Setting the requirements for a method (including aspects of MU)
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For a validation study we need to have several requirements...

- Target uncertainty
- Measurand
- Robustness

Focus on these 3 performance characteristics

- Sample types
- Measurement range
- Precision
- Trueness (bias)
With clear and distinct requirements on an analytical method we can assess fitness for purpose.
The whole method validation process

“from the customer problem
to the laboratory decision
on whether or not the customer request
can be carried out with an identified method”

Text cited From Eurachem Guide Fitness for purpose of analytical methods, page 17
Requirements
Step 1 in the method validation process

Transferring the client issue
into analytical requirement
that can be used
in the validation study

Analytical requirements

Specify the analytical requirement on
performance characteristics such as:

- Measurement range
- Precision
- Trueness
- Measurement uncertainty
### Chapter 6.3 Working range - method

Instrument calibrated according to method/procedure.

![Graph](image)

- Working range
-Measured concentration
- Concentration in test sample

### Chapter 6.3 Working range - instrument

- Working range
- Linear range
- LOD
- LOQ
- Analytical sensitivity

![Graph](image)

- Signal from instrument
- Concentration in standards used for calibration
Analytical requirements

Specify the analytical requirement on performance characteristics such as:

- Measurement range
- Precision
- Trueness
- Measurement uncertainty

Precision

Increasing standard deviation

- Same prepared sample
- Instrument repeatability
- Repeatability
- Intermediate precision within-lab reproducibility
- Reproducibility

- Within laboratory
- Between laboratories
Analytical requirements

Specify the analytical requirement on performance characteristics such as:

- Measurement range
- Precision
- Trueness
  - Specify max bias
- Measurement uncertainty

Analytical requirements

Specify the analytical requirement on performance characteristics such as:

- Measurement range
- Precision
- Trueness
- Measurement uncertainty
  - Set target uncertainty
  - For validation – translate to precision and trueness
Requirements when comparing

When comparing 2 results using the same method precision limits can be used

- Same lab – same day
  - Repeatability limit
- Same lab – different days
  - Withinlab reproducibility limit
- Different labs
  - Maybe Reproducibility limit

Precision limits

Precision limit

In 19 cases out of 20 the difference between 2 results will be less than...

e.g. the repeatability limit, \( r \)

\[
\begin{align*}
r &= k \sqrt{s_r^2 + s_r^2} = 2 \sqrt{2s_r^2} = 2\sqrt{2}s_r \\
s_r &= \frac{r}{2.8}
\end{align*}
\]


Process control

- Is the process under control?
- Demand on $s_{Rw}$ at the level of interest

NOTE – to process from lab, communicate
95 % confidence interval i.e. $4 s_{Rw}$

Process control

Fluid cracking catalyst poisoned by nickel in crude oil

Nickel mg/kg

Time

1-Feb 22-Mar 10-May 28-Jun

17
Specification

MSA – Measurement System Analysis – often physical measurement e.g. length
- Bias ≈ 0
- Acceptable $s_{RW} < 5\%$ of specification
- Good $s_{RW} < 1,7\%$ of specification

SPC – Statistical process control – Capability index, $C_p$
- Acceptable $s_{process} < 10\%$ of specification
- Acceptable $s_{RW} < ?$

Legal limits & EU directives

At a given concentration level (parametric value) the performance characteristics for the method to be used are specified:
- Bias < 10\%
- Within-lab reproducibility, 2 $s_{RW} < 10\%$
- LOD < 10\%
Legal limits & EU directives

At a given concentration level (environmental quality standard) the performance characteristics for the method to be used are specified:
- Measurement Uncertainty, $U < 50\%$
- LOQ < 30\%

Legal limits – Danish law

Requirements environmental measurements 2011*
Performance characteristics $s_{Rw}$ CV$_{Rw}$ LOD U$_{abs}$ U$_{rel}$

Example Ground water

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>$s_{Rw}$</th>
<th>CV$_{Rw}$</th>
<th>LOD</th>
<th>U$_{abs}$</th>
<th>U$_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel</td>
<td>µg L</td>
<td>0.08</td>
<td>3%</td>
<td>0.03</td>
<td>0.1</td>
<td>20%</td>
</tr>
<tr>
<td>Copper</td>
<td>µg L</td>
<td>0.03</td>
<td>3%</td>
<td>0.03</td>
<td>0.1</td>
<td>20%</td>
</tr>
<tr>
<td>Selenium</td>
<td>µg L</td>
<td>3</td>
<td>1%</td>
<td>0.05</td>
<td>0.1</td>
<td>20%</td>
</tr>
<tr>
<td>Vanadium</td>
<td>µg L</td>
<td>0.2</td>
<td>2%</td>
<td>0.2</td>
<td>0.3</td>
<td>50%</td>
</tr>
<tr>
<td>Zinc</td>
<td>µg L</td>
<td>0.3</td>
<td>5%</td>
<td>0.3</td>
<td>0.5</td>
<td>20%</td>
</tr>
</tbody>
</table>

Shellfish

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Unit</th>
<th>LOD</th>
<th>CV</th>
<th>U$_{abs}$</th>
<th>U$_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDV pp-</td>
<td>µg kg PV</td>
<td>0.2</td>
<td>20%</td>
<td>0.05</td>
<td>50%</td>
</tr>
<tr>
<td>DDE pp-</td>
<td>µg kg PV</td>
<td>0.2</td>
<td>20%</td>
<td>0.05</td>
<td>50%</td>
</tr>
</tbody>
</table>

*www.retsinformation.dk/pdfPrint.aspx?id=174970
Legal limits - Blood alcohol

- **Measurand including** Concentration of EtOH in a blood sample delivered to the laboratory

- Upper limit 0,200 mg/g

- A decision limit 0,220 mg/g

*Target U calculated to be *0.026 mg/g

*The concentration above which it can be decided with a statistical certainty of 99.9 % that the permitted limit has been truly exceeded.

Translate requirements

- $u_{Rw}$ Reproducibility within laboratory
- $u(bias)$ Bias
- $u$ Measurement Uncertainty
Translate requirements
From LOQ & U to $s_{RW}$

The Trollbook – Nordtest Tr 565 proposes
- Example 2 - LOQ
  - Acceptable within-lab reproducibility
    $s_{RW} < \text{LOQ}/10$

Example 1 – Measurement uncertainty
- Acceptable within-lab reproducibility
  $s_{RW} < U/4$

Setting requirements
– target uncertainty
- Many more examples are given in our EURACHEM/CITAC guide
For a validation study we need to have several requirements...

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- Robustness
- Sample types
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- Trueness (bias)

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Thank you for your attention!