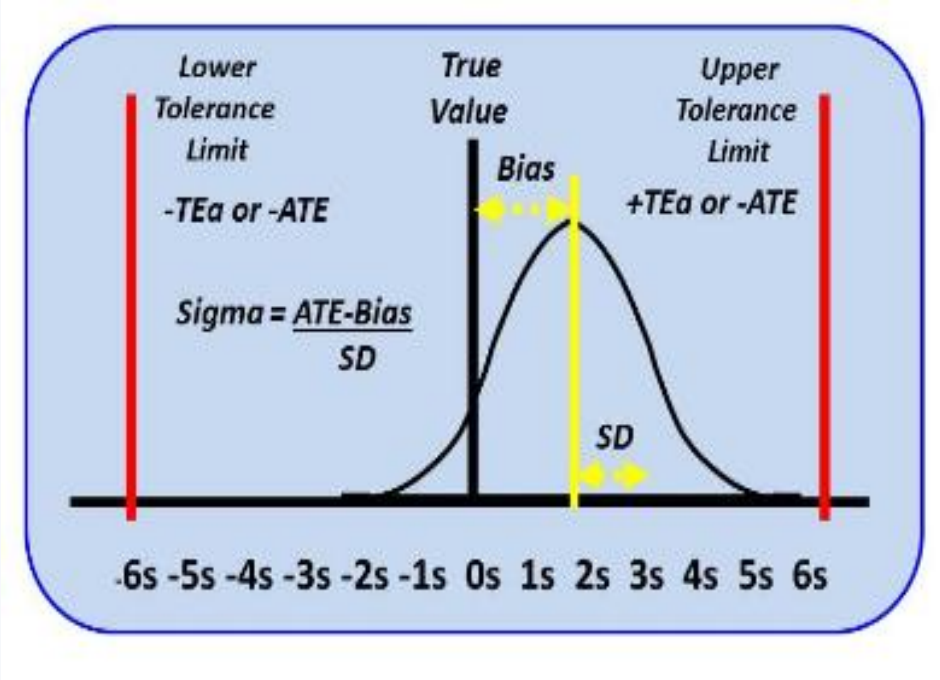


Yield	dpmo	Sigma (σ)
.840	160,000	2.50
.870	130,000	2.63
.900	100,000	2.78
.930	70,000	2.97
.935	65,000	3.01
.940	60,000	3.05
.945	55,000	3.10
.950	50,000	3.14
.955	45,000	3.20
.960	40,000	3.25
.965	35,000	3.31
.970	30,000	3.38
.975	25,000	3.46
.980	20,000	3.55
.985	15,000	3.67
.990	10,000	3.82
.995	5,000	4.07
.998	2,000	4.37
.999	1,000	4.60
.9995	500	4.79
.99975	250	4.98
.9999	100	5.22
.99998	20	5.61
.9999966	3.4	6.00

Sigma metric calculation

$$\text{Sigma} = \frac{\%TEa - \%Bias}{\%CV}$$

- Quality demand for the test (TEa)
- Imprecision of the method
- Inaccuracy of the method



From: http://www.westgard.com/ate-tea.htm

How to apply Six-sigma and Sigma metrics to coagulation lab

Defect

Variation

Pre-analytical process

Specimen collection	Clot สลับ specimen
Specimen transport	>2 hrs
Specimen processing	Plt>10x103/uL ปั่นหลอดแตก

Analytical process

IQC	%CV
EQA/PT	%bias
IQC-Interlaboratory	%CV %bias

Post-analytical process

Result report and approval	รายงานผลผิด
Transmission of result	Interface error

Sigma metrics calculation: aPTT test

PTT	Normal	High
%CV	2.24	1.26
%Bias	2.14	2.14
TEa	15	15
Sigma: (TEa - %bias)/%CV	5.7	10.2
Normalized inaccuracy: (%bias/TEa) x 100	14.3	14.3
Normalized imprecision:(%CV/TEa) x 100	14.9	8.4
Test performance (Normalized Method Decision chart)	Excellent	Excellent
QC rules_PTT	**1_3.5S**	**1_3.5S**

PT	Normal	High
%CV	2.70	3.30
%Bias	3.41	3.41
TEa	15	15
Sigma: (TEa - %bias)/%CV	4.3	3.5
Normalized inaccuracy: (%bias/TEa) x 100	22.8	22.7
Normalized imprecision:(%CV/TEa) x 100	18.0	22.0
Test performance (Normalized Method Decision chart)	Excellent	Good
QC rules_PT	**1_2.5S**	**1_2S**

Impact of TEa on Sigma metric

PTT	Normal	High
%CV	2.24	1.26
%Bias (EQA/PT)	2.14	2.14
TEa (CLIA'88)	15	15
TEa (BV)	4.5	4.5

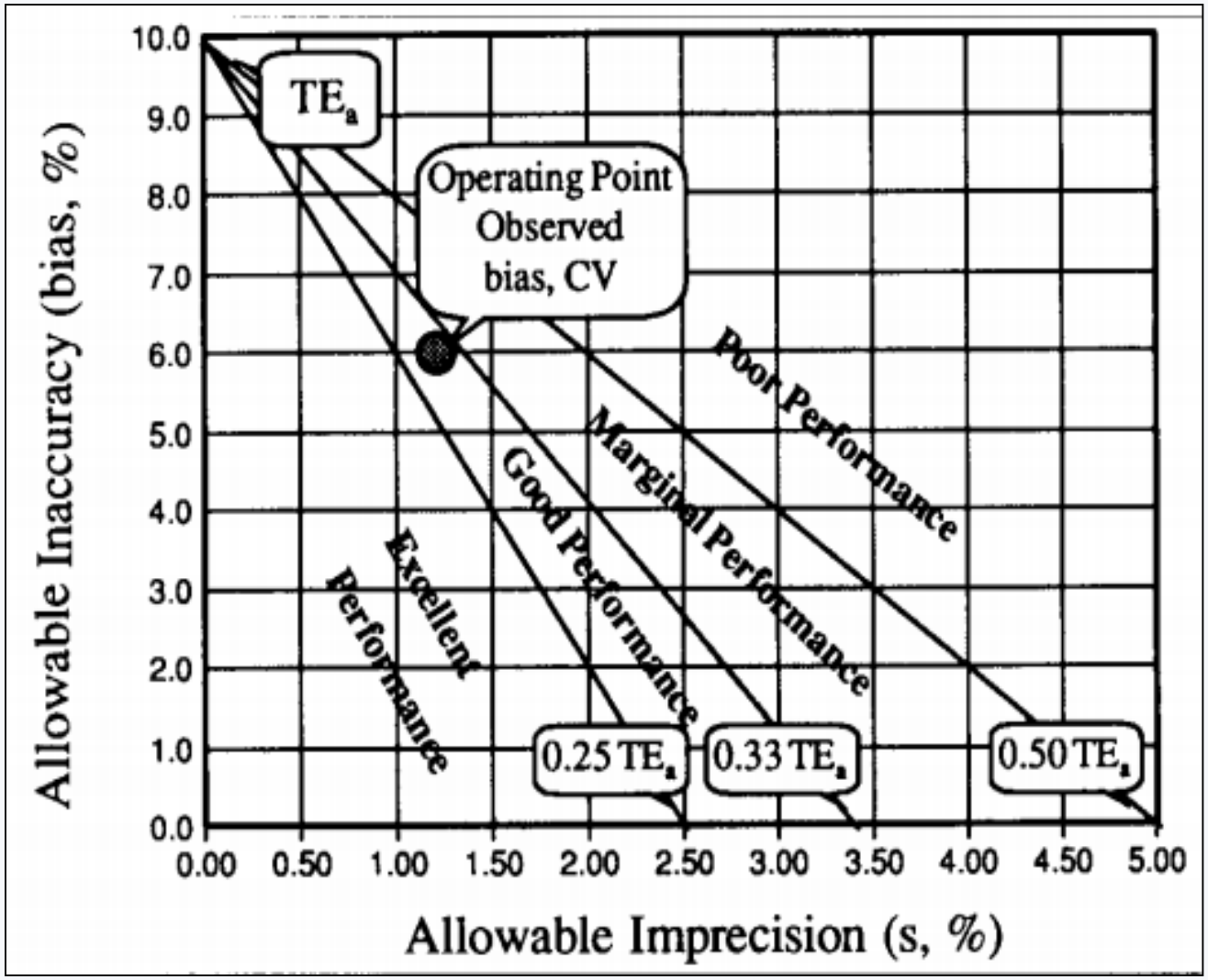
Sigma: (TEa - %bias)/%CV

TEa (CLIA'88)	5.7	10.2
TEa (BV)	1.1	1.9

The advantage of Sigma Metrics

- ตอบโจทย์ clinical requirements
- ใช้ได้กับข้อมูลเชิงคุณภาพ (defects) และข้อมูลเชิงปริมาณ (variations)
- ทำได้ไม่ยากนัก
- ใช้เป็นตัวติดตามประเมินผล การทำ CQI
- ใช้วางแผนเลือกกฎควบคุมคุณภาพ

5. Method Evaluation Decision chart

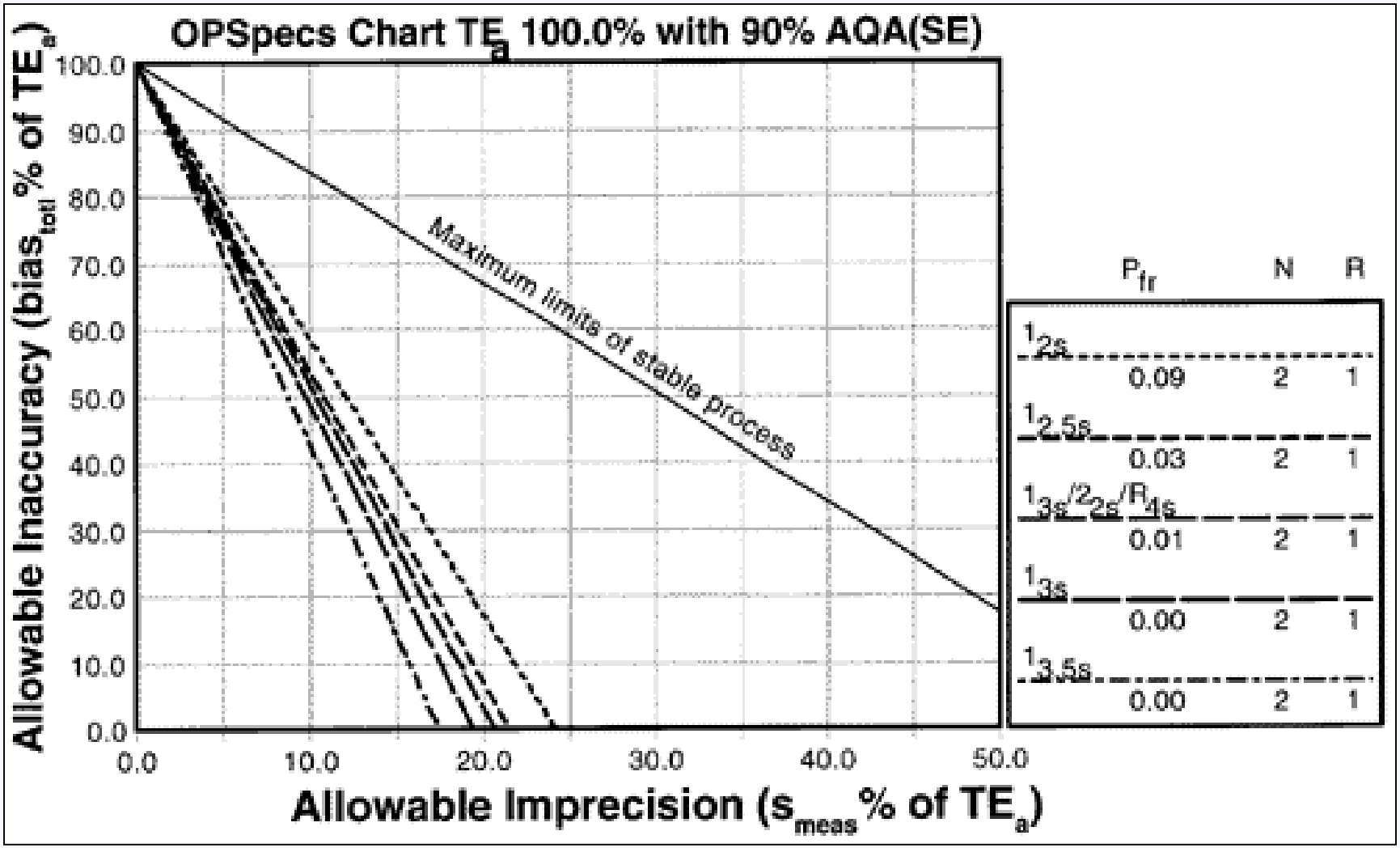


Westgard JO. Clin Lab Sci. 1995 Sep-Oct;8(5):277-83.

6. Sigma value and QC planning

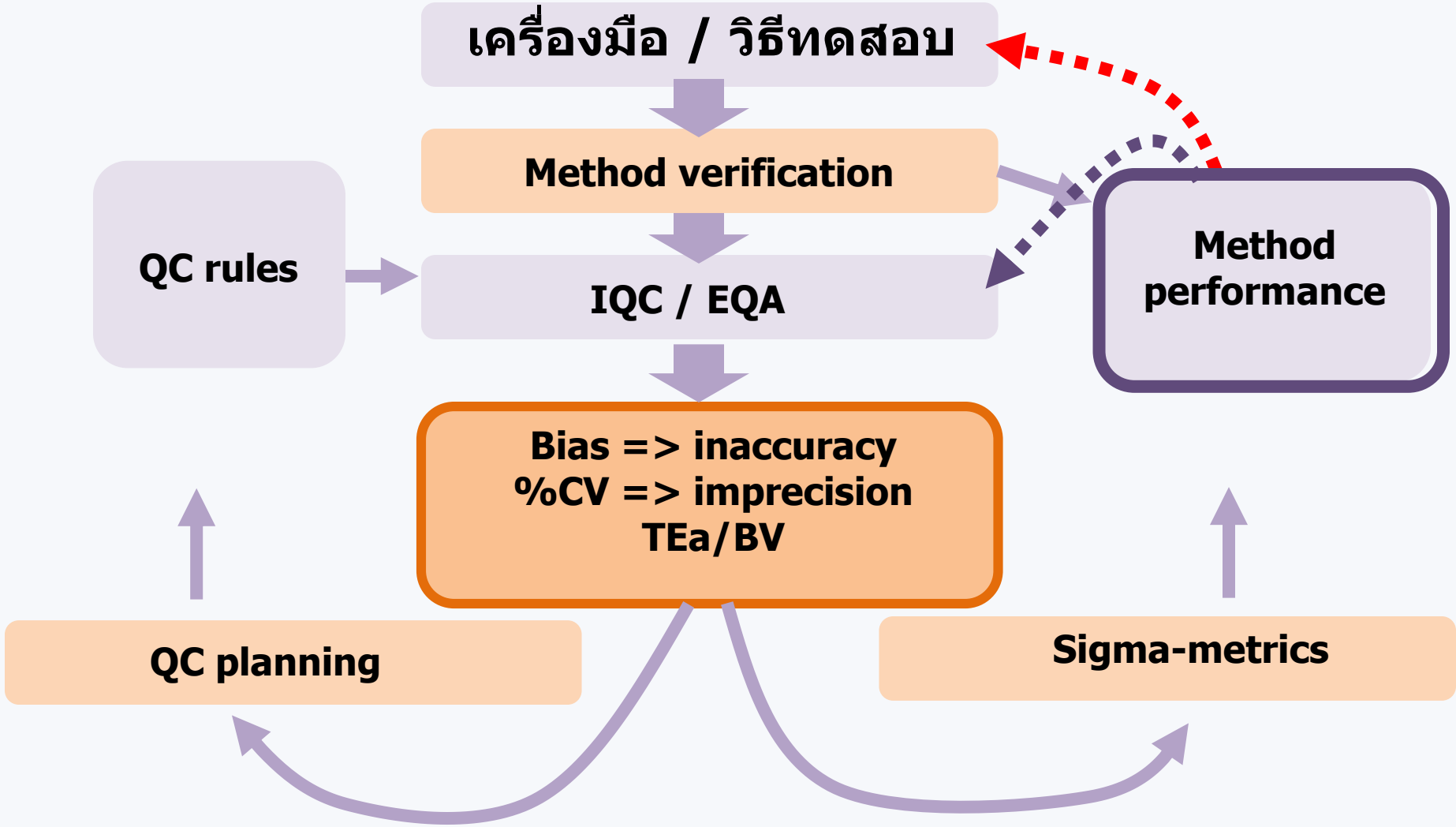
Sigma Value	Performance	QC strategy
≥ 4	Excellent performance	one QC per day (alternating levels between days) and a 1:3.5 s rule
≥ 3	Good performance	two levels of QC per day and the 1:2.5 s rule
≥ 2	Marginal performers	a combination of rules with two levels of QC twice per day
< 2	poor performers or Unacceptable	maximum QC, three levels, three times a day

OPSpec chart



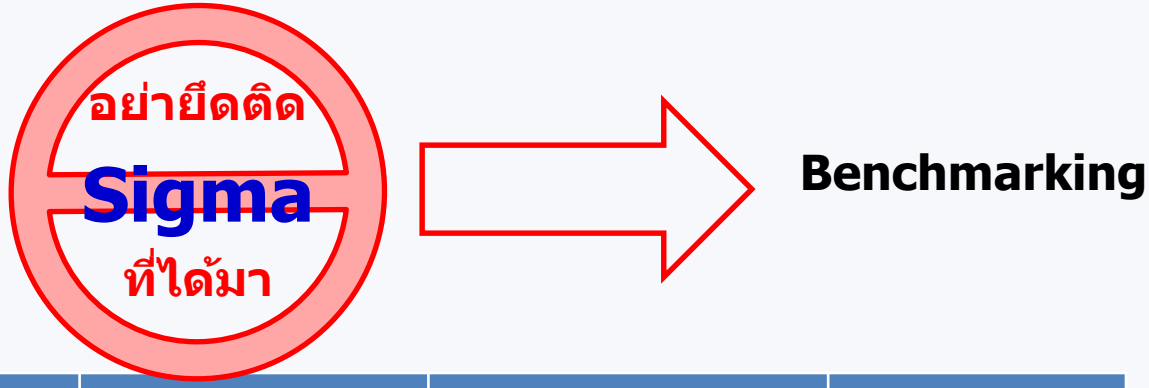
Quality improvement

การพัฒนาความสามารถของวิธีวิเคราะห์อย่างต่อเนื่อง



How to improvement

- วิเคราะห์เจาะลึกหาจุดอ่อน ค่าใดสูง ค้นหาสาเหตุที่ทำให้เกิดความแปรปรวน ทำการแก้ไขให้ตรงจุด
- ทบทวนอย่างสม่ำเสมอ อย่างน้อย 1 ครั้งใน 12 เดือน
- ติดตามดูแนวโน้ม



	TEa	CV	Bias	Sigma metrics
CLIA	15%	IQC	EQA/PT	
BV	PTT 4.5% PT 5.3%	IQC	EQA/PT	

Peer groups

Peer groups