Uncertainty of Measurement in the Medical Laboratory

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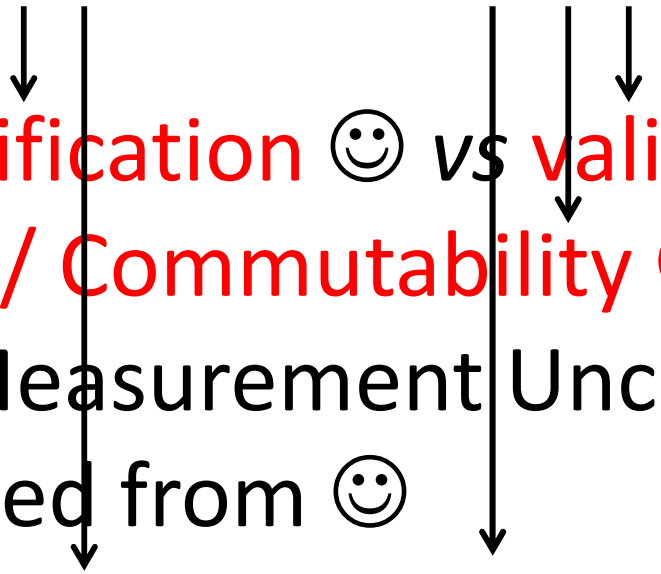
EFLM Workgroup Standards & Accreditation
Barcelona - May 21 2019

Relevant Standards

- EU IVD Regulation
- ISO 15189
- Technical standards

Message #1

Standards don't ask for much
neither from us ☺ or from the industry ☹

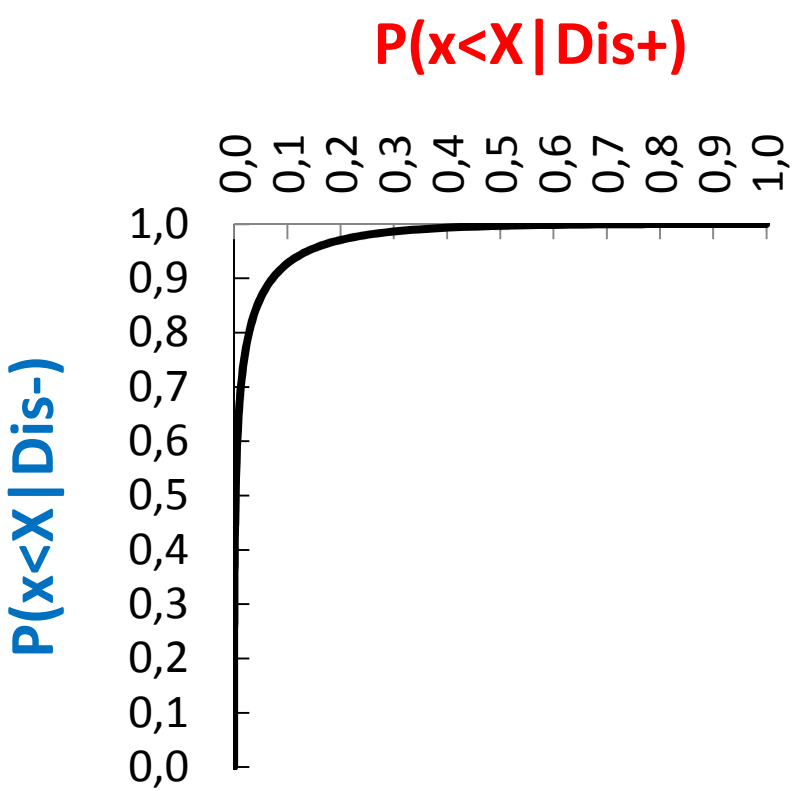


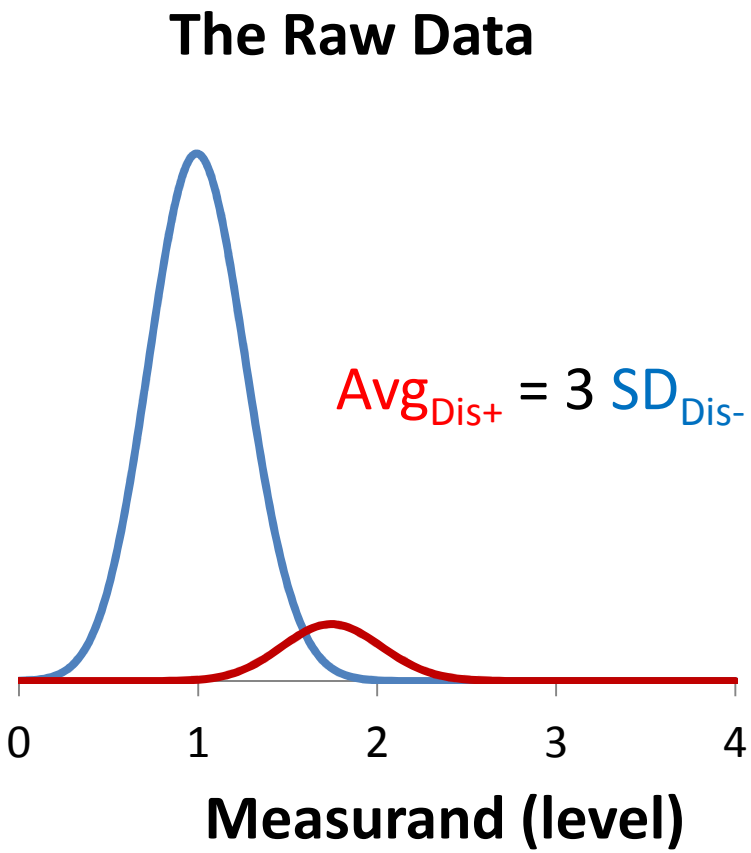
- Method verification ☺ *vs* validation
- Traceability / Commutability ☹
- Budget of Measurement Uncertainty can be derived from ☺ internal Quality Control Data ☹
- …

Casus:
Typical Method Implementation

Fit for the Intended Use?

Clinical Validation: ROC-curve



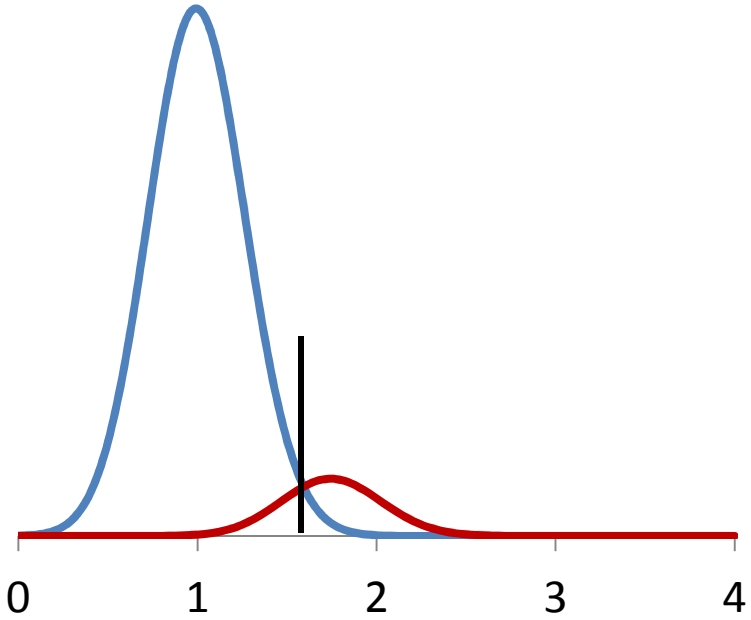


Avg_{Dis+} at 3 SD_{Dis-} = Definition of Limit of Detection

Does this make it a test unfit for purpose?

Dichotomic Analysis

Black – Gamble – White



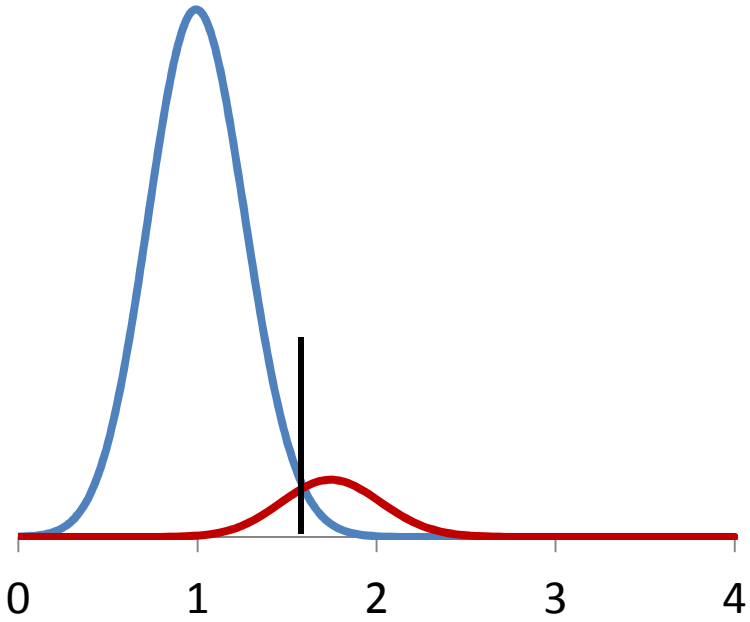
Loss of Truth due to misclassification

	D-	D+
T-	1	-1
T+	-1	1

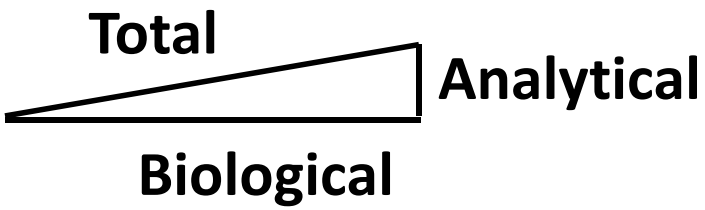
Kappa-weights

Dichotomic Analysis

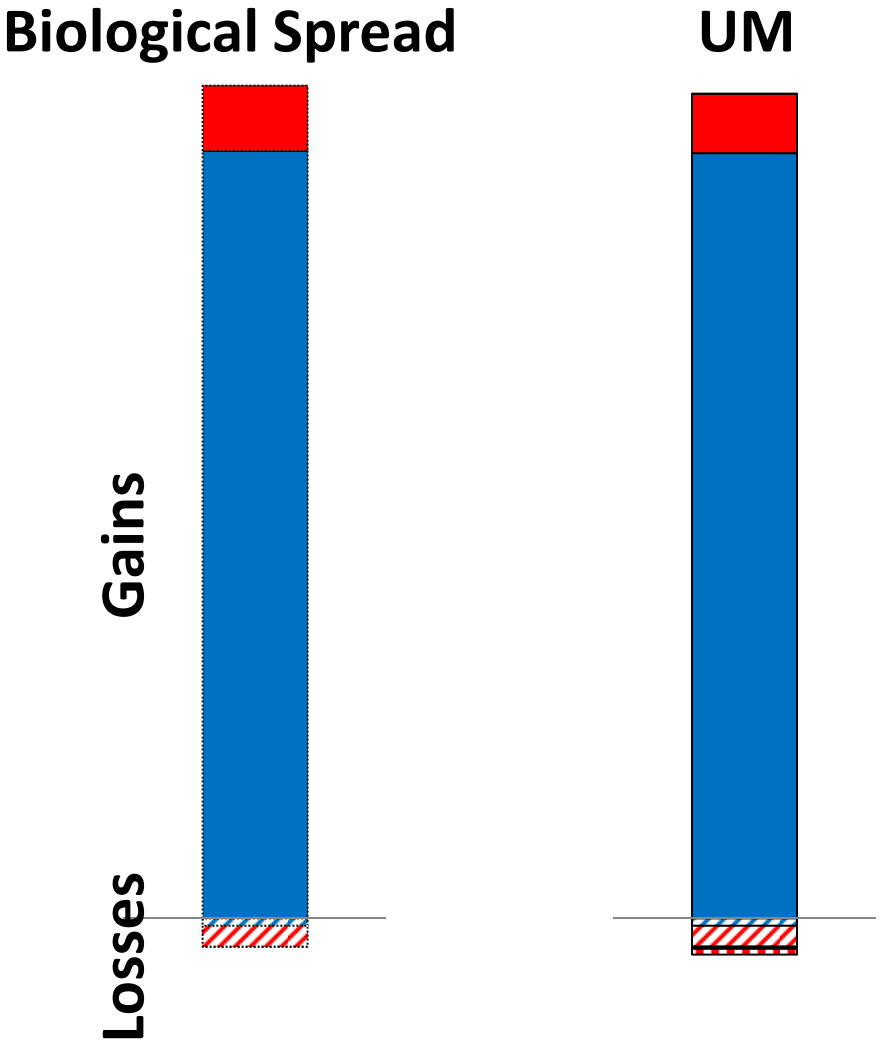
Black – Gamble – White



Uncertainty Budget

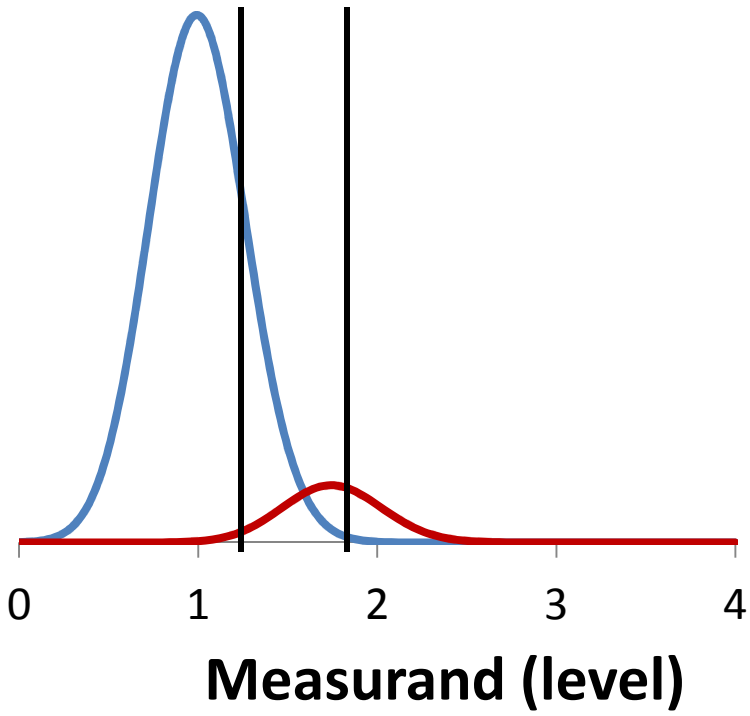


Loss of Certainty due to



How a Test Result is Interpreted

Black – Grey – White



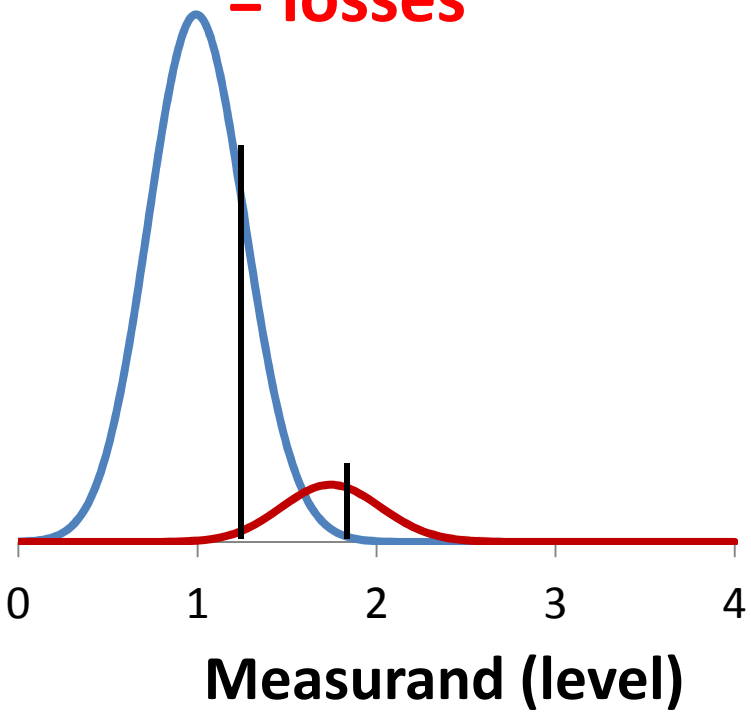
Differential Diagnosis

- Don't miss what
  needs urgent intervention
- Workup
  list of common causes
- But also exclude rare causes

You need not to confirm doubt
but to exclude Dis- or Dis+

Dichotomic Analysis

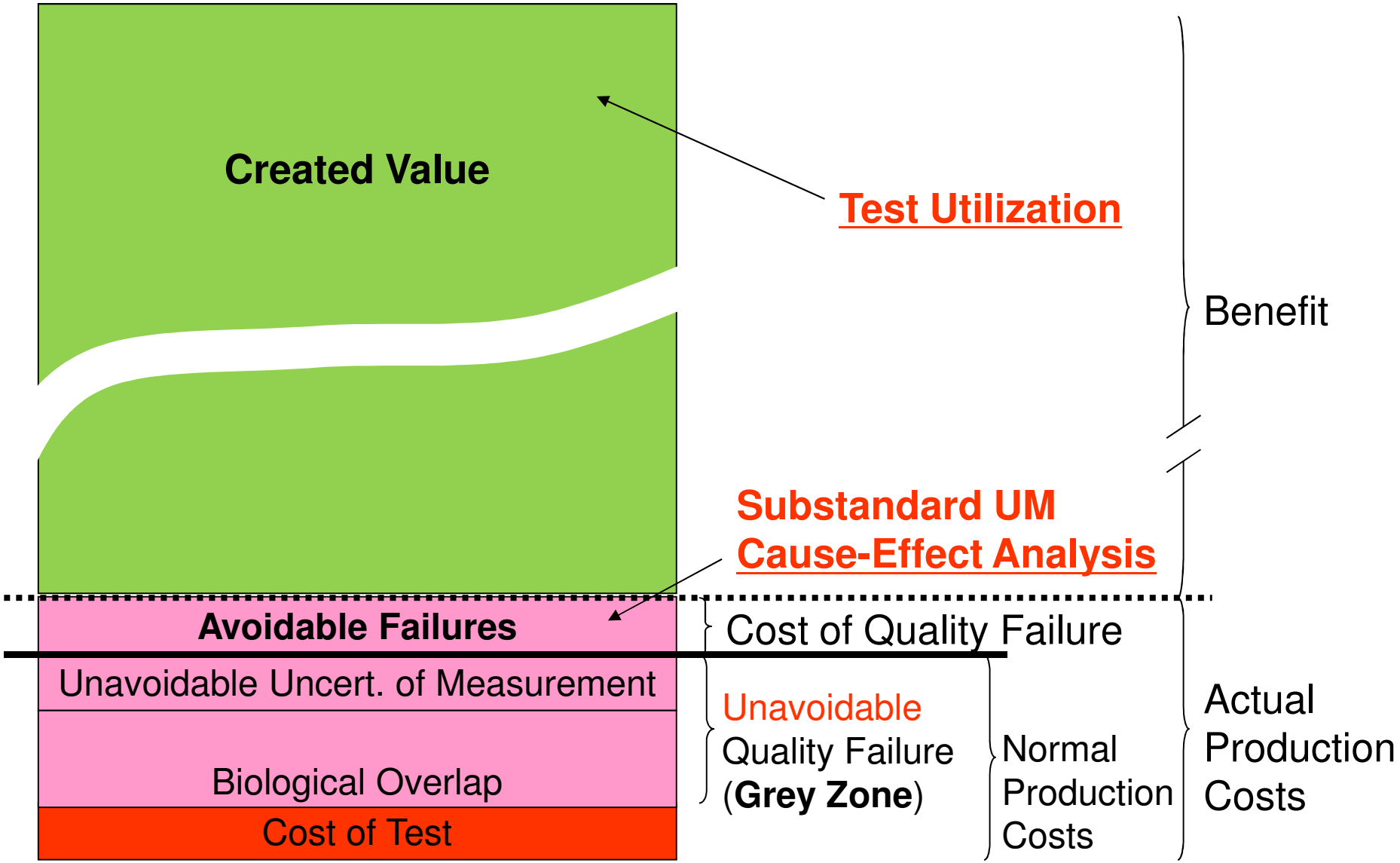
Black – Undecided – White
= losses



If you refuse to Gamble

predictive value increases
trade-in: sensitivity
& specificity

Where can the validation exercise create value ?



Message #2

Diagnostic Value depends on whether you ordered a test with Power of Exclusion

Typically, Analytical Uncertainty has little effect on Diagnostic Power ☺

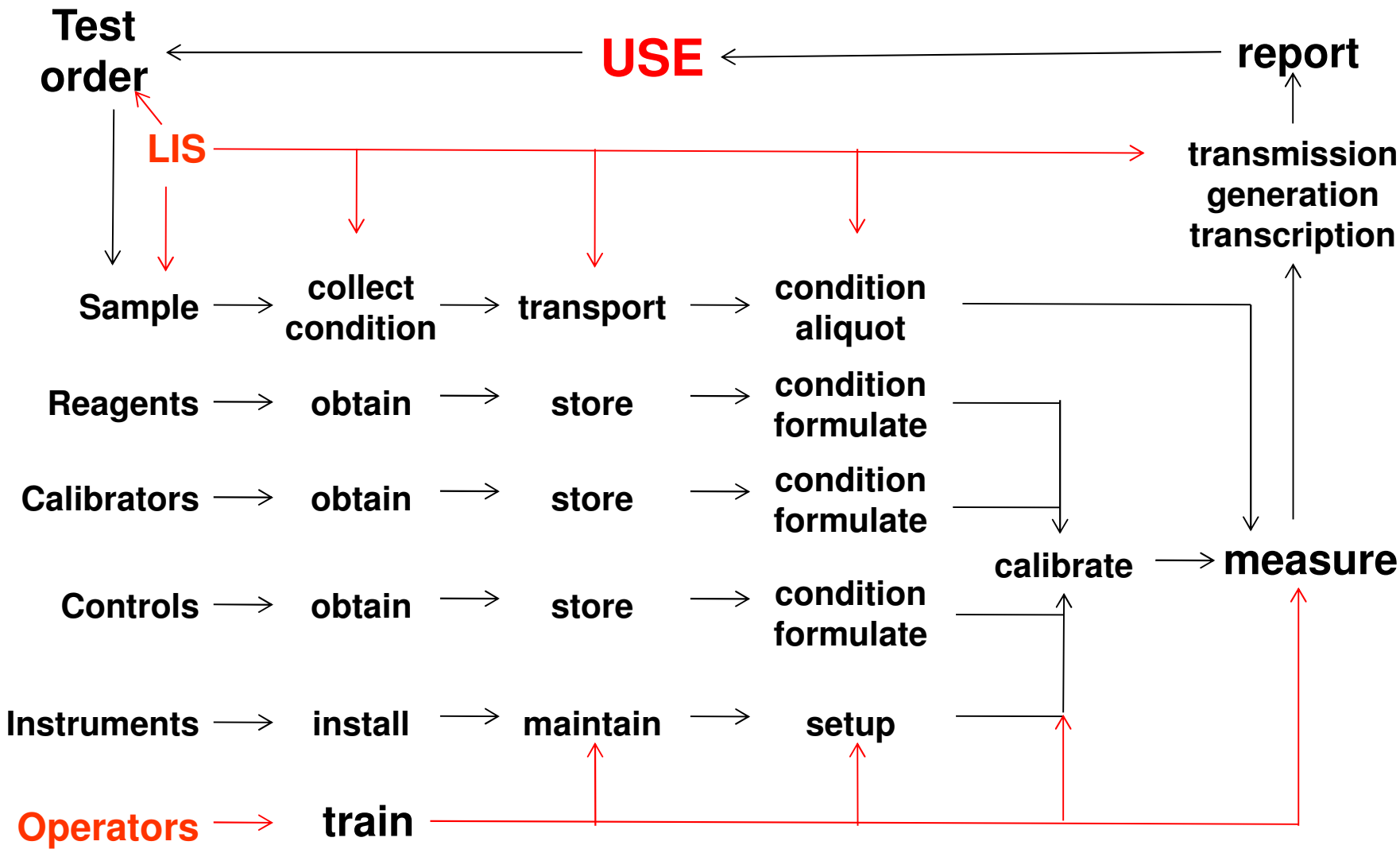
UM doesn't ruin a good test
& can't rescue a bad test

Casus:
The Nuts and Bolts of UM Evaluation

UM Evaluation starts with

Inventory of Sources of Error

Risk Analysis Generic Laboratory Process



After ISO/TS 22367:2008 **= Workshop Approach**

= Fishbone analysis

Risk Analysis: Failure-Mode analysis: What can cause relevant failures?

Test Ordering

Right Test at the Right Time … for the Right Patient …

Pre-analytical

Biological Variation
Pulsitility, Diurnal & Seasonal Variation
Physiological (Starvation, Exercise, …) Variation, TimeStamp

Specimen Collection
Posture
Stasis, Hemolysis, Filling of the tube
Right patient, Correct labelling, sample, recipient, …

Interpretation

Adequacy, sampling details , specimen quality, …, …
Adequacy cut-offs, reference ranges, …
Adequacy interpretation support

Process Approach of Diagnostic Cycle

Post-analytical

Reporting for the right patient
Transcription errors , …, …
Data transfer errors, ….

Analytical = Measurement Process

Sample reception & processing
Right identification of primary and secondary sample
Completeness of coagulation, …
Micro cloths: obstruction needle, light scattering, …
Membrane ghosts and fragments, …

Uncertainty of Measurement
Bias, Specificity, …
Calibration, Linearity, …
Inter-batch random error, …
Other sources of (random) imprecision
Equipment faults (aspiration, carry-over, sporadic faults, ..)

Clasical Focus of Method Validation
Is this where most relevant failures originate?

Message #3

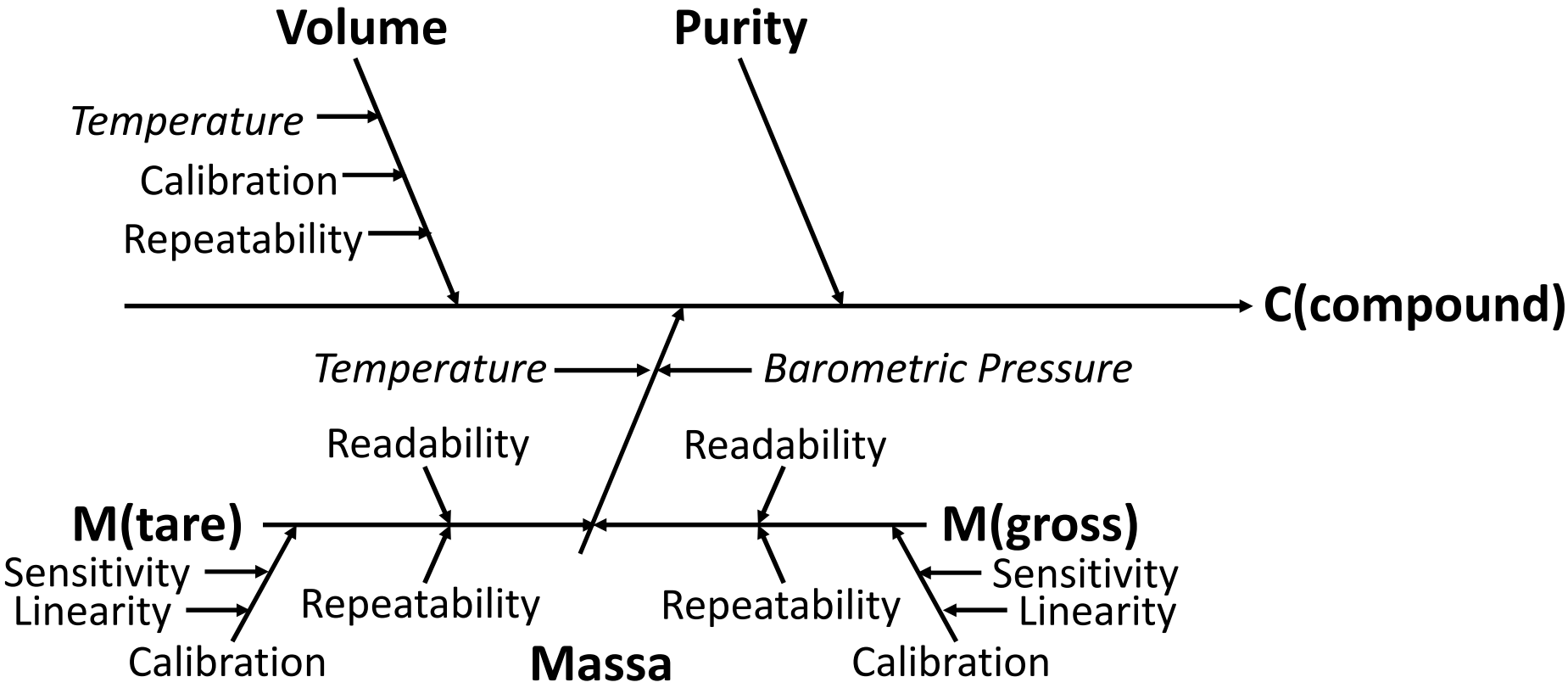
The Core Analytical Process
and the associated UM
should not be your only focus,
maybe not even your primary focus?

UM Evaluation
(in the narrow sense)

Approach #1
Inventory of Sources of Analytical Error

Fishbone Analysis of an Analytical Assay

e.g. Calibrator formulation



Message #4

Fishbone Analysis identifies

- Input Variables

= Model Equation (see next section)

- & *Influence Variables*

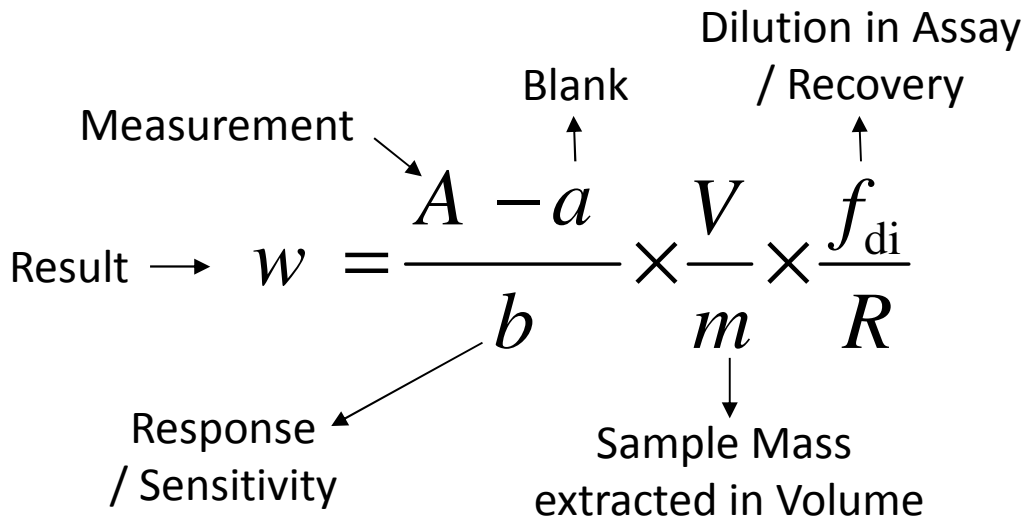
typically not represented in the model

did your supplier develop a rugged test?

Approach #2

Model Equation -> Error Propagation: Sensitivity or Ruggedness Analysis

Example: Extraction & Calibration



What are the critical issues ?

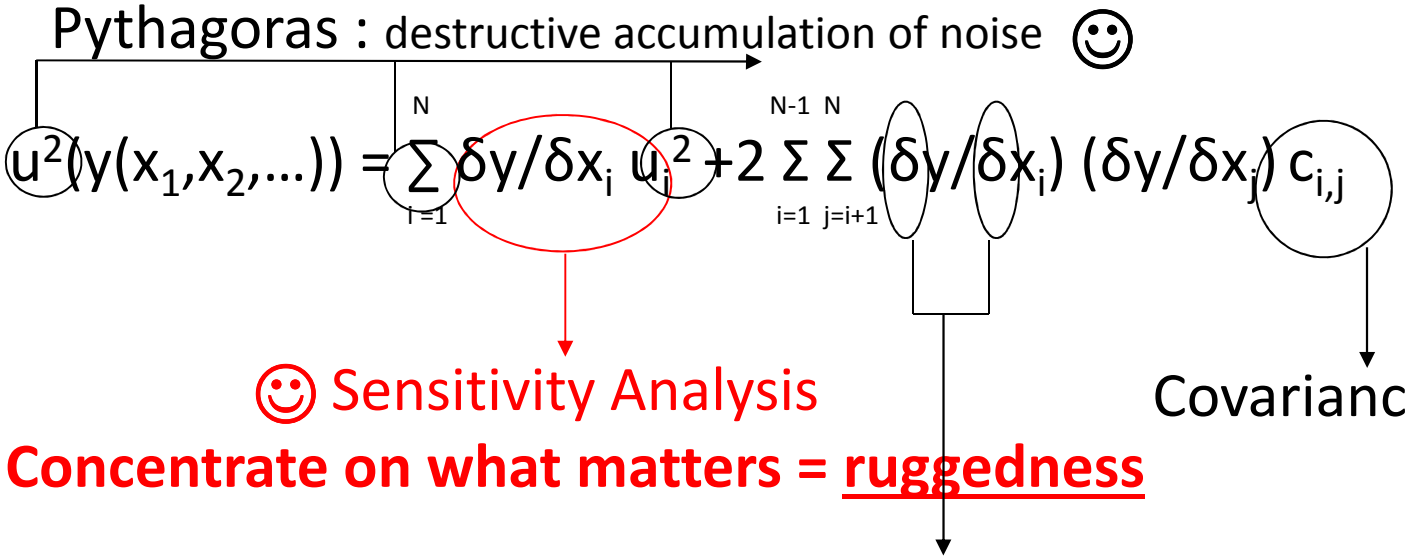
m/V: Unfavourable?
f_{di}: Unfavourable dilution in the assay?
R: Incomplete and haphazard extraction?
(A-a)/b: Unfavourable dynamic Range A *vs* a; Low response factor A/b?
a: Constructed Blank or Extrapolated from Calibration Line ?
b: Historical Colour Yield or In Run Calibration ?

Message #5

Writing down the Model Equation & critically inspecting it tells you a lot ☺

First order Taylor Series approximation of the process

The combined standard uncertainty =
reasonable dispersion of measurement results =
function of the uncertainty of the component quantities



Partial derivatives ? Don't panick :
mostly additions/subtractions & multiplications/divisions ☺

For independent parameters, the second term is absent ☺

Kragten (or spreadsheat) Method:

The simplest of cases

$$X = A*B/C$$

X: concentration resulting from

- **A: dilution of the sample**
- **B: measurement**
- **C: calibration factor**

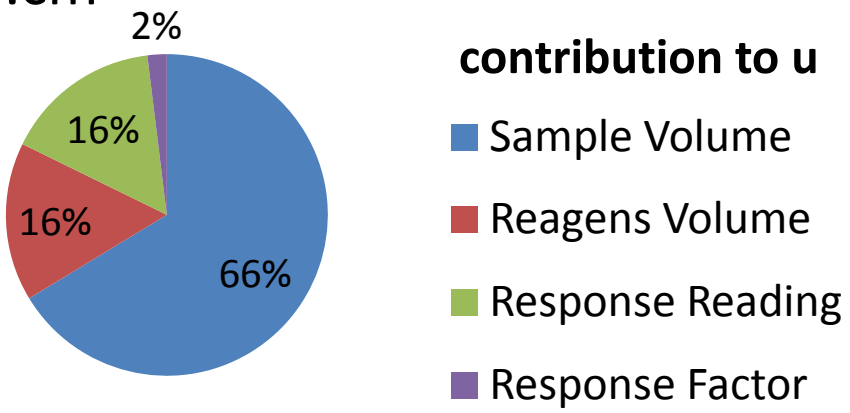
Kragten Method: Propagation of error

Model		Effect of partial disturbances		
X = A*B/C		u_a	u_b	u_c
A	a	$a + u_a$	a	a
B	b	b	$b + u_b$	b
C	c	c	c	$c + u_c$
Evaluation	x	x_a	x_b	x_c
	$u_{x,n}^2$	$(x_a - x)^2$	$(x_b - x)^2$	$(x_c - x)^2$
	$\sum u_{x,n}^2$			u^2

Propagation of error: An Example

A sample is diluted in a reagent mix. At the end point of the reaction the color yield is read, and divided by a calibration factor.
That result is multiplied with the dilution factor.

		Value	SI	u_i/x_i	
y	**$= (x_3/x_4)(x_1+x_2)/x_1$**	**359**	**mM**	**0.1%**	
x_1	Sample volume	5	µL	4%	from pipet control program
x_2	Reagens volume	200	µL	2%	from pipet control program
x_3	Response Reading	0.7	cm^{-1}	0.05%	from equipment specs
x_4	Response Factor	2000	10^6.L. $mol^{-1}.cm^{-1}$	0.02%	Epistemic variable (literature)



Message #6

Don’t be scared ☺ of a Taylor Series ☺

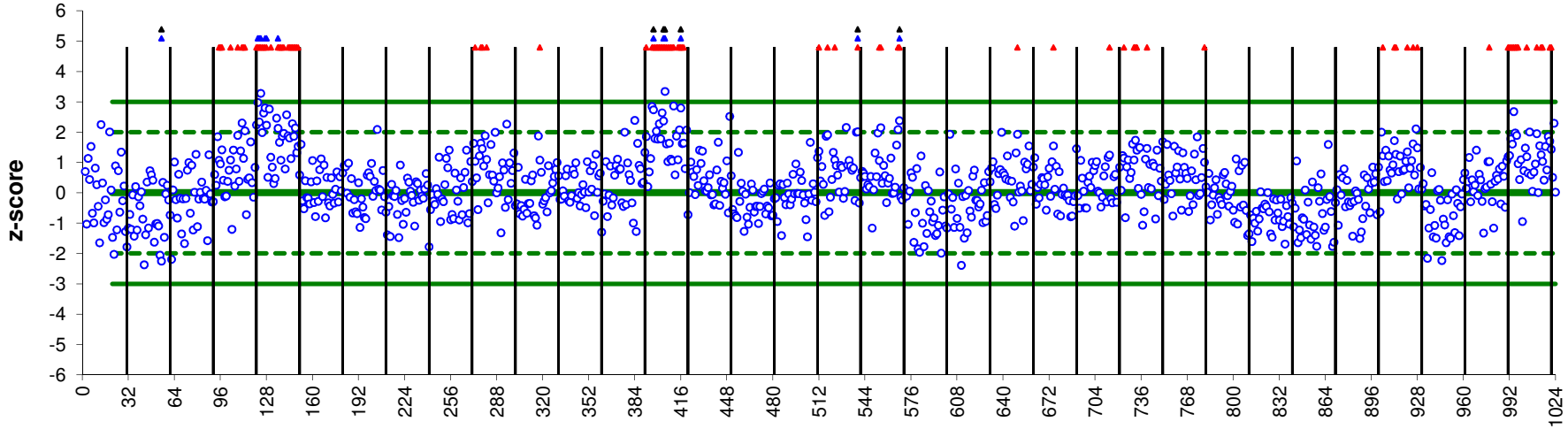
Now you know what to focus on ☺

Approach #3a

Measurement Uncertainty From Internal Quality Data

Internal Quality Control Data

Typical immunometric assay



There are episodes where results consistently differ from the majority of results?

Do we have a problem?

ANOVA of Internal Quality Control Data

#	Component of variation	CV	Comments: Typical sources of variability
1	Cal. Nominal Uncert.	1.0%	Applies to each new calibrator batch
2	Cal Manipulations	1.0%	Applies to manipulations and conditioning
3	Between Reagent 1	1.4%	Applies to start-up of new reagent batch
4	Within Reagent 1	0.7%	Applies to conditioning of individual reagent packs
5	Between Reagent 2	1.4%	Idem as 1
6	Within Reagent 2	0.7%	Idem as 1
7	Maintenance	1.0%	Maintenance
8	Start-Up procedure	0.0%	Start-Up procedure
9	Operator	0.0%	Operator dependent variability
10	Between Run	5.0%	Applies to long-term variability of the analytical system
10	Within Run	5.0%	Applies to short-term variabilityof the analytical system
12	iQC Manipulations	1.0%	Applies to manipulations and conditioning
Total	**UM**	**10%**	**Uncertainty of measurement**

- The effects of calibrations, lots, ... **persist**
- Certain events are **synchronous**

Message #7

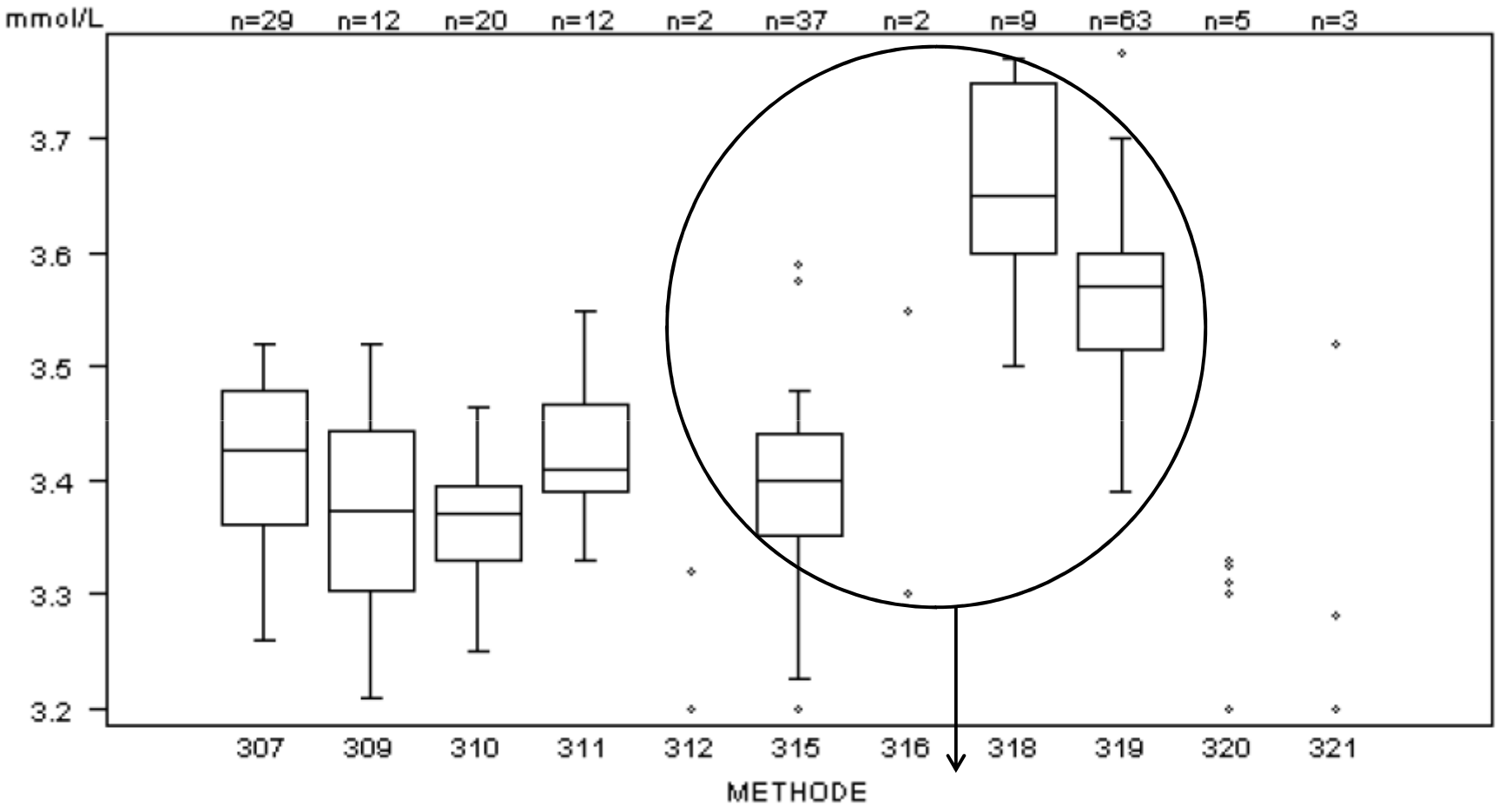
The example was a simulation:
nothing abnormal was happening
random variation within expectations ☺

ANOVA of iQC data = UM Budget
helps you
to avoid panick & futile interventions ☺

Approach #3b

Measurement Accuracy
From Proficiency Testing Data

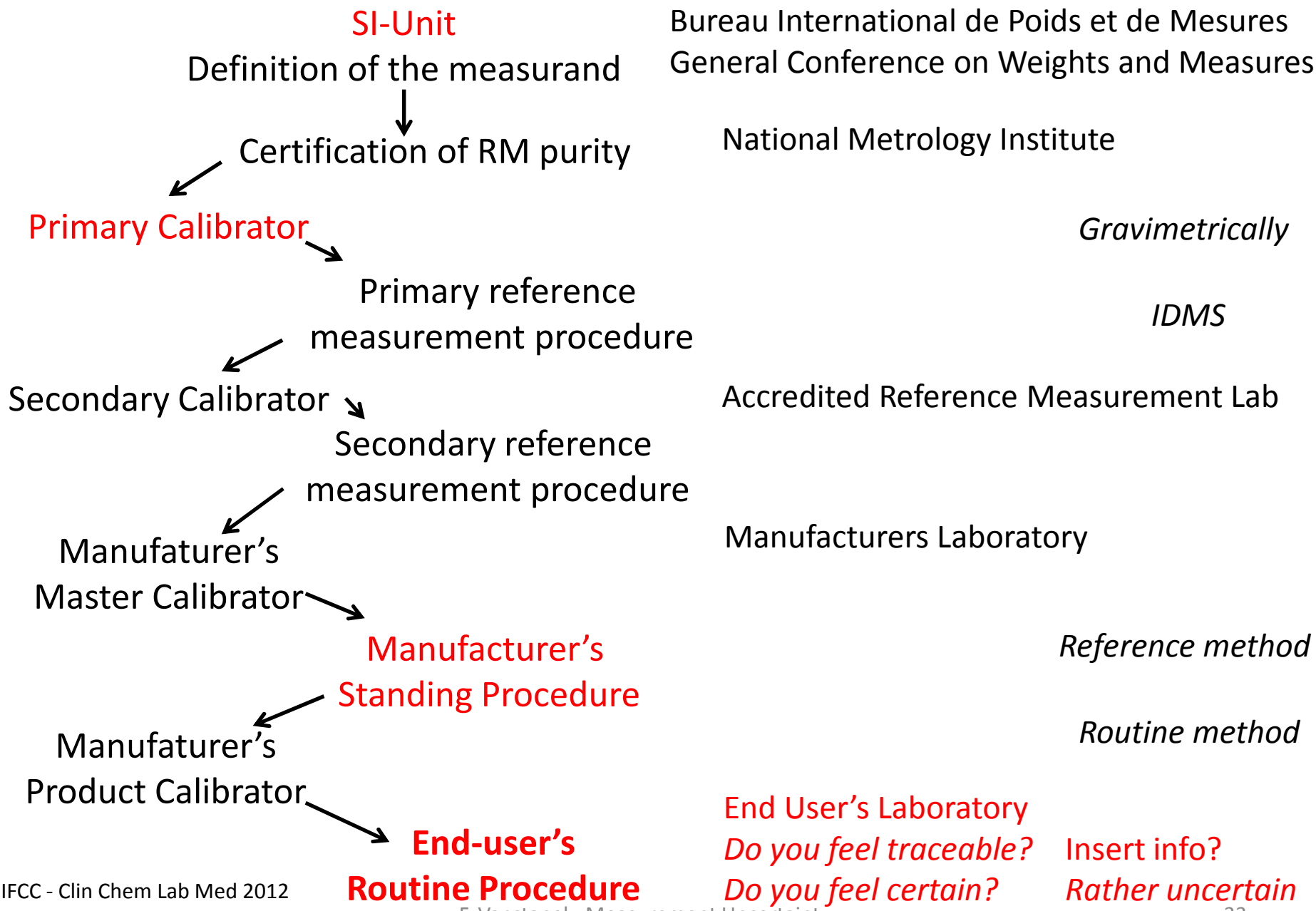
Belgian Proficiency Testing Scheme: Chemistry Calcium



EQAS commutability

single manufacturer? not OK

ISO 17511: Hierarchical scheme of traceability



Message #8

“Proficiency” Schemes:

- document non-commutability

The design of proficiency testing is flawed:

- mostly measure “relative” bias
- differences may or may not be attributable to matrix effects

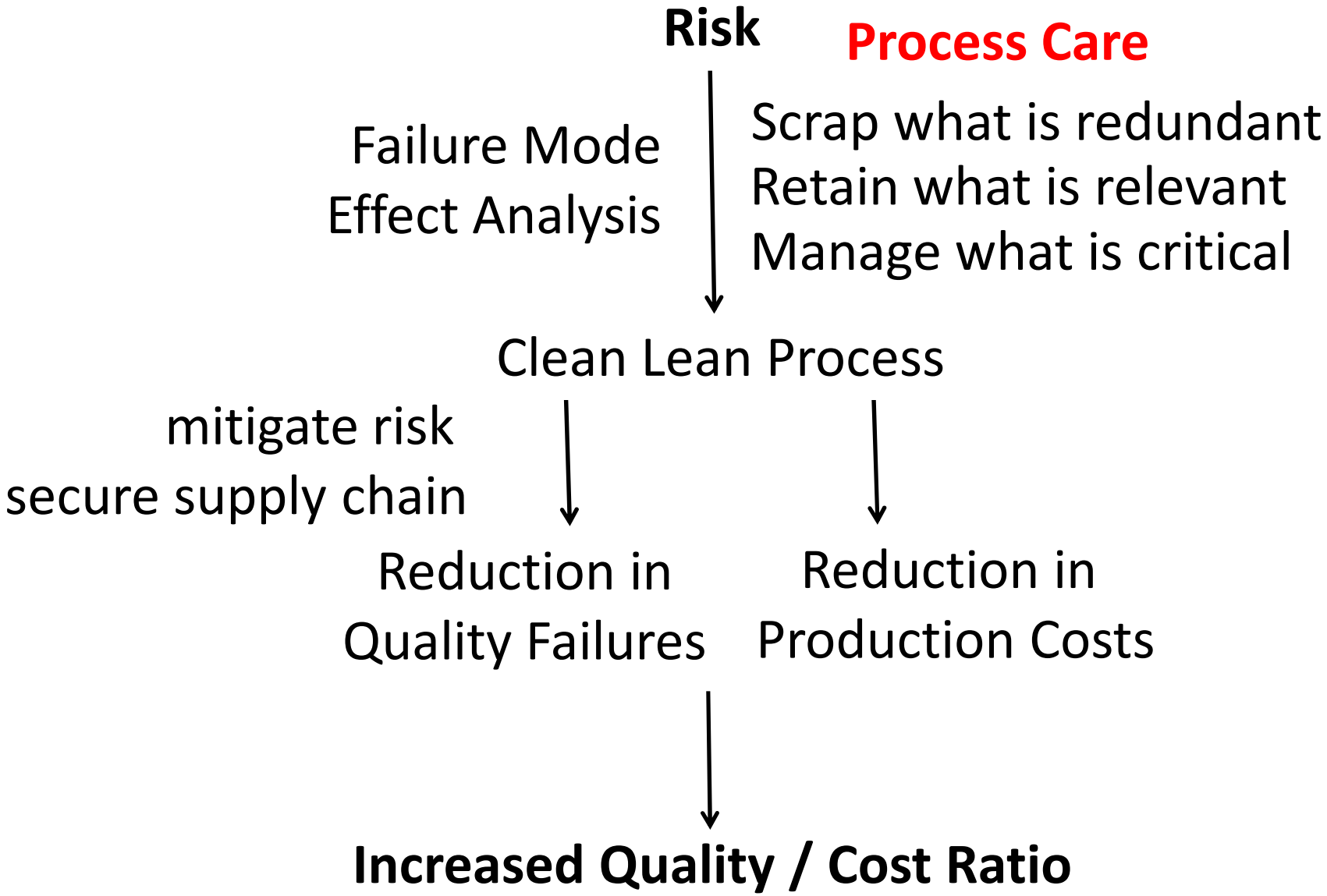
The perversion of “Matrix Effects”

- makes it harder to switch methods

Summary

Reaping the Fruits

The Economy of your Quality System



CONCLUSIONS

UM = Root-Cause en Failure-Mode Analysis
= Risk Analysis Tools ☺

Risk-Mitigation
= Process-Care Tool ☺

Process-Care
= Quality at No Cost ☺

CONCLUSIONS

Understanding UM allows

Production Department:

- to focus on what matters
- not to spend resources on futile projects

Interfacing with Prescribers:

- analytical precision suffices ☺
- except for transmural commutability ☹

TO DO

Develop Rugged Methods

to reduce waste activities (iQC, etc.)

Commercialize

- **Commutable Calibrators**
- **Harmonization Panels**

to realize

longitudinal coordinated transmural care