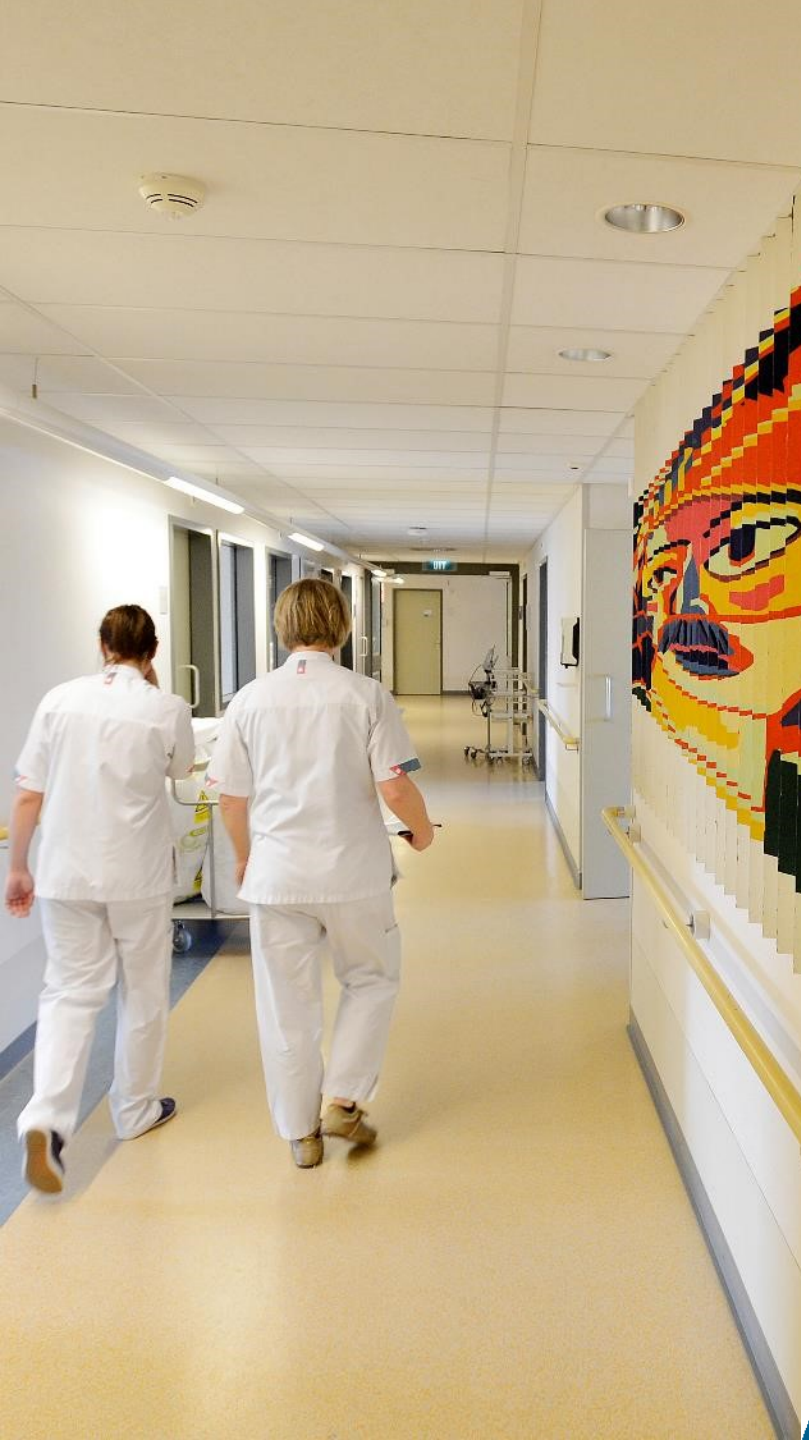


# Biological variation, quality specifications and Six Sigma

René Idema, Amphia Hospital Breda

ECAT Participants Meeting November 8th 2018

# Disclosures

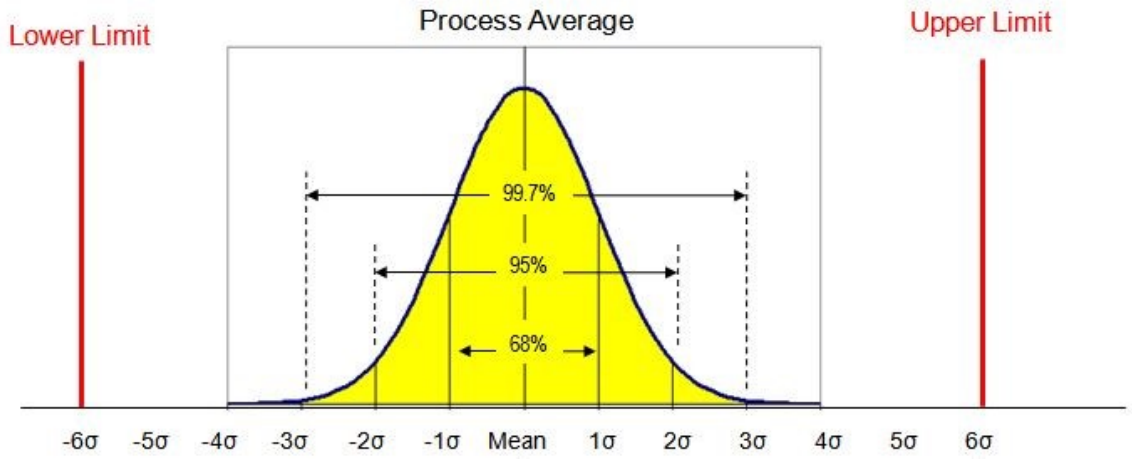
none

# Six Sigma

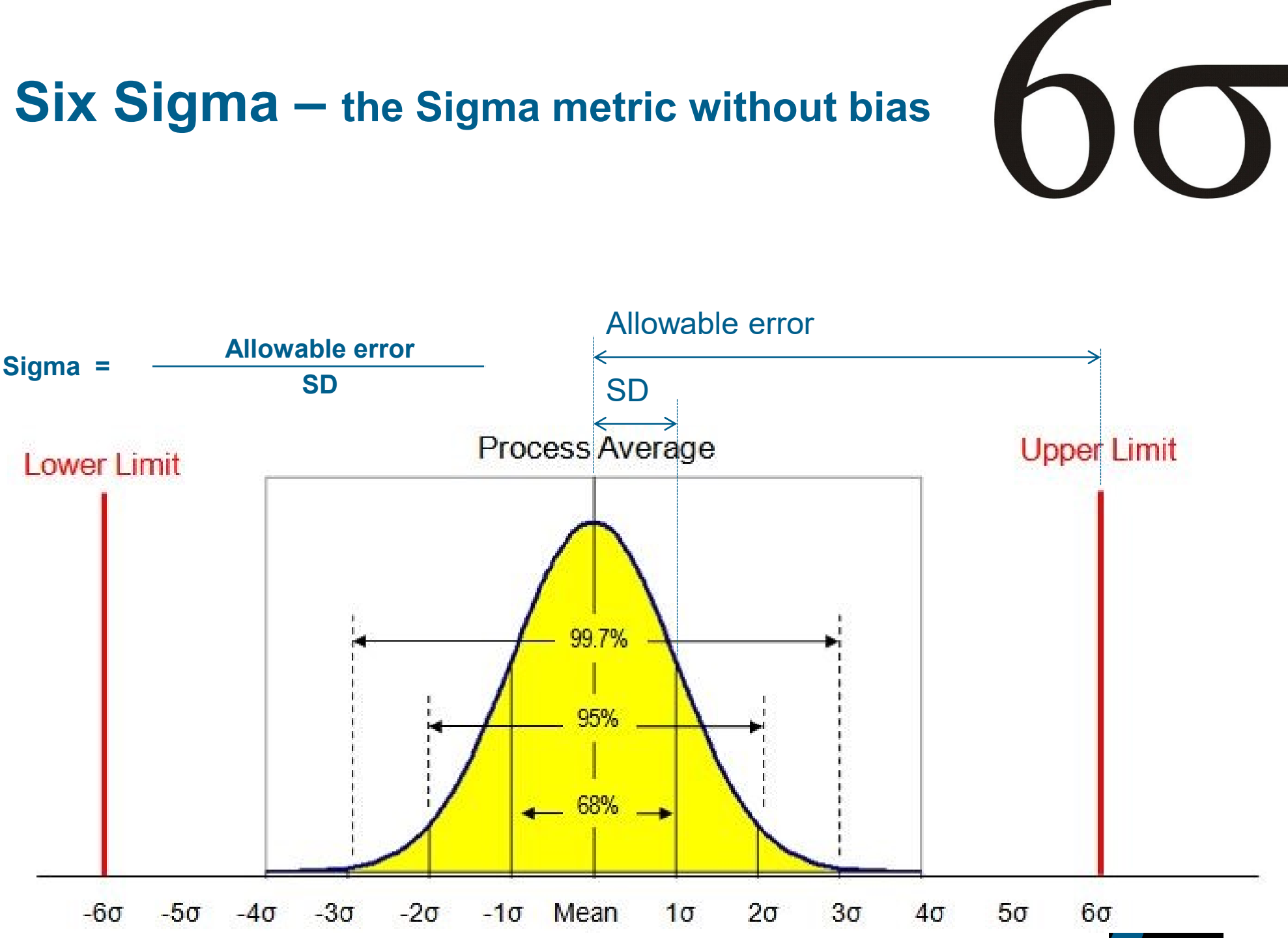
- Engineer Bill Smith (Motorola, 2006)

- Set of techniques and tools for continuous improvement
  - process
  - Product

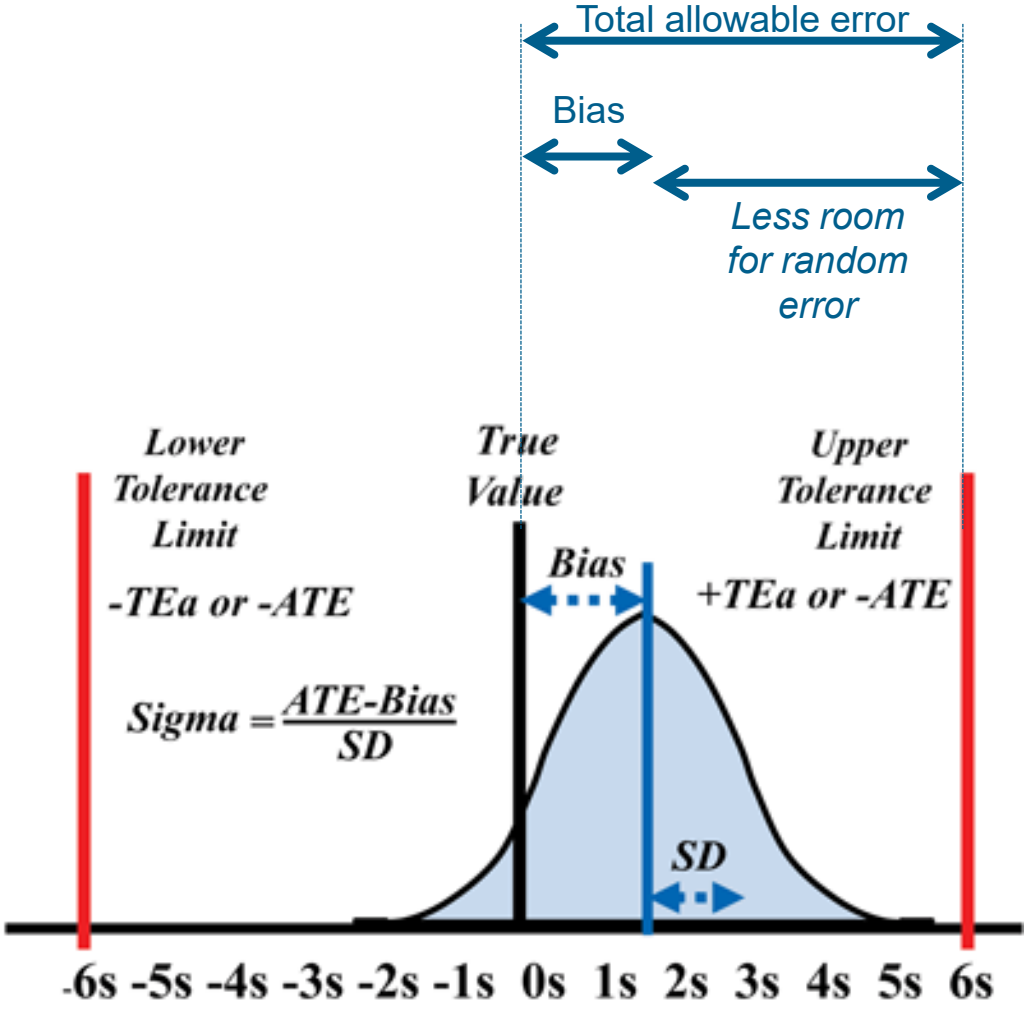
- A Six Sigma process produces
  - fresh: 2 defects per billion products ($10^9$)
  - long term:  3.4 errors per million ($10^6$)



# Six Sigma – the Sigma metric without bias



# Six Sigma – the Sigma metric with bias




$$\text{Sigma} = \frac{\text{TEA} - \text{bias}}{\text{SD}}$$

$$\text{Sigma} = \frac{\text{TEA}_{\%} - \text{bias}_{\%}}{\text{VCA}_{\%}}$$

# Six Sigma – the Sigma Metric

| Sigma level | Fraction of errors |
|---|---|
| 3 | 6.7% |
| 4 | 0.62% |
| 5 | 0.023% |
| 6 | 0.00034% |

# Sigma value determines QC-rule selection

| Sigma | Westgard rule | Levels | Number of measurements /run | p error detection | p false rejection |
|---|---|---|---|---|---|
| **6.0** | 1 3.5s | 2 | 1 | 0.98 | 0.01 |
| **5.8** | 1 3.5s | 2 | 1 | 0.98 | 0.00 |
| **5.6** | 1 3s | 2 | 1 | 0.97 | 0.00 |
| **5.4** | 1 3s | 2 | 1 | 0.94 | 0.00 |
| **5.2** | 1 3s | 2 | 1 | 0.91 | 0.00 |
| **5.0** | 1 2.5s | 2 | 1 | 0.96 | 0.03 |
| **4.8** | 1 2.5s | 2 | 1 | 0.93 | 0.03 |
| **4.6** | 1 2.5s | 2 | 1 | 0.92 | 0.01 |
| **4.4** | 1 2.5s | 2 | 1 | 0.96 | 0.04 |
| **4.2** | 1 2.5s | 2 | 1 | 0.92 | 0.04 |
| **4.0** | 1 3s/2 2s/R 4s/4 1s | 2 | 2 | 0.91 | 0.03 |
| **3.8** | 1 3s/2 2s/R 4s/4 1s | 2 | 2 | 0.86 | 0.03 |
| **3.6** | 1 3s/2 2s/R 4s/4 1s | 2 | 2 | 0.79 | 0.03 |
| **3.4** | 1 3s/2 2s/R 4s/4 1s | 2 | 2 | 0.65 | 0.03 |
| **3.2** | 1 3s/2 2s/R 4s/4 1s | 3 | 2 | 0.48 | 0.03 |
| **3.0** | 1 3s/2 2s/R 4s/4 1s | 3 | 2 | 0.36 | 0.02 |

CHH Schoenmakers et al. Practical application of Sigma Metrics QC procedures in clinical chemistry. Clin Chem Lab Med 2011;49(11):1837–1843 (4.6 sigma corrected)

# Six Sigma in Laboratory Medicine

1. Introduced in 2006 (Westgard, Gras)
2. Analytical process (selection of QC-rules)
3. Pre- and post-analytical process (fraction of errors)

| Sigma | Westgard rule | Levels | Number of measurements /run | p error detection | p false rejection |
|---|---|---|---|---|---|
| 6.0 | 1 3.5s | 2 | 1 | 0.98 | 0.01 |
| 5.8 | 1 3.5s | 2 | 1 | 0.98 | 0.00 |
| 5.6 | 1 3s | 2 | 1 | 0.97 | 0.00 |
| 5.4 | 1 3s | 2 | 1 | 0.94 | 0.00 |
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| 3.0 | 1 3s/2 2s/R 4s/4 1s | 3 | 2 | 0.36 | 0.02 |

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*CHH Schoenmakers et al. Practical application of Sigma Metrics QC procedures in clinical chemistry. Clin Chem Lab Med 2011;49(11):1837–1843 (4.6 sigma corrected)

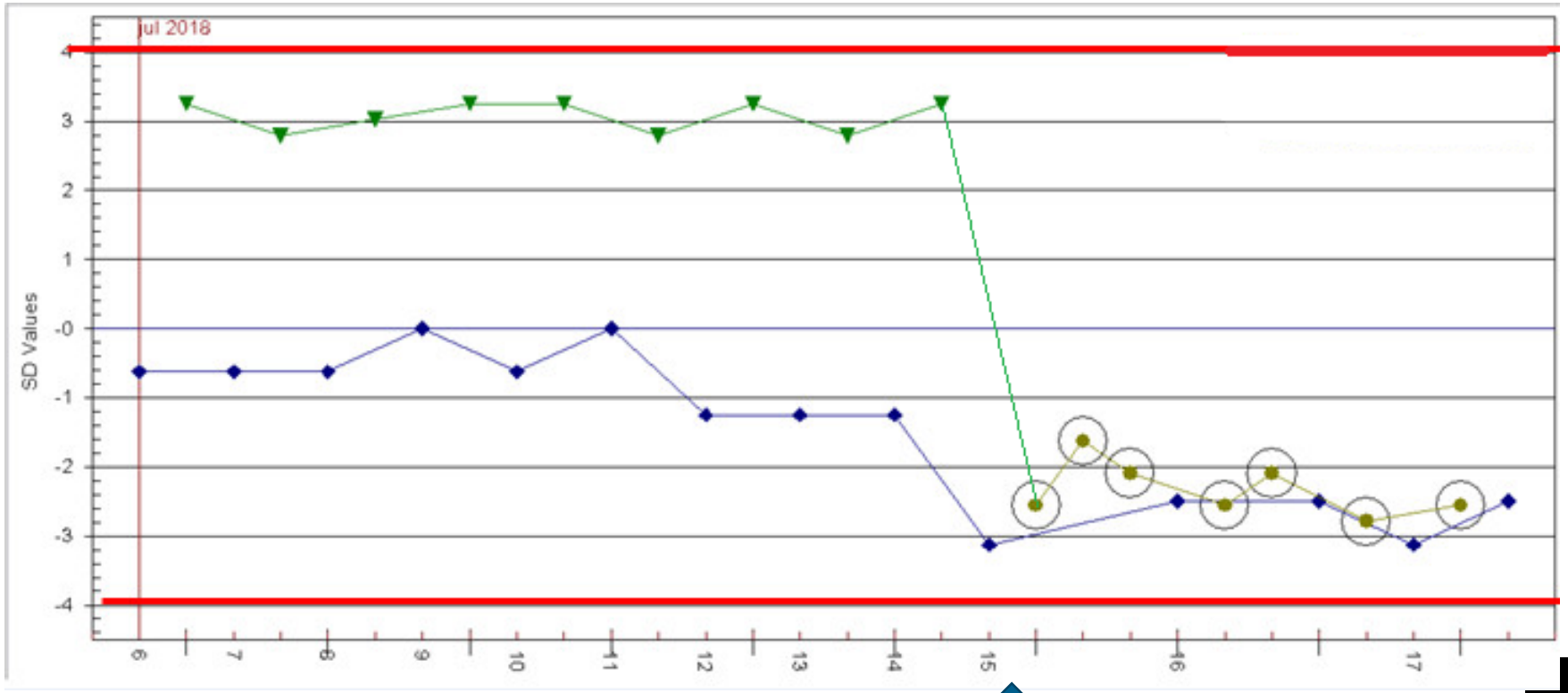
# Implemenation of Six Sigma in iQC

1. Determine total allowable error TEA
2. Determine analytical specifications (VCA, bias)
3. Calculate Sigma score
4. Look up Westgard QC-rules in table

*CHH Schoenmakers et al. Practical application of Sigma Metrics QC procedures in clinical chemistry. Clin Chem Lab Med 2011;49(11):1837–1843 (4.6 sigma corrected)

# Six Sigma in Clinical Chemistry

## iQC Lipase (11 sigma)




Control rule: 4 SD.

reagent lot change

# Application of Six Sigma in Haemostasis*

A team of 3 diagnostic laboratories using 3 different brand analyzers set out to implement Six Sigma in routine haemostatis diagnosis and to publish the log of this journey.

Goals

1. Rational and objective basis for internal QC rules
2. Is our quality fit-for-purpose?
3. Less unnecessary internal QC measurements and corrective actions

*** MJ Hollestelle, J Ruinemans-Koerts, RN Idema, P Meijer, MPM de Maat. Determination of sigma score based on biological variation for haemostasis assays: fit-for-purpose for daily practice? Clin Chem Lab Med (accepted for publication)**

# Six Sigma iQC in Haemostasis

# Application of Six Sigma cookbook

1. Determine total allowable error TEA
2. Determine analytical specifications (VCA, bias)
3. Calculate Sigma score
4. Look up Westgard QC-rules

# 1. Determine Total Allowable Error

How do we determine Total Allowable Error in Six Sigma?

1. As a multiple of analytical variation, e.g. 2.5 * $SD_{analytical}$
2. Equal to biological variation (BV)
3. Stated by the manufacturer
4. None of the above

# 1. Determine Total Allowable Error

In Six Sigma, TEA is the maximum allowable deviation of the true value.
The laboratory is responsible to define it.

The maximum allowable deviation can be based on (Milan 2014 criteria):

1. Clinical outcome
   *Few data*

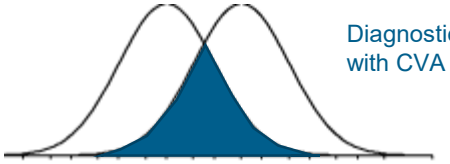
2. Biological variation (BV)
   *Available. Based on intra- and inter-individual variation.*

3. State-of-the-art analytical performance
   *Readily available but no clinical basis*

* Sandberg S, Fraser CG, Horvath AR, Jansen R, Jones G, Oosterhuis W, et al. Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med 2015;53:833-5

# 1.2 TEA based on biological variation


Diagnostic error with CVA = 0



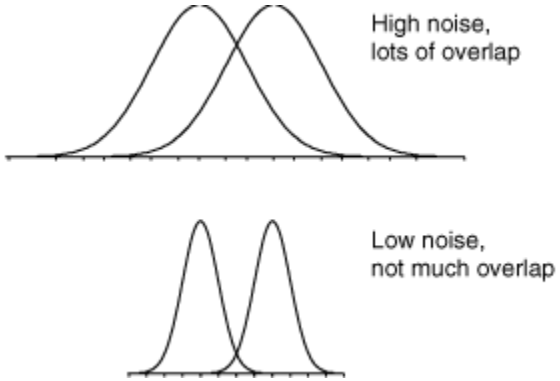
Diagnostic error with CVA > 0

- Intra- and inter-subject variation (BV) cause errors in diagnosis
- Analytical variation adds proportionally to these errors
- Arbitrary criteria are defined for *optimal*, *desirable* and *minimum* performance

# 1.2 TEA based on biological variation

Desirable* TEA = $0.25\sqrt{(CVI^2+CVG^2)} + 1.65x(0.5xCVI)$

CVI : within-person biological variation
CVG : between-person biological variation



# 1.2 TEA based on literature BV

| | TEA (%) | | |
|---|---|---|---|
| | minimum | median | maximum |
| **PT** | 3.1 | 3.5 | 7.0 |
| **APTT** | 3.2 | 4.8 | 8.4 |
| **Fibrinogen** | 9.7 | 14.5 | 22.2 |
| **AT** | 1.6 | 4.7 | 7.7 |

Spread 2-4 fold (sigma 3 vs 6). Quality of studies?

# Biological Variation Checklist*

1. Developed by EFCCLM workgroup (Milan 2014 *spin off*)
2. Verifies whether study  includes all factors impacting veracity of BV
3. Is in the process of validation
4. Has been applied in clinical chemistry
5. Published in 2018 (Clin Chem)

* Aarsand et al. The Biological Variation Data Critical Appraisal Checklist: A Standard for Evaluating Studies on Biological Variation. Clin Chem 2018;64:501-14.

# Biological Variation Checklist*

**Clinical Chemistry** 64:3
000–000 (2018)

Evidence-Based Medicine and Test Utilization

## The Biological Variation Data Critical Appraisal Checklist: A Standard for Evaluating Studies on Biological Variation

Aasne K. Aarsand,[1,2*] Thomas Røraas,[2] Pilar Fernandez-Calle,[3,4] Carmen Ricos,[4] Jorge Díaz-Garzón,[3,4] Niels Jonker,[5] Carmen Perich,[4,6] Elisabet González-Lao,[4,7] Anna Carobene,[8] Joana Minchinela,[4,9] Abdurrahman Coşkun,[10] Margarita Simón,[4,11] Virtudes Álvarez,[4] William A. Bartlett,[12] Pilar Fernández-Fernández,[4] Beatriz Boned,[4,13] Federica Braga,[14] Zoraida Corte,[4,15] Berna Aslan,[16] and Sverre Sandberg[1,2,17] on behalf of the European Federation of Clinical Chemistry and Laboratory Medicine Working Group on Biological Variation and Task and Finish Group for the Biological Variation Database

* Aarsand et al. The Biological Variation Data Critical Appraisal Checklist: A Standard for Evaluating Studies on Biological Variation. Clin Chem 2018;64:501-14.

# Biological Variation Checklist

**Table 1.** BIVAC with criteria for achieving A, B, C, and D scores for the different quality items and their rationale. *(Continued from page XX)*

| QI | Quality question | Quality scoring | | | | |
|---|---|---|---|---|---|---|
| | | A | B | C | D[a] | Rationale |
| 5: Preanalytical procedures | Are preanalytical procedures described and standardized to minimize preanalytical variation? | Yes | Insufficient detail on preanalytical treatment is given, but it is unlikely to be of importance for the measurand in question. | Insufficient detail on preanalytical treatment is given, which may be of importance for the measurand in question.<br>No details on preanalytical procedures/ treatment given. | – | Appropriate preanalytical procedures are necessary to avoid that preanalytical variation affects the $CV_I$ estimate. |
| 6: Estimates of analytical variation | Are estimates of analytical variation based on replicate analysis, and are estimates presented? | Yes, estimates are presented, with all replicates for the same subject having been analyzed in the same run. | Estimates are presented but have been obtained by other method than replicate analysis or replicate analyses of samples have been performed in different runs. | No estimates are presented. | – | Replicate analysis performed in the same run provides the most correct estimate of analytical variation when calculating the $CV_I$. |
| 7: Steady state | Are all included individuals in steady state, or have data been adequately transformed? | Yes | Individual trend analysis has not been performed, but this is unlikely to be of importance for the measurand in question. | Individual trend analysis has not been performed, and this may be of importance for the measurand (e.g., hormones) or clinical setting (e.g., diseased subjects). | – | For the obtained estimate of $CV_I$ to be reliable, subjects must be in steady state. |

*Continued on page XX*

# Biological Variation Checklist*

Rates studies from A to D on 14 relevant aspects e.g. steady state, definition of study population

Aspect 6:

- Biological variation should be corrected for analytical variation
- Analytical variation should be calculated from replicate measurements
- All replicates for the same subject should be analyzed in the same run

* Aarsand et al. The Biological Variation Data Critical Appraisal Checklist: A Standard for Evaluating Studies on Biological Variation. Clin Chem 2018;64:501-14.

# 2. Determine analytical performance

How do we best determine analytical performance (VC, bias) of a method?

1. During validation (e.g. EP5 protocol for VC)
2. Specified by the method manufacturer (e.g. ‘typical VC’)
3. Based on internal QC (VC)
4. Based on external QC (VC, bias)
5. Otherwise

# 2. Determine analytical performance

Recommendation:

- calculate actual analytical performance as VC
  over a representative period
- period includes changes of lots, maintenance, re-calibration, ...
  (e.g. 1 year)

Ignore bias

- Bias is unknown, if it is known it should be corrected
- Estimation of bias from eQC is imprecise (few data points)
- Bias fluctuates over time and therefore behaves like analytical
  variation

# 3. Calculate Sigma Scores

Analytical variation and  and Sigma scores for analyzer B

| | CVA (%) | TEA (%) | | | Sigma Score | | |
|---|---|---|---|---|---|---|---|
| | | minimum | median | maximum | minimum | median | maximum |
| **PT** | 1.0 | 3.1 | 3.5 | 7.0 | 2.9 | **3.4** | **6.8** |
| **APTT** | 3.7 | 3.2 | 4.8 | 8.4 | 0.9 | 1.3 | 2.2 |
| **Fibrinogen** | 6.6 | 9.7 | 14.5 | 22.2 | 1.5 | 2.2 | **3.4** |
| **AT** | 3.3 | 1.6 | 4.7 | 7.7 | 0.5 | 1.4 | 2.4 |

# How is this possible?

How can we explain that we succesfully use these assays in daily practice?

- TEA based on requirements for monitoring.
  But: monitoring e.g. VKA-therapy, requires that patient is the range 2-3 INR, it does not require that we can reliably detect small changes within this range
- Our subjects are often sick or hospitalized (increased ‘biological’ variation that hides analytical variation)
- When in doubt we perform repeated measurements
- We cannot measure better than ‘state of the art’
- We use tests that have no “true” value e.g. APTT
- We are used to this effect

# Six Sigma in Heamostasis - conclusions

- Six sigma is a well established and sound concept
- In high-sigma assays its implementation in iQC is straightforward
- Six sigma shifts focus of the laboratory specialist from “selecting appropriate control rules” to “selecting appropriate TEA”
- Appropriate = fit for the intended use (population)
- TEA is a field for discussion
- If it TEA based on BV is not achievable we can calculate TEA based on state-of-the-art assay performance.
- BV studies should be based on the Aarberg checklist


The Wizard of Oz≠urselves
The End
A Walt Disney
PRODUCTION