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The Measurement Cycle

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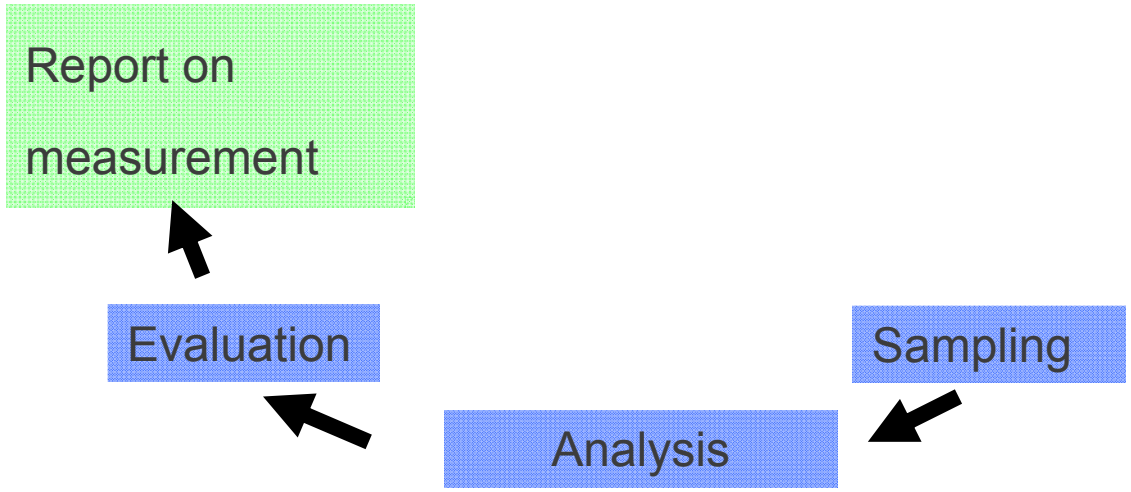
Eurachem

A FOCUS FOR ANALYTICAL CHEMISTRY IN EUROPE

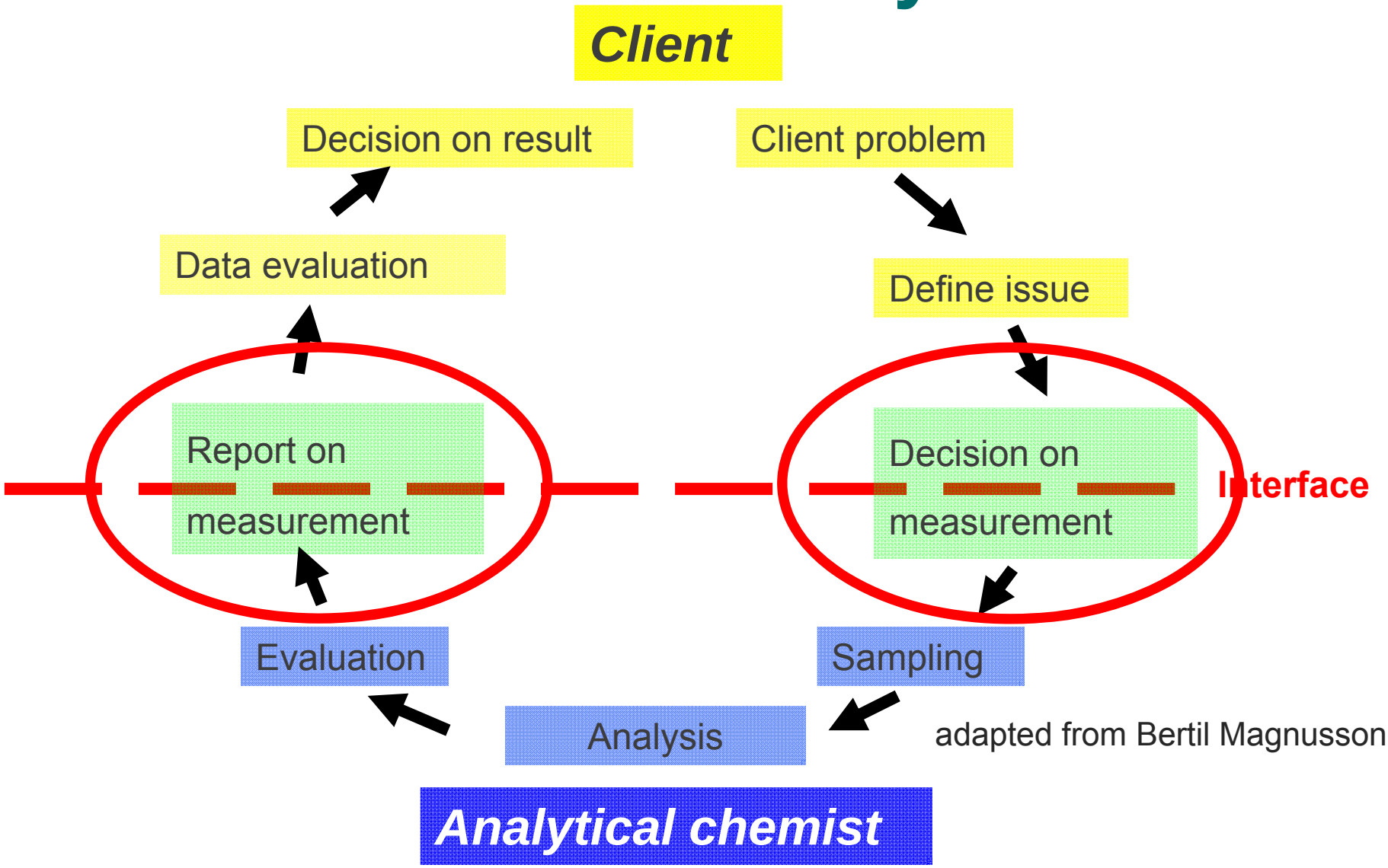
Outline

- Problems: 25 years later
- Goal: „better“ measurements for „cleaner“ decisions
- Interfaces in the measurement cycle
- Functioning of the guard band
- Systematic approaches through quality-by-design
- Outlook

Practice of analytical chemistry: detached activities ?

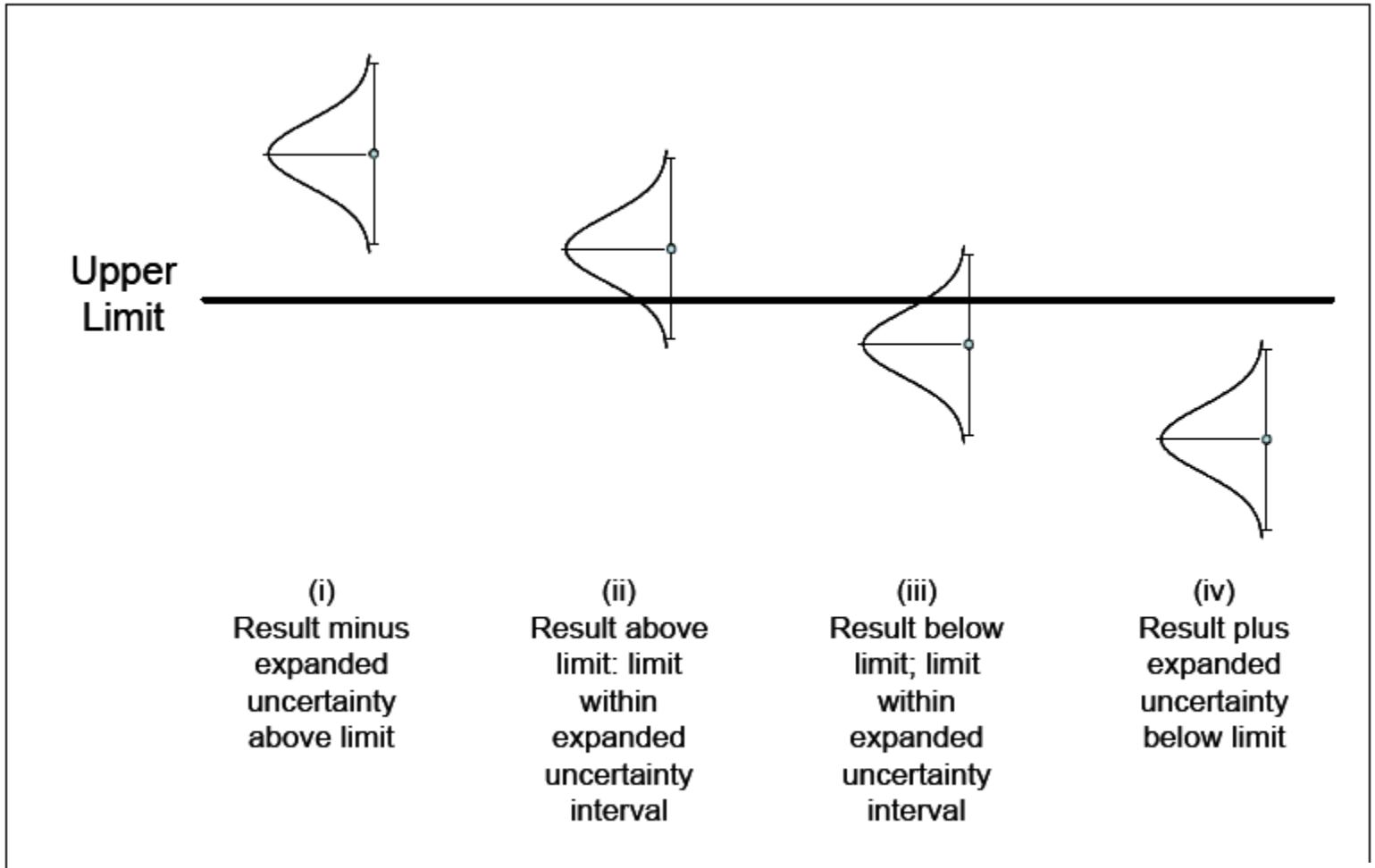


Measurement Cycle



Decisions under uncertainty

Figure 1 Assessment of Compliance with an Upper Limit

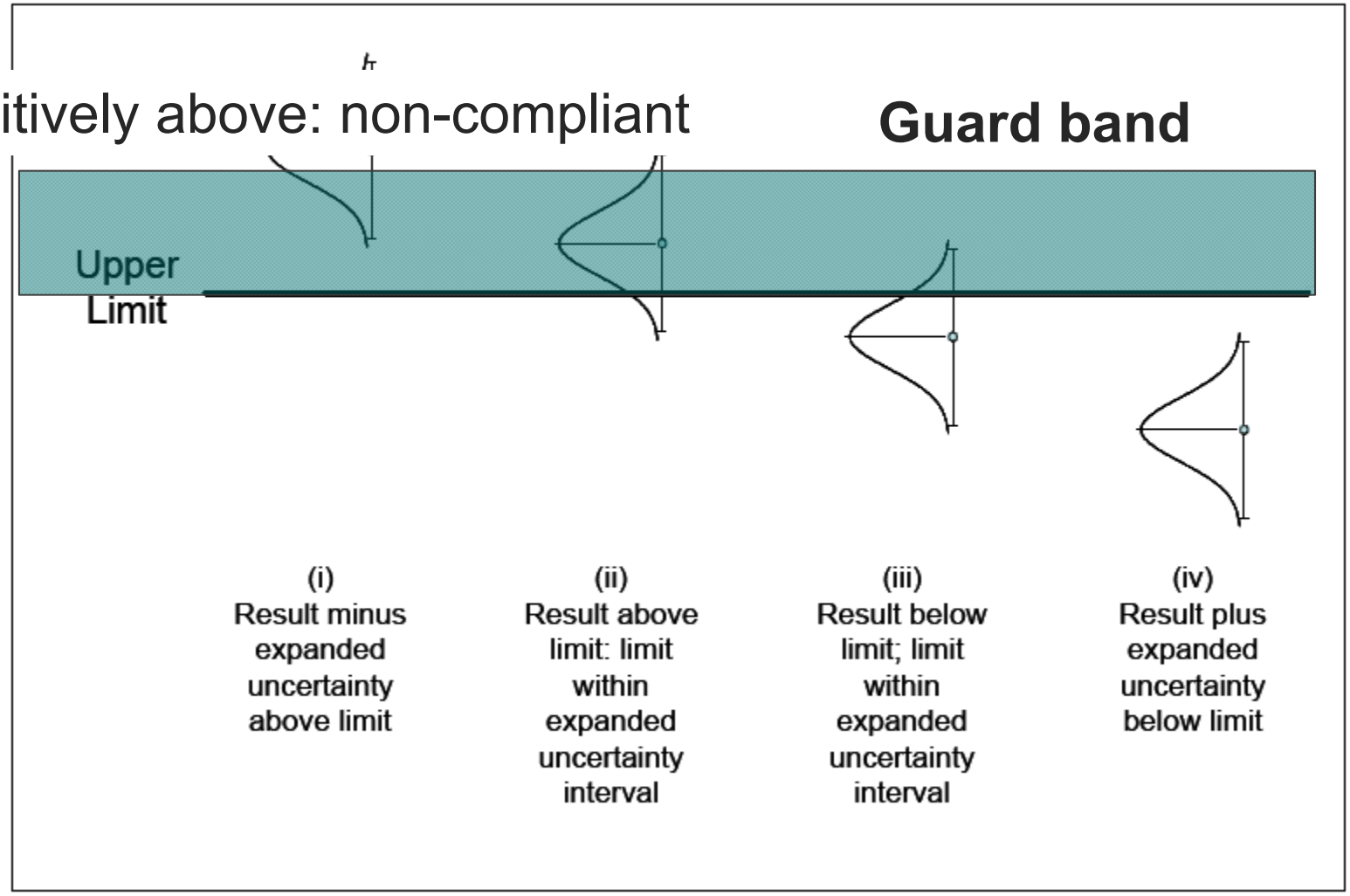


http://www.eurachem.org/index.php/publications/guides/uncertcompliance

Decisions under uncertainty

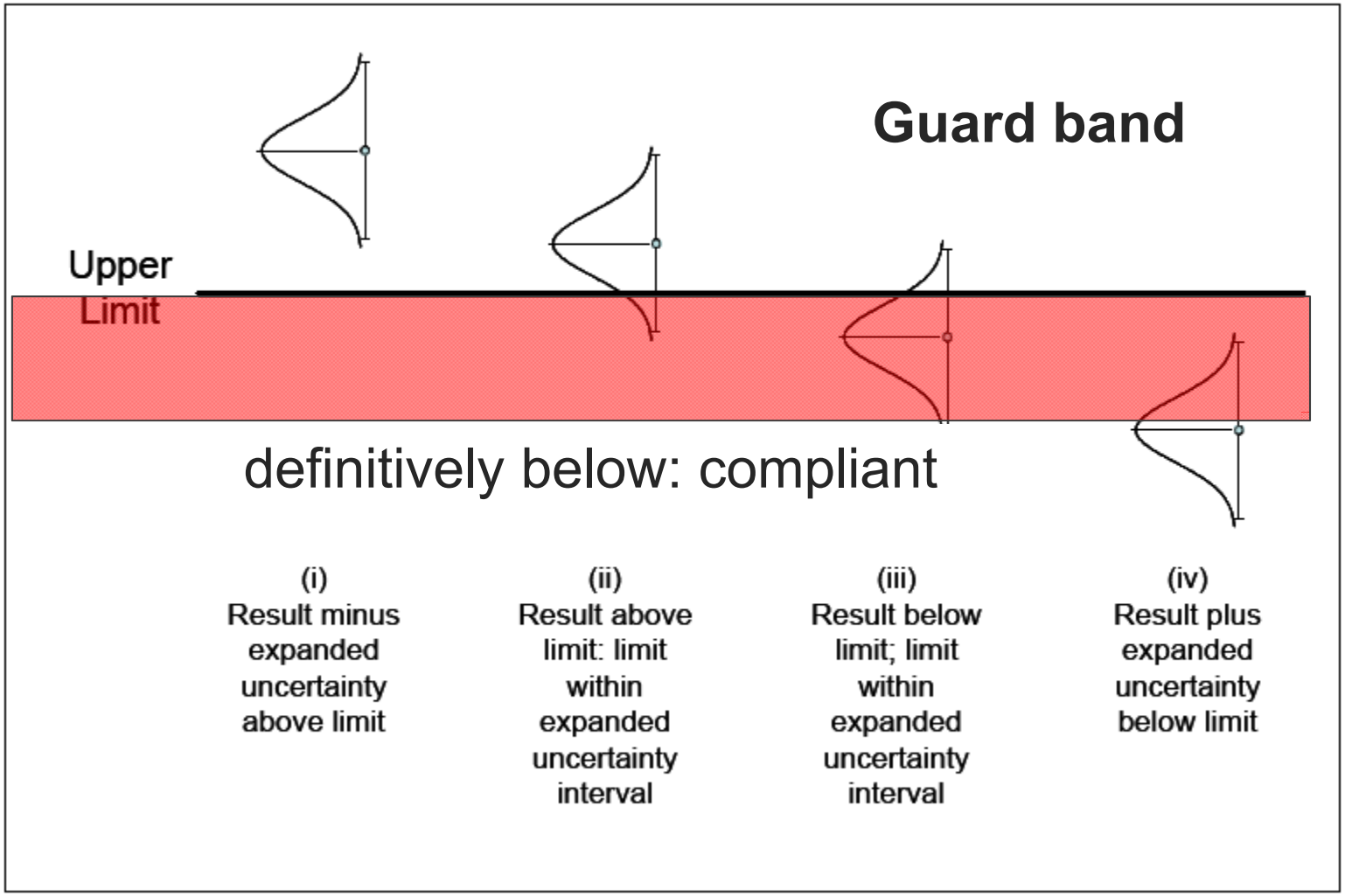
definitively above: non-compliant

Figure 1 Assessment of Compliance with an Upper Limit



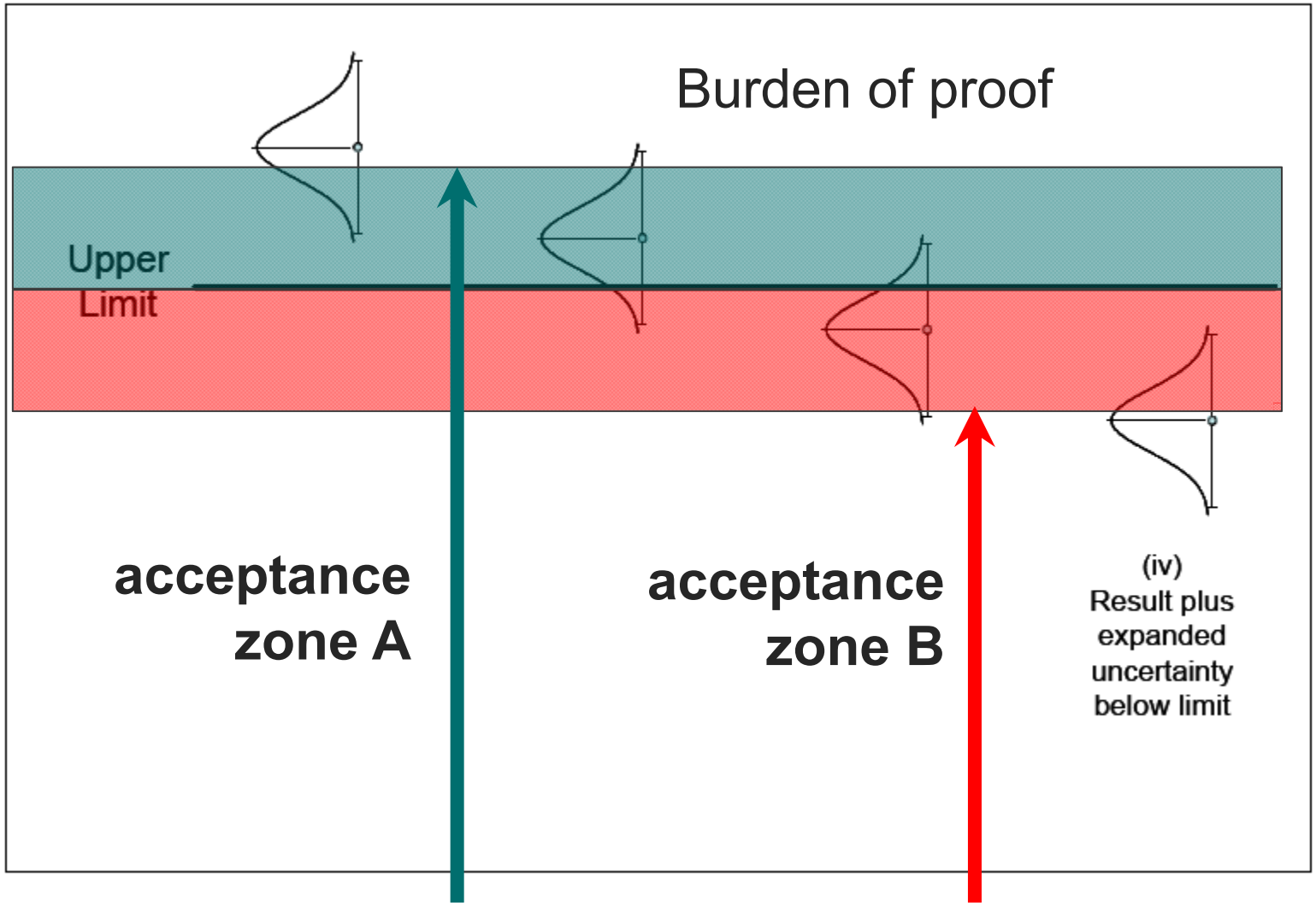
Decisions under uncertainty

Figure 1 Assessment of Compliance with an Upper Limit



Decisions under uncertaintv

Figure 1 Assessment of Compliance with an Upper Limit



„Poor“ measurements induce „wrong“ decisions

- Generally accepted that „better“ measurements leads to „clearer“ decisions
- Wrong decisions:
  - Decide on too high (too low) when it is not
  - Decide on low enough (high enough) when it is not
  - No decision within the guard band

Size of guard band:
change k or u

$$g = k * u = U \qquad k \propto (1-\alpha)_{CI}$$

k...coverage factor

Greater k
leads to better coverage (subject to pdf)

but impairs decision process

Smaller u
leads to better decisions

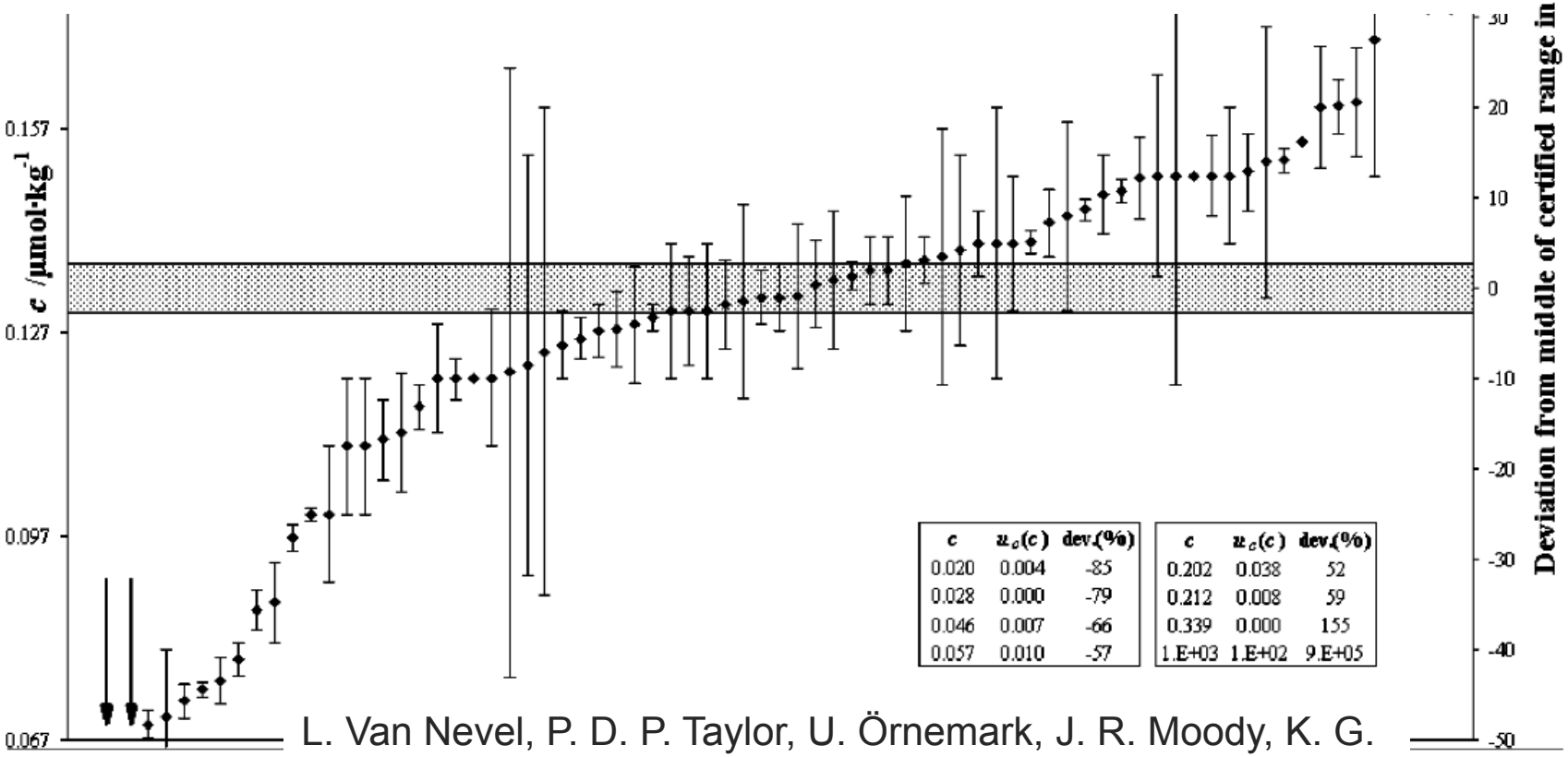
but makes development of procedures and their operation more costly

http://www.eurachem.org/index.php/publications/guides/uncertcompliance

What is an optimal value for k ?
The problem of „heavy tails“

Example 0: Lead in Water IMEP 6

75 laboratories



c	$u_c(c)$	dev.(%)
0.020	0.004	-85
0.028	0.000	-79
0.046	0.007	-66
0.057	0.010	-57

c	$u_c(c)$	dev.(%)
0.202	0.038	52
0.212	0.008	59
0.339	0.000	155
1.E+03	1.E+02	9.E+05

L. Van Nevel, P. D. P. Taylor, U. Örnemark, J. R. Moody, K. G. Heumann, P. De Bièvre, Accred Qual Assur (1998) 3 : 56–68

What is an optimal value for k ?
Results from expert laboratories

Example 1:

CCQM Key Comparison K19: pH

11 laboratories

Standard skewness: 3.45

Standard kurtosis: 5.54

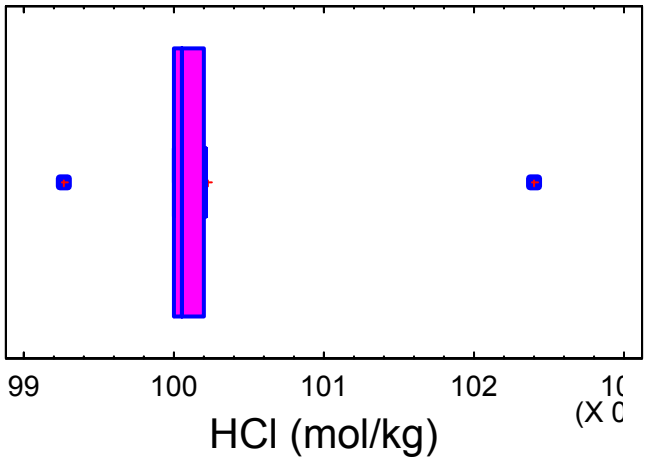
Central limit theorem is not working:

we fail to observe normal distributions

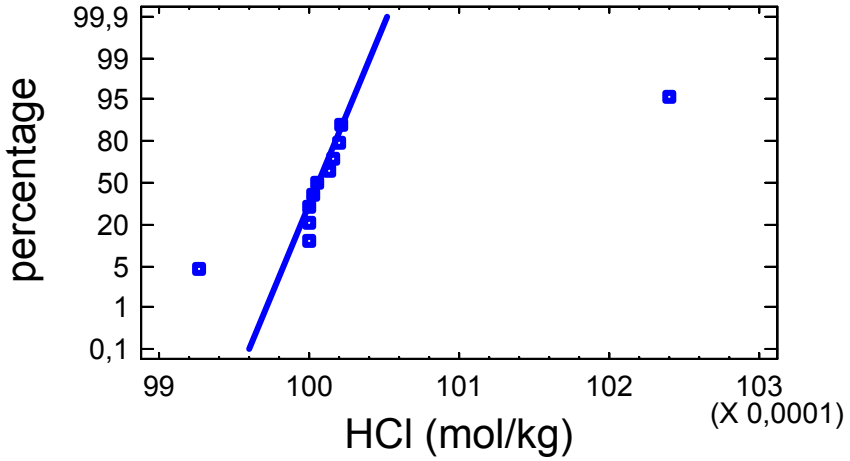
http://www.bipm.org/utils/common/pdf/final_reports/QM/K19/CCQM-K19.pdf

What is an optimal value for k ?

CCQM K19: pH measurement



CCQM K19: pH



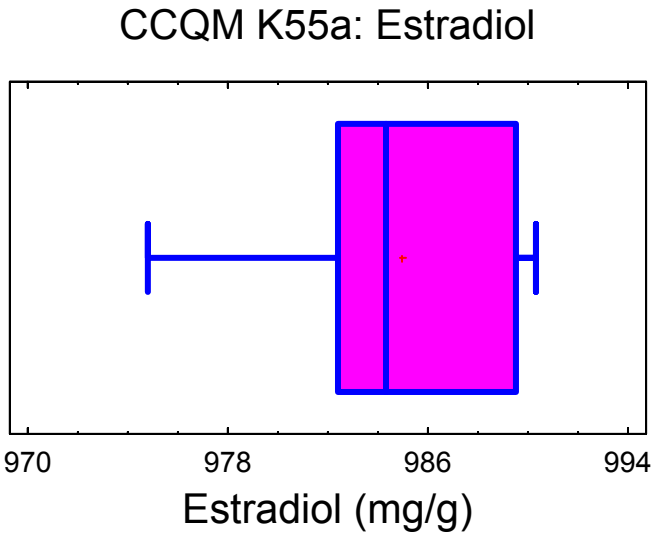
http://www.bipm.org/utils/common/pdf/final_reports/QM/K19/CCQM-K19.pdf

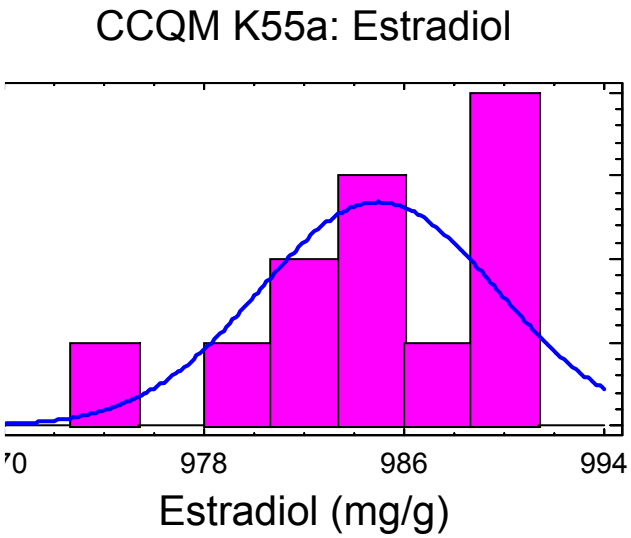
What is an optimal value for k ?

Example 2:

CCQM Key Comparison K55a: 17β-Estradiol

19 laboratories





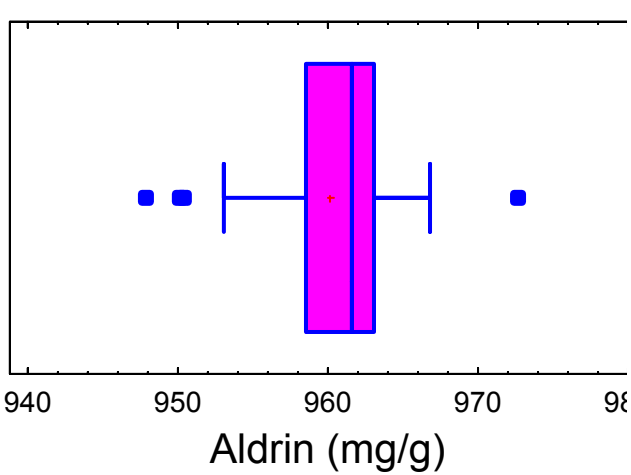
http://www.bipm.org/utils/common/pdf/final_reports/QM/K55/CCQM-K55.a.pdf

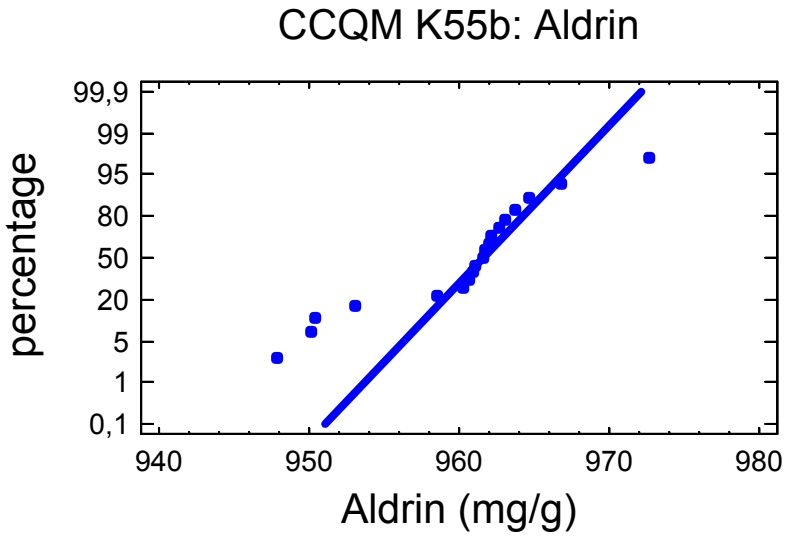
What is an optimal value for k ?

Example 3:

CCQM Key Comparison K55b: Aldrin

11 laboratories





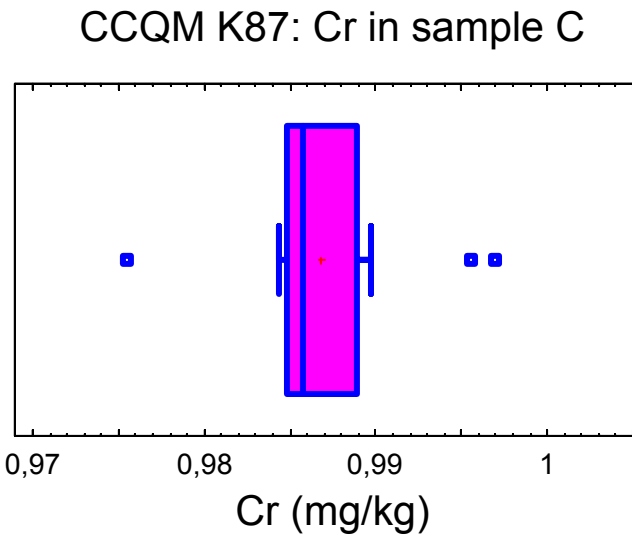
http://www.bipm.org/utils/common/pdf/final_reports/QM/K55/CCQM-K55.b.pdf

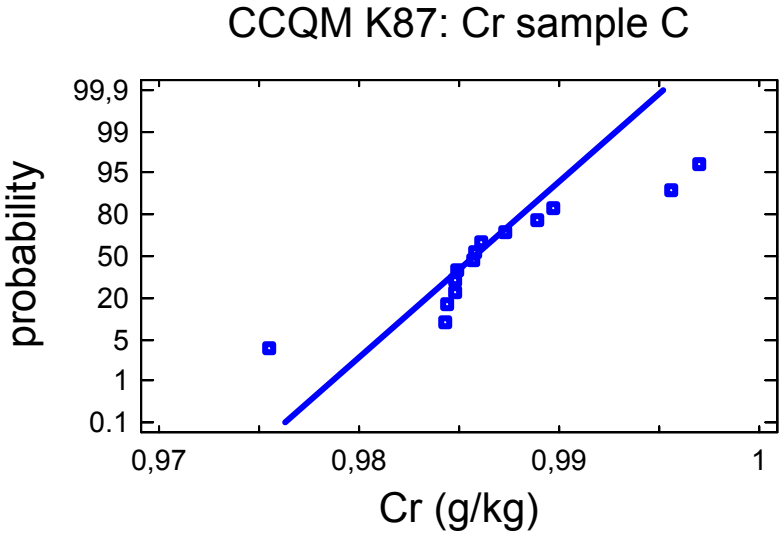
What is an optimal value for k ?

Example 4:

CCQM Key Comparison K87: Cr in sample C

14 laboratories





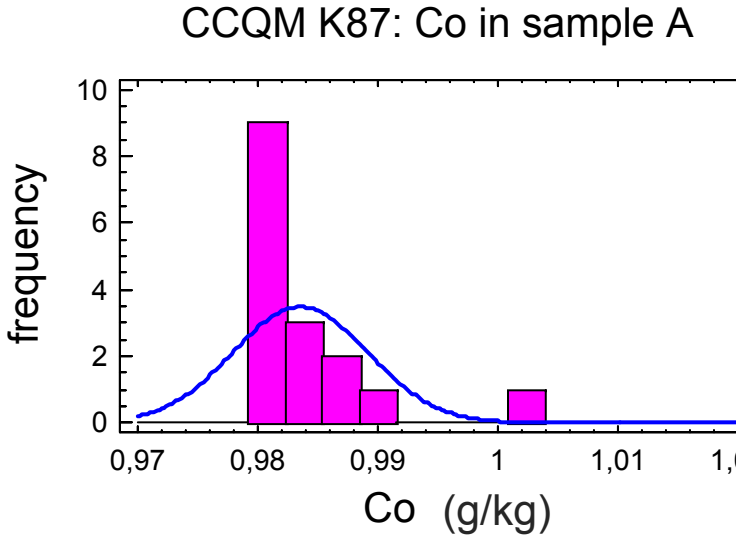
http://www.bipm.org/utils/common/pdf/final_reports/QM/K87/CCQM-K87.pdf

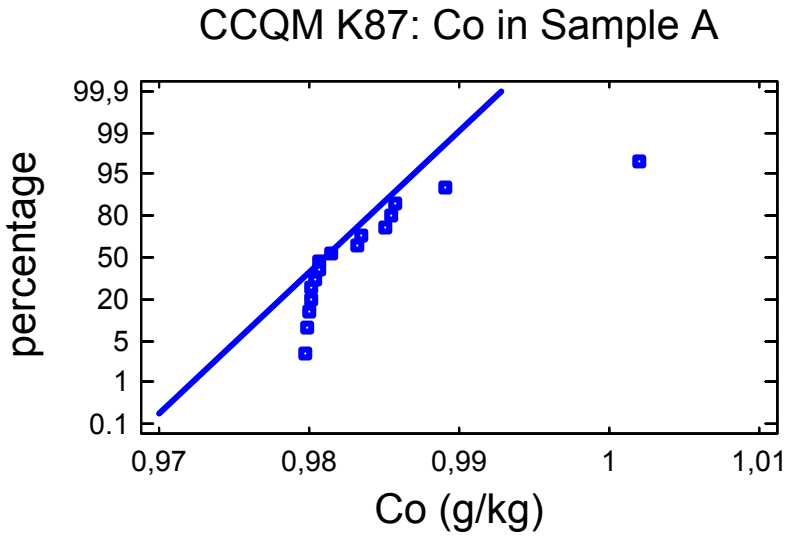
What is an optimal value for k ?

Example 5:

CCQM Key Comparison K87: Co in sample A

17 laboratories





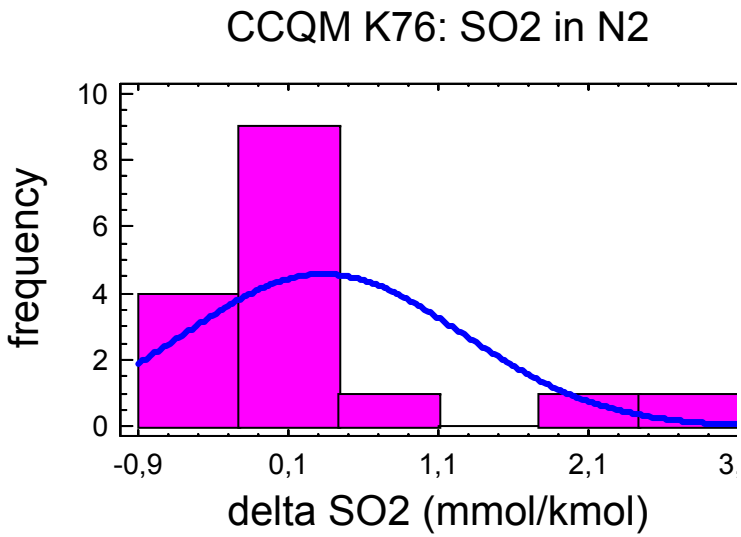
http://www.bipm.org/utils/common/pdf/final_reports/QM/K87/CCQM-K87.pdf

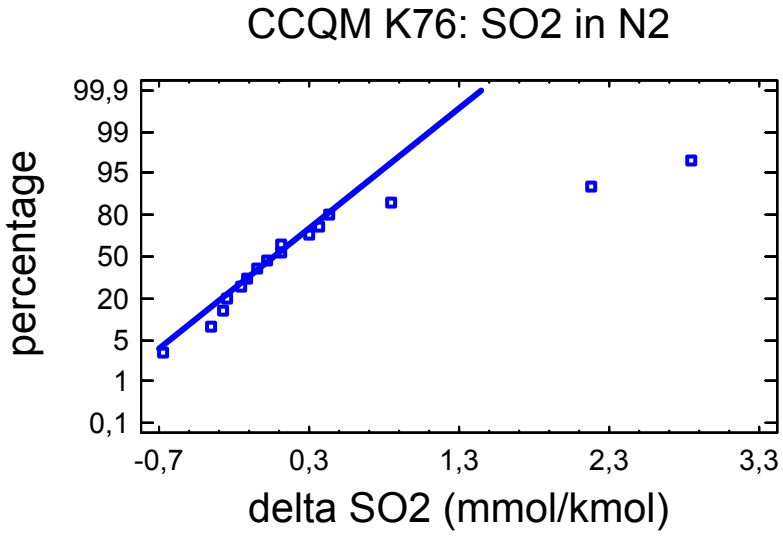
What is an optimal value for k ?

Example 6:

CCQM Key Comparison K76: SO_2 in N_2 at 100 μmol/mol

16 laboratories





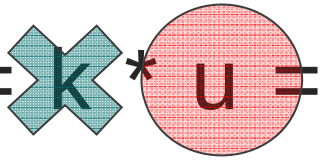
http://www.bipm.org/utils/common/pdf/final_reports/QM/K76/CCQM-K76.pdf

What is an optimal value for k ?

Conclusion:

It is not trivial to find a suitable value for k that is (uniformly) related to probability / reliability

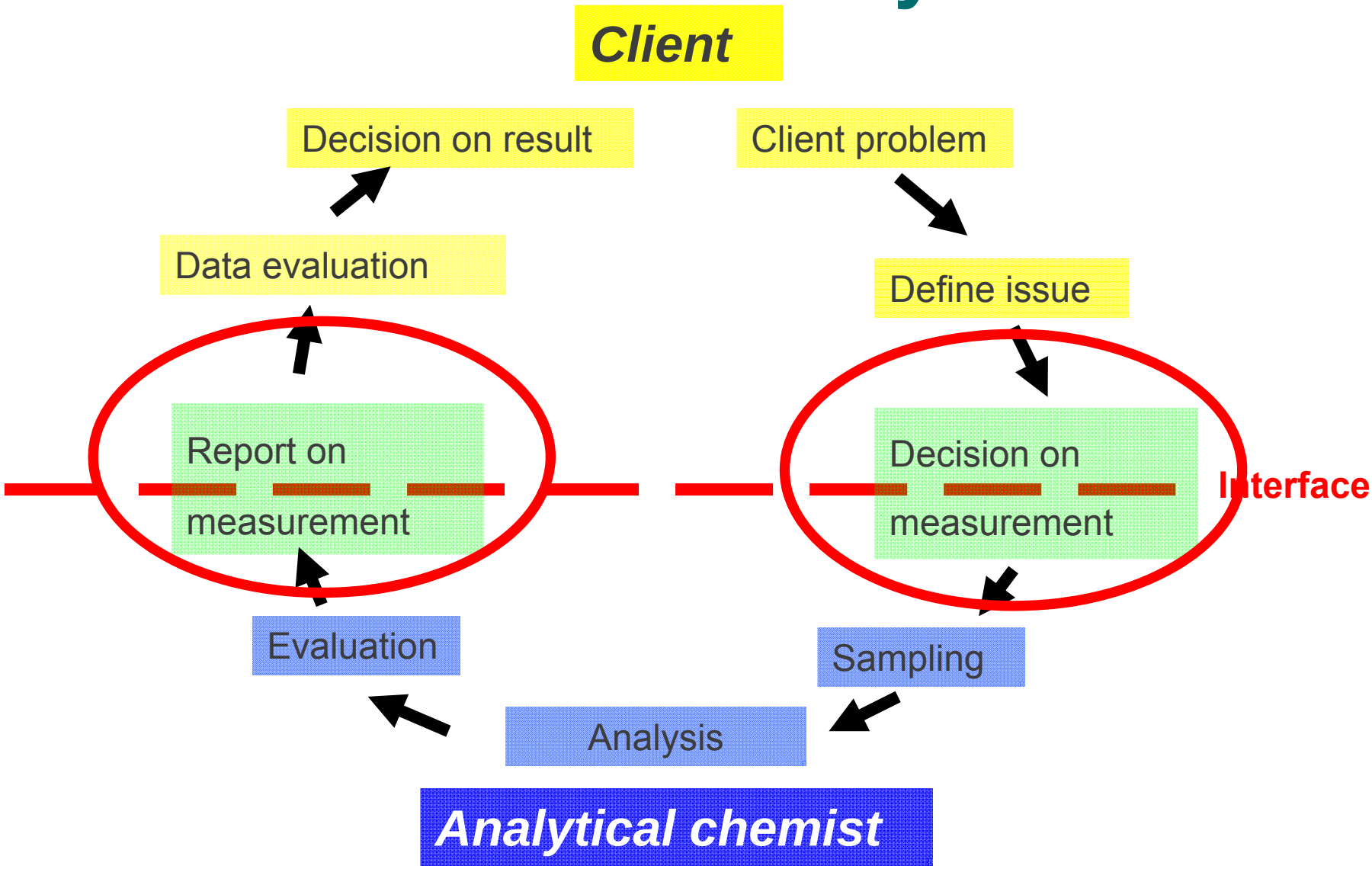
Size of guard band:
change k or u



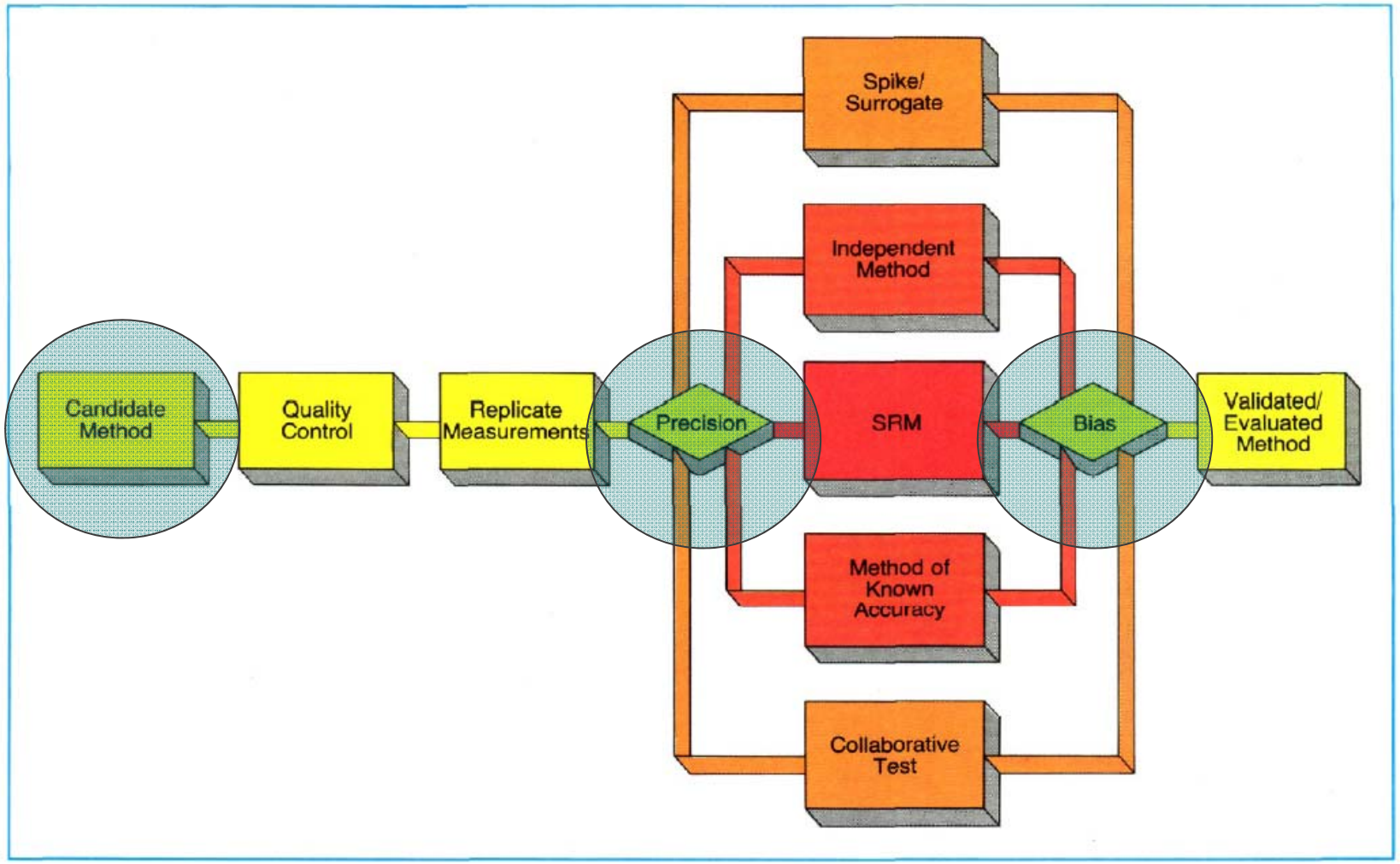
rational choice of k is not an option

Alternative:
reduce u

Measurement Cycle



Validation of Analytical Methods

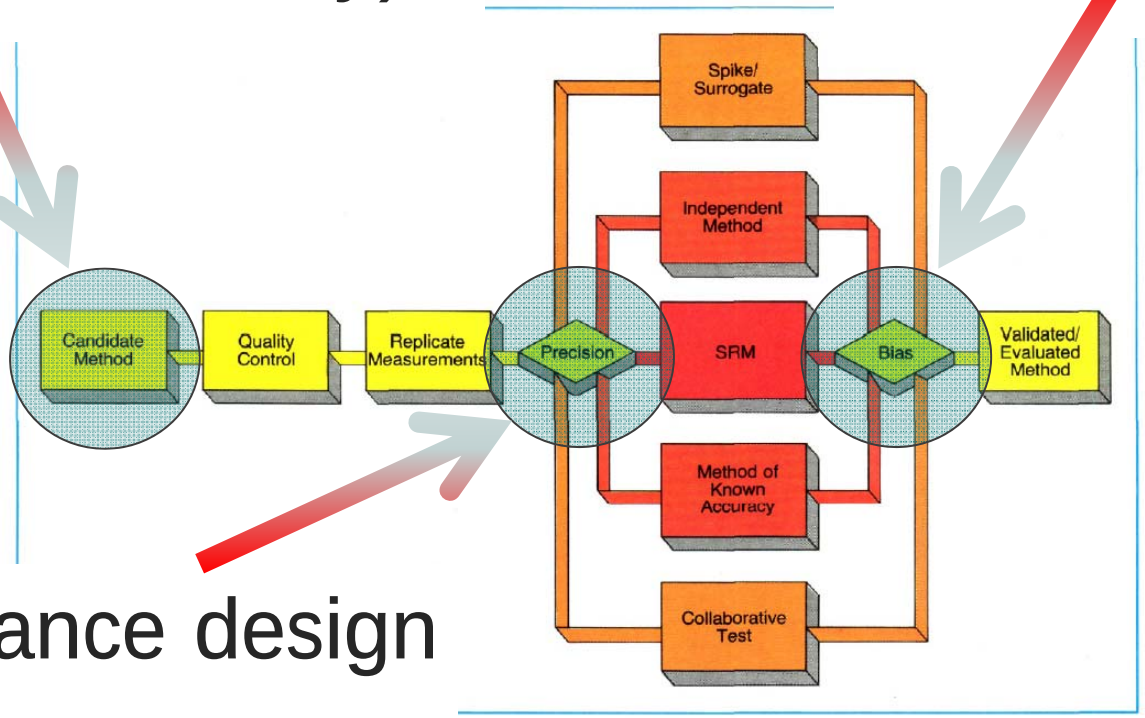


J.K. Taylor, Anal. Chem. 55/6 (1983) 600A-608A

Validation and Quality-by-Design:
systematic development

System design
(optimal feasibility)

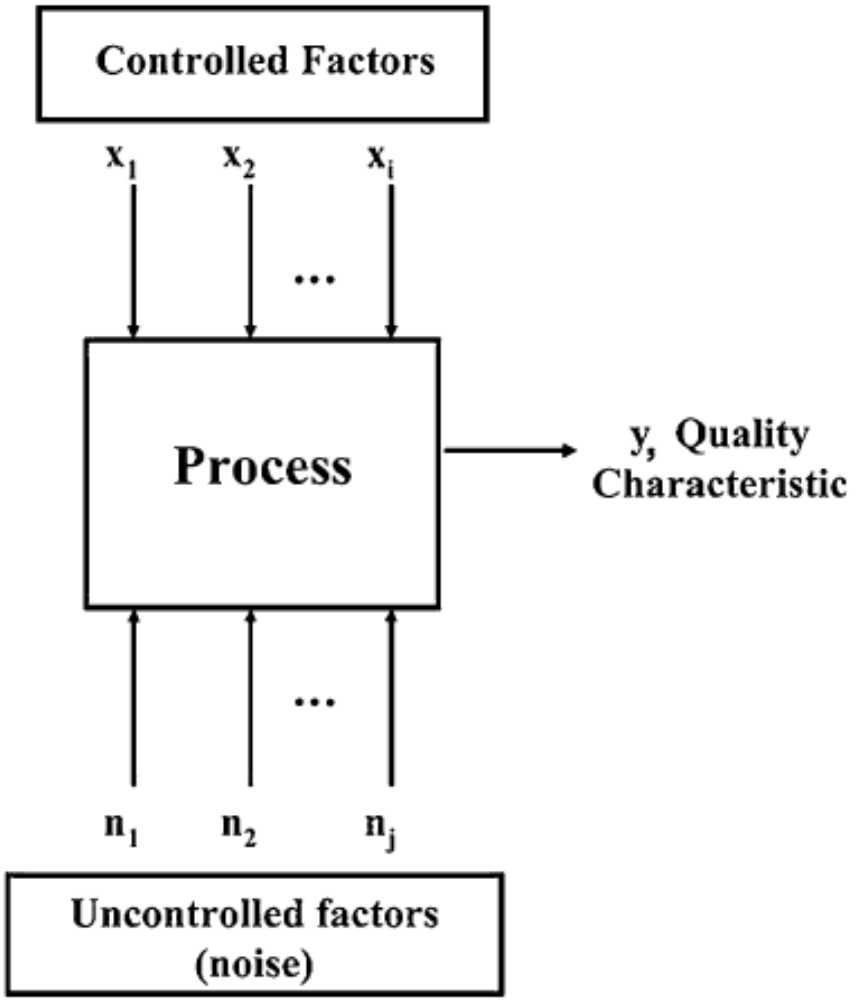
Parameter design
(trueness)



Tolerance design
(precision)

J.K. Taylor, Anal. Chem. 55/6 (1983) 600A-608A

Process of generating data



Three components/stages:

- System design (optimal feasibility)
- Parameter design (trueness)
- Tolerance design (precision)

E. Korakianiti, D. Rekkas, Pharm Res (2011) 28:1465–1479

System design:
what process are we talking about?

- Qualitative screening of candidate systems/methods

W. Wegscheider “Validation: an Example” in B. Neidhart, W. Wegscheider: Quality in Chemical Measurements, Springer Verlag, 79-87 (2000)

System design
criteria for evaluation of candidate methods

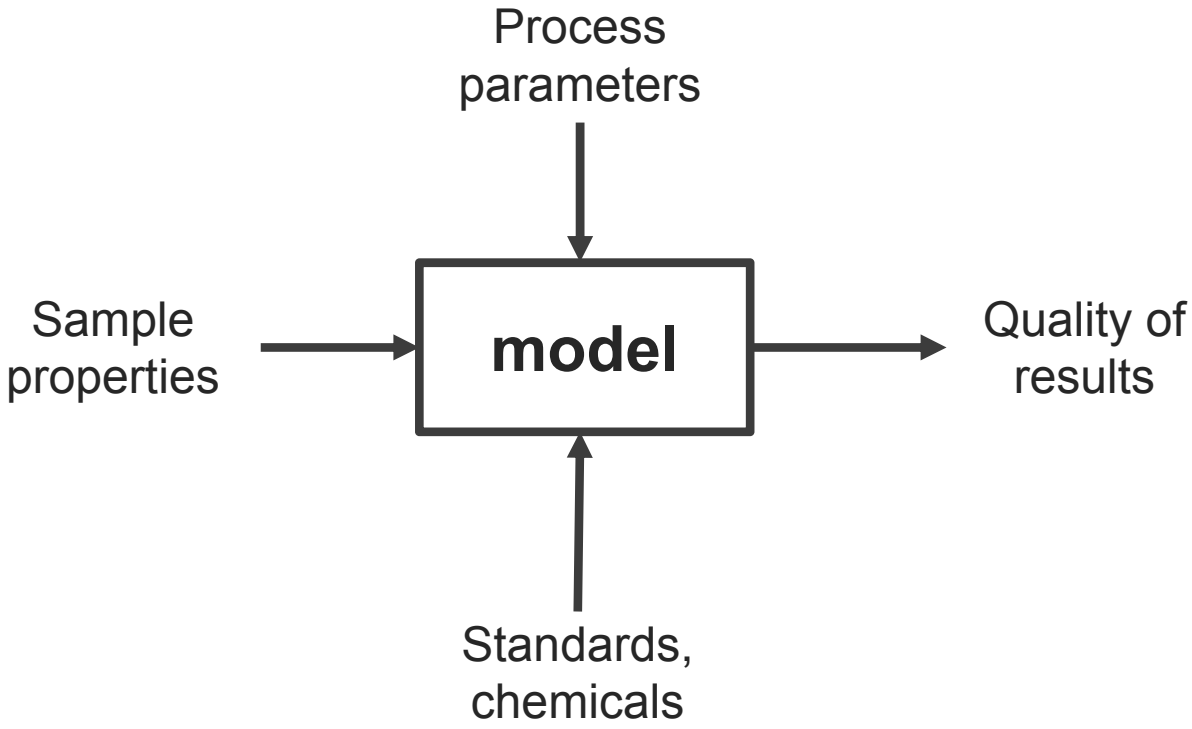
Anticipated requirements

- Time to deliver
- Cost
- Expertise in laboratory
- Currently practiced
- Equipment ready
- Robustness
- Uncertainty, LOD, LOQ, linearity, selectivity, ...

W. Wegscheider “Validation: an Example” in B. Neidhart, W. Wegscheider, eds.: Quality in Chemical Measurements, Springer, 79-87 (2000)

Use of direct model

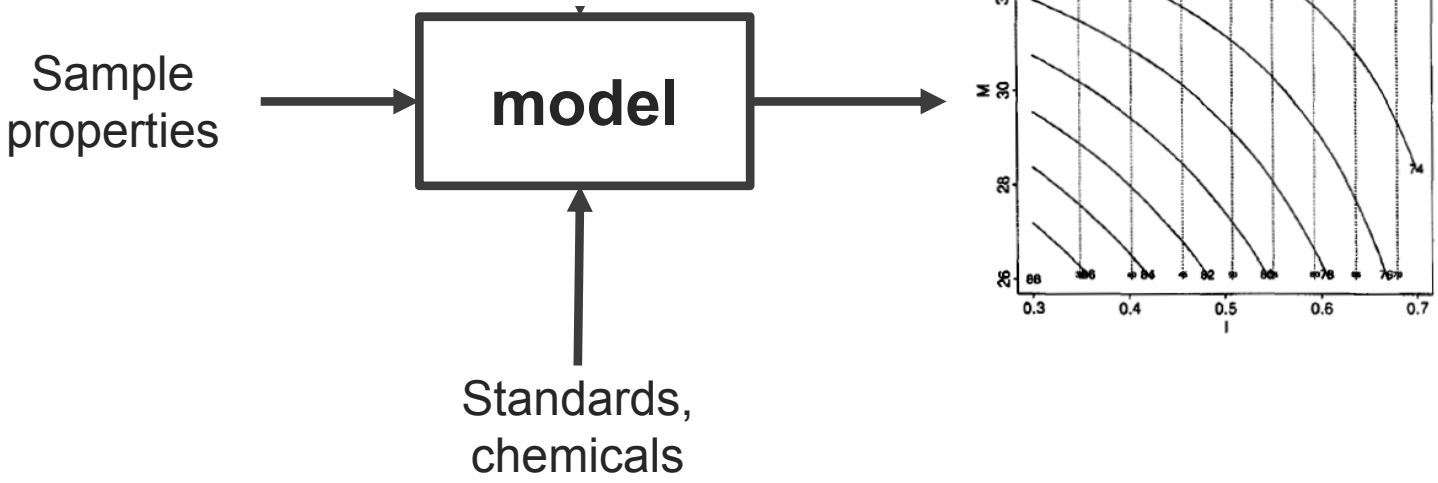
Adapted from: E. Tomba et al., Int J Pharm 457 (2013) 283-297



Product property prediction

Use of direct model:
vary according to a plan and model quality

Run	C	I	M	P	Y
1	1	−1	−1	−1	76
2	1	−1	−1	1	75
3	1	−1	1	−1	70
4	1	−1	1	1	71
5	1	1	−1	−1	69
6	1	1	−1	1	69
7	1	1	1	−1	65
8	1	1	1	1	67
9	−1	−1	−1	−1	89
10	−1	−1	−1	1	88
11	−1	−1	1	−1	82
12	−1	−1	1	1	83
13	−1	1	−1	−1	85
14	−1	1	−1	1	84
15	−1	1	1	−1	81
16	−1	1	1	1	82

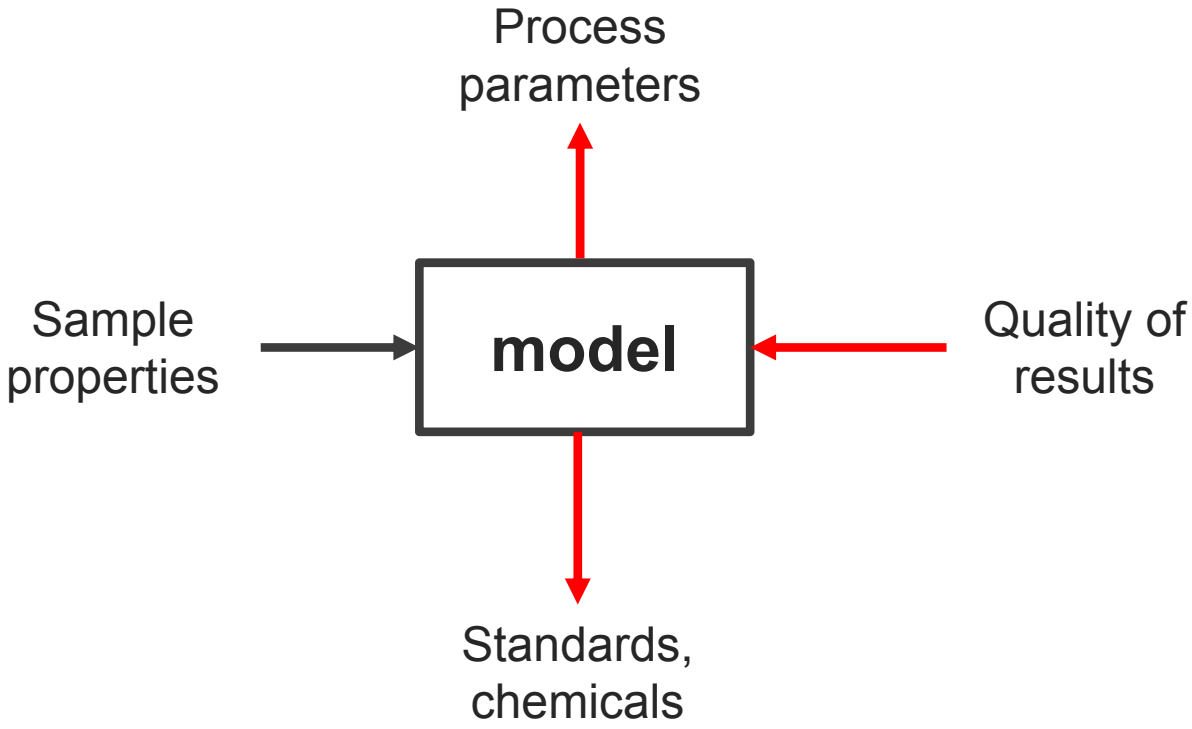


Product property prediction (both trueness and precision)

Y.L. Grize, J. Chemom. 9 (1995) 239-262

Model inversion for quality by design

Adapted from: E. Tomba et al., Int J Pharm 457 (2013) 283-297

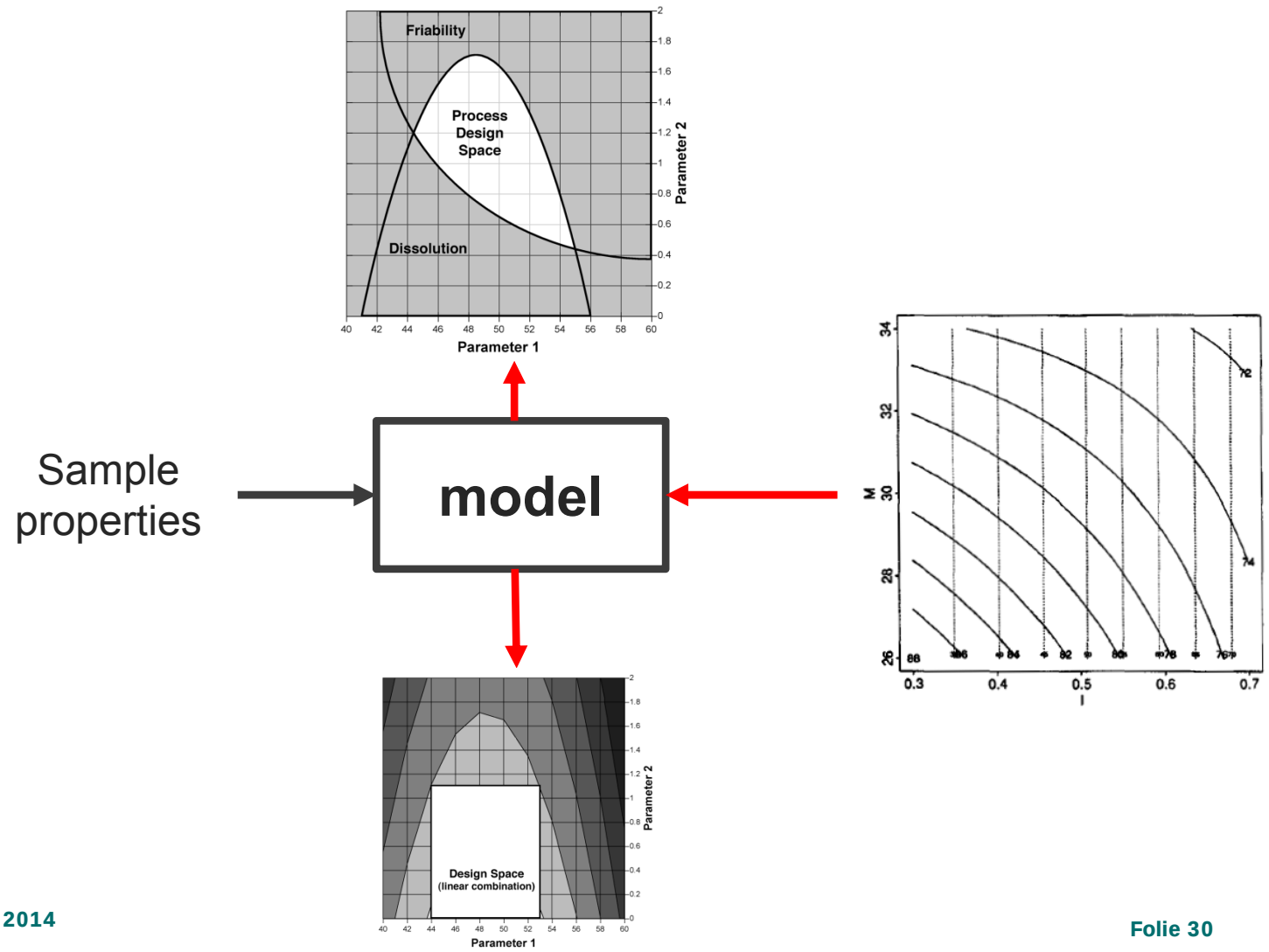


Product and process design
(trueness, precision and ruggedness)

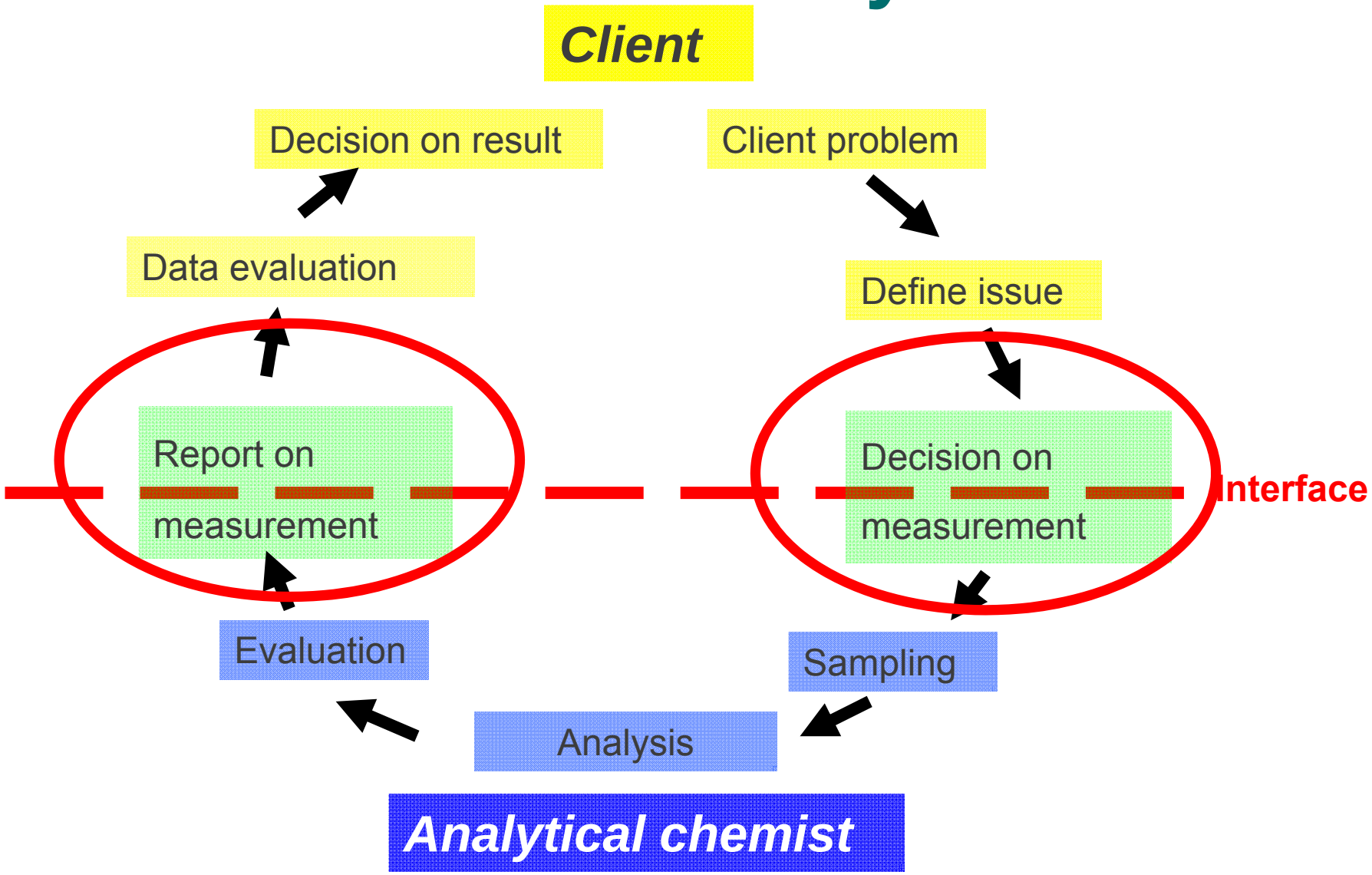
Model inversion for quality by design

define appropriate design space

ICH Guideline, Pharm. Developm. Q8(R2), 2009



Measurement Cycle



Conclusions

- Interface between client and analyst is critical
- No good way to decide on k
- Reduction of u is the more rational choice
- Systematics of reduction of u
  - Systems design
  - Parameter design
  - Tolerance design
- Match up with risk

Thank you for your interest