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 should fulfil requirements in

- Pharmacopoeias
- ICH Guidelines
- ISO-10576
- GUM

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

<table>
<thead>
<tr>
<th>ICH/OMCL</th>
<th>ISO GUM/VIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Measurand</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Trueness</td>
</tr>
<tr>
<td>Intra-assay precision</td>
<td>Repeatability</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Reproducibility</td>
</tr>
<tr>
<td><strong>No exact equivalent</strong></td>
<td>Uncertainty components</td>
</tr>
<tr>
<td>Typical variations</td>
<td>Determination of a major component</td>
</tr>
</tbody>
</table>

### Determination of a parameter

**TESTING**
- Test result in arbitrary units
- method dependent
- accepted method
- reproducibility

**MEASUREMENT**
- Analytical result in SI-units
- method independent
- traceability
- 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

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

\[ u_c^2(y) = \sum_{i=1}^{N} \left( \frac{\partial f}{\partial x_i} \right)^2 u^2(x_i) \]
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
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
  \[ u_c^2(y) = \sum_{i=1}^{N} \left( \frac{\partial f}{\partial x_i} \right) u^2(x_i) \]
- Expanded uncertainty
  \[ U(y) = k \cdot u(y) \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Uncertainty component</th>
<th>Standard uncertainty</th>
<th>Degrees of freedom</th>
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<tbody>
<tr>
<td>A_1</td>
<td>Peak area</td>
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<td>Abs*min</td>
<td>Analysis</td>
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<td>11</td>
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<tr>
<td>A_2</td>
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<td>Abs*min</td>
<td>Analysis</td>
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<td>11</td>
</tr>
<tr>
<td>F_1</td>
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<td>Dilution</td>
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<td>1</td>
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<tr>
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<td>1</td>
<td>Dilution</td>
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<td>( \infty )</td>
</tr>
<tr>
<td>( \lambda_{\text{ref}} )</td>
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<tr>
<td>( C_{\text{ref}} )</td>
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<td>( \mu \text{mol/L} )</td>
<td>Calibration</td>
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<tr>
<td>( \delta_{\text{batch}} )</td>
<td>Batch homogeneity</td>
<td>0</td>
<td>( \mu \text{mol/L} )</td>
<td>Sampling</td>
<td>8.4</td>
<td>27</td>
</tr>
</tbody>
</table>
Homogeneity contribution

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

*Intra-batch heterogeneity contribution* \( \delta = 0 \)

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**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 \( u(x_i) \ll x_i \) 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

\[
y = f(x_p, x_j, x_k, \ldots)
\]

\[
p(y|x_p, x_j, x_k)
\]
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

A result with an incorrect statement of uncertainty is dangerous - because
Wrong conclusions can be made from it
Verification of the uncertainty budget

$\chi^2$-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