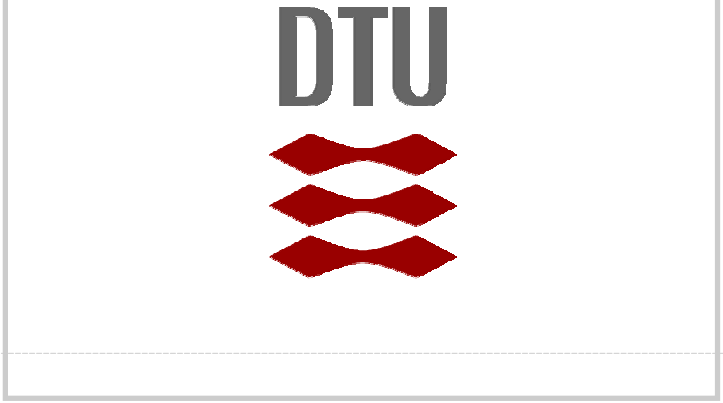


The uncertainty budget in pharmaceutical industry

Kaj Heydorn
Department of Chemistry

Definition of Uncertainty

Parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand

VIM/GUM

Uncertainty budget

Definition

List of sources of uncertainty and their associated standard uncertainties, compiled with a view to evaluating a combined standard uncertainty associated with a measurement result

ISO/TS 21748:2004(E)

Measurements in the pharmaceutical industry I

serve to ascertain

The Quality of a product

The Control of a process

Measurements in the pharmaceutical industry II

serve to demonstrate

- Compliance with specifications
- Conformity with regulations
- Potency of the product

Measurements in the pharmaceutical industry III

should fulfil requirements in

- Pharmacopoeias
  ICH Guidelines
- ISO-10576
- GUM

European Pharmacopoeia

Specified limits take into account:

Acceptable variations in production
Normal analytical errors
in validated procedures
Acceptable deterioration of reference substances and other materials

Therefore: Compliance testing
needs no further tolerances
needs no statement of uncertainty

ICH Guidelines

Q2A: Validation of analytical procedures
to ascertain reproducible product quality
maintain control of stability

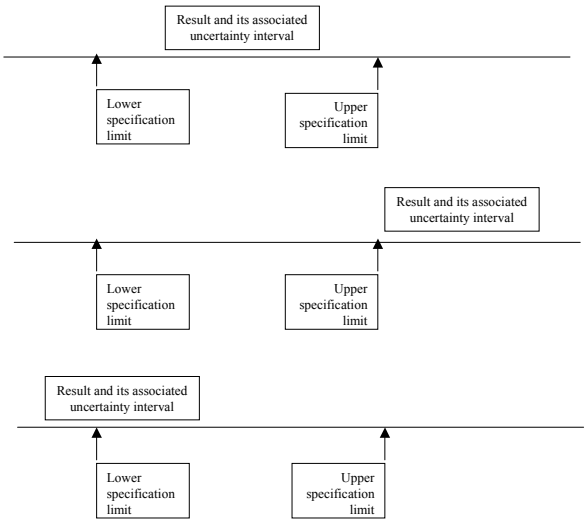
Q2B: Terminology and Methodology
validation characteristics
adequate reference materials

Legal or global regulations

Specified limits do not take into account:
Differences in analytical methods
Variations in performance
Deterioration of reference
substances and other materials

Therefore: Conformity testing
needs bias correction
and statement of uncertainty

Conformity testing according to ISO 10576



Definition of the Measurand

"Quantity intended to be measured"

VIM 3 (2004)

Equivalent terms

ICH/OMCL	ISO GUM/VIM
• Parameter	• Measurand
• Accuracy	• Trueness
• Intra-assay precision	• Repeatability
• Uncertainty	• Reproducibility
• No exact equivalent	• Uncertainty
• Typical variations	• Uncertainty components
• Assay	• Determination of a major component

Determination of a parameter

TESTING	MEASUREMENT
• Test result in arbitrary units	• Analytical result in SI-units
• method dependent	• method independent
• accepted method	• traceability
• reproducibility	• uncertainty

Requirements for accreditation

Test reports shall include

where applicable, a statement on the estimated uncertainty of measurement

ISO/IEC 17025:1999

Uncertainty Budgets Why?

1) Applicable to non-routine analysis
2) Adapts readily to modifications
3) Points out major sources of variability
4) Permits adaptation to analytical needs
5) Offers elimination of unnecessary effort

Uncertainty Budgets How?

- 1: *Specify measurand*
- *2: Identify uncertainty sources*
- *3: Quantify uncertainty components*
- *4: Calculate combined uncertainty*

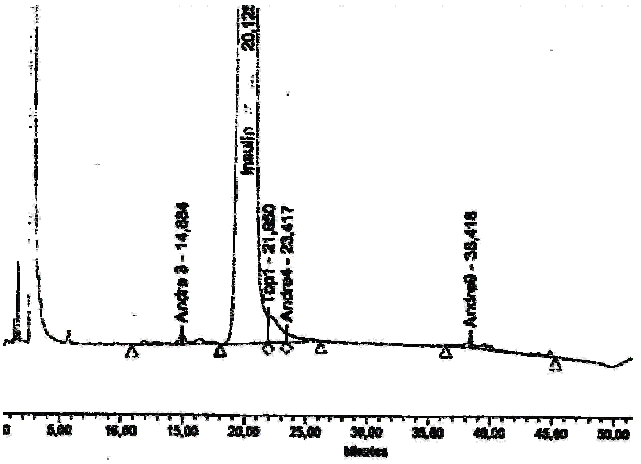
1 The measurand

$$y = f(x_1, x_2, x_3 \ldots\ldots\ldots\ldots x_N)$$

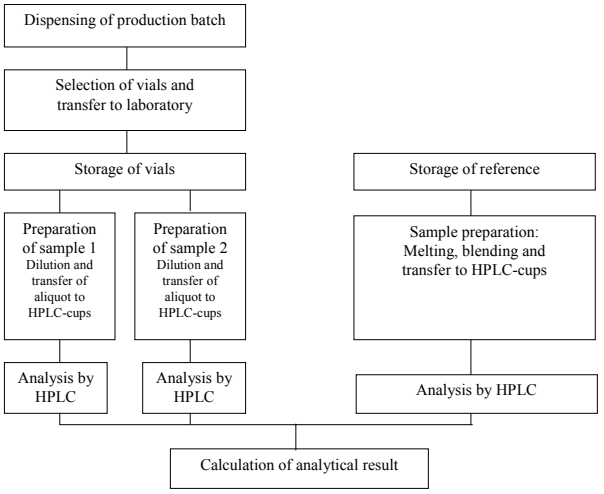
$$u_c^2(y) = \sum_1^N \left(\frac{\partial f}{\partial x_i} \right)^2 u^2(x_i)$$

Human Insulin Penfill®

HPLC chromatogram of protein reference



Flow chart for the determination of batch protein concentration



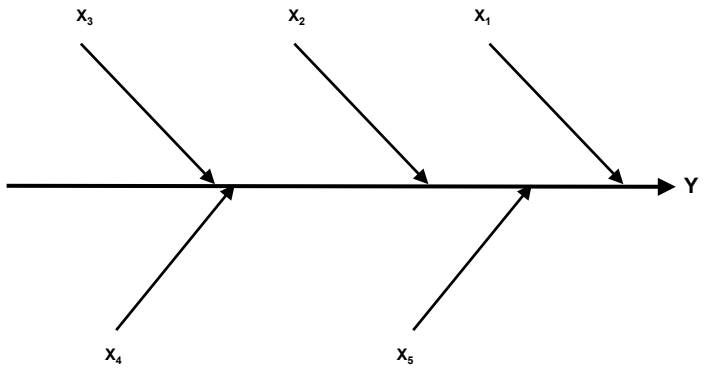
Calculation of the measurand

$$C = \frac{A_1 F_1 + A_2 F_2}{2 A_{ref}} C_{ref}$$

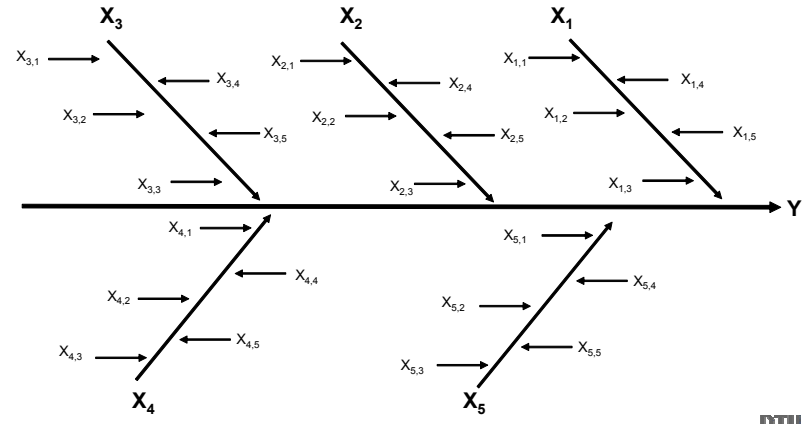
2 Uncertainty sources

- Parameters in the model function
- Environmental and other parameters
- Measurement procedure *r* and R
- Sample or specimen effects
- Calibration and traceability
- Sampling process

Cause and Effect diagrams ad modum Ishikawa



Ishikawa Diagram



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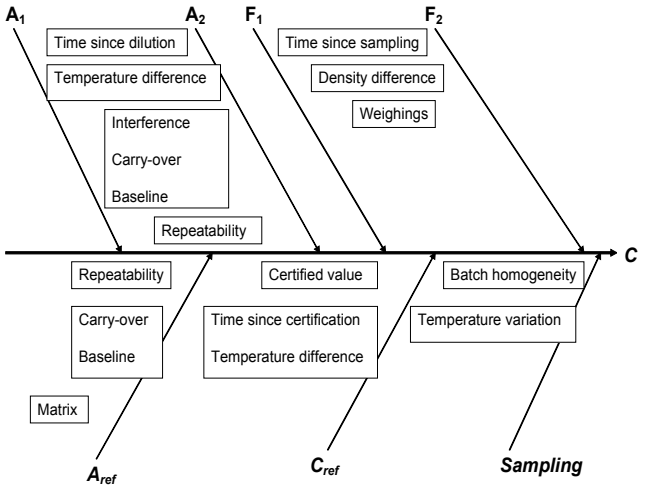
Cause-effect diagram for HPLC-assay



3 Quantifying uncertainty

- Validation data
- Historical data
- Planned experiments
- Experience
- Specifications
- A priori knowledge

The GUM estimation of uncertainty

- Category A

  Uncertainty components, whose contribution is estimated by statistical methods

- Category B

  Uncertainty components, whose contribution is evaluated by any other method

Evaluation of uncertainty components

- Type A
  - Repeatability
  - Homogeneity
  - Interference
  - Calibration
- Type B
  - Base-line
  - Carry-over
  - Dilution factor
  - Traceability

Certified Reference Material VIM 1993

- A Reference Material, accompanied by a certificate
- establishing traceability to a realization of the units of the property values
- each certified value accompanied by a statement of its uncertainty

Ph.Eur.
Chemical Reference Substance

- Widely acknowledged as having appropriate qualities
- Value accepted without reliance on comparison to another chemical substance
- Uncertainty is assumed to be negligible
- Value is established for a specific method
- No certificate - report is confidential

Primary Reference Material
Novo PRM

- Certificate issued by NovoNordisk
- No traceability to SI units
- Fulfils specifications with respect to
  - Homogeneity
  - Content according to specified method
  - Comparison within ±2 %
  - Specified impurities below upper limits

4 Combined uncertainty

- Sensitivity coefficients

$$u_c^2(y) = \sum_1^N \left(\frac{\partial f}{\partial x_i} \right) u^2(x_i)$$

- Expanded uncertainty

$$U(y) = k \cdot u(y)$$

Values and uncertainties for the calculation of u(C)

Parameter	Description	Value	Unit	Uncertainty component	Standard uncertainty	Degrees of freedom
A_1	Peak area	100	Abs*min	Analysis	0.58	11
A_2	Peak area	100	Abs*min	Analysis	0.58	11
F_1	Dilution factor	4	1	Dilution	0.003	∞
F_2	Dilution factor	4	1	Dilution	0.003	∞
A_{ref}	Calibration	100	mg	Repeatability	0.26	21
C_{ref}	Reference	600	µmol/L	Calibration	1.7	35
δ_{batch}	Batch homogeneity	0	µmol/L	Sampling	8.4	27

Homogeneity contribution

$$C = \frac{A_1 F_1 + A_2 F_2}{2A_{ref}} C_{ref} + \delta$$

Intra-batch heterogeneity contribution $\delta = 0$

Evaluation of Sensitivity coefficients

- Differentiation of the Model function
- Kragten's Method
- Designed experiment
- Theoretical considerations

Kragten's method

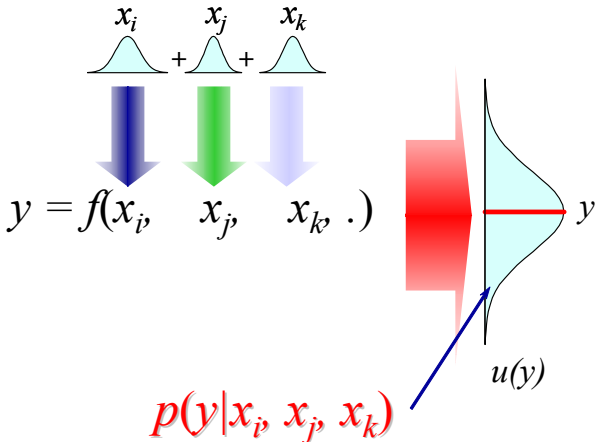
for combined standard uncertainty

$$\frac{\partial y}{\partial x_i} = \frac{f(...x_i...) - f(...(x_i - \Delta x_i)...)}{\Delta x_i} \quad \text{for} \quad \Delta x_i \to 0$$

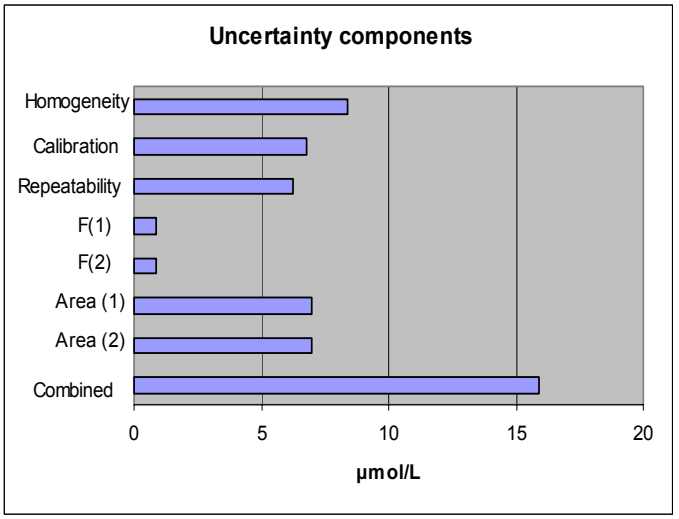
If $u(x_i) << x_i$ or $f(...x_i...)$ is linear in x_i

$$u(y, x_i) \approx f(...x_i...) - f(...(x_i - u(x_i))...)$$

Propagation of uncertainty



Contributions to the combined uncertainty



Reporting analytical results

The result of a measurement shall include

- Definition of the measurand
- Reported value of the measurand
- ± its expanded uncertainty
- The coverage factor used

Uncertainty

A result without a statement of uncertainty is useless - because

No conclusions can be made from it

Uncertainty

A result with an incorrect statement of uncertainty is dangerous - because

Wrong conclusions can be made from it

Verification of the uncertainty budget

χ^2-distribution with v degrees of freedom

$$T = \sum_{j=1}^{j=m} \frac{(y_{1j} - y_{2j})^2}{u(y_{1j})^2 + u(y_{2j})^2}$$

$$v = m$$

Evolution - no revolution in the pharmaceutical industry

Uncertainty budgets will be used

1) starting with statutory requirements
2) followed by critical process parameters
3) and environmental conditions

Conclusion

The uncertainty budget is

- a necessity in the age of globalization
  but it is also
- a tool to optimize and reduce the cost of
  chemical analysis

Thank you
for your attention

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