Planning method validation studies

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Overview

- Importance of planning
- Content of a validation plan
- Experimental designs
- Eurachem guidance
Importance of planning

• Method validation is a potentially complex activity
  – Can generate a significant amount of data

• Many decisions to be made
  – Which performance characteristics are important, which materials should be analysed, how many replicates are needed, how should the data be processed, how is ‘fitness-for-purpose’ assessed…

• To ensure the validation study is ‘fit-for-purpose’ all of these issues should be addressed before starting work

• Using a planning template
  – Allows a consistent approach
  – Validation plan can easily be converted to a validation report
Content of a validation plan

- Method to be validated
- Status of method and purpose of validation study
- Analytical requirement
- Performance characteristics
- Performance targets
- Summary
- Approval
Content of a validation plan

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Method to be validated – setting the scene

Method Title

The determination of A {analyte or measurand} in the presence of B {interference} in C {sample type/matrix} using D {principle}

Include method reference number if applicable

A: What quantity is being measured?
B: Are there any known interferences that can be accommodated by the method?
C: What sample types/matrices will be analysed using the method?
D: What measurement technique/measuring instrument will be used?

Method status

Is the method, e.g. a published standard method (unmodified), based on a published standard method (with modification), a method developed in-house?

Purpose of the study

Outline the purpose of the study, e.g. to validate a new in-house method, to verify the performance of a published standard method, to validate the extension of the scope of the method.

- Validation should start with a documented method
- Method title
- Status of method
  - Standard method (unmodified)
  - Modified standard/published method
  - In-house method
- Purpose of study
  - Full validation
  - Verification
Purpose of validation study

• Why is the validation study being undertaken?
  – Full validation of a method developed in-house
  – Verification of implementation of a published method for which data on performance characteristics are available
  – Validation of change of scope of a method
  – Re-valuation following change in operating conditions
  – Re-valuation after period of non-use
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Analytical Requirement (1)

- **Analyte**
  - Specify the analyte(s) (e.g. copper, creatinine, hexavalent chromium)

- **Measurand**
  - Quantity intended to be measured
    - Total concentration, amount extracted under specified conditions?
    - Measurement units
    - Required range (e.g. expected concentration range in samples)
Analytical Requirement (2)

• Matrix and form
  – Sample matrix/matrices, physical form

• Purpose of measurement
  – Why are the measurements required?
    • Check compliance with a regulation
    • Monitoring a production process
    • R&D project

<table>
<thead>
<tr>
<th>Analytical requirement</th>
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</thead>
<tbody>
<tr>
<td><strong>Analyte</strong></td>
</tr>
<tr>
<td><strong>Measurand</strong></td>
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<td></td>
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<tr>
<td><strong>Matrix and form</strong></td>
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<tr>
<td><strong>Purpose of measurement</strong></td>
</tr>
</tbody>
</table>
Content of a validation plan

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Which performance characteristics need to be evaluated?

<table>
<thead>
<tr>
<th>Performance characteristic</th>
<th>Type of analytical application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Identification</td>
</tr>
<tr>
<td>Selectivity</td>
<td>✔</td>
</tr>
<tr>
<td>Limit of detection</td>
<td></td>
</tr>
<tr>
<td>Limit of quantitation</td>
<td></td>
</tr>
<tr>
<td>Working range/linearity</td>
<td></td>
</tr>
<tr>
<td>Trueness (Bias)</td>
<td></td>
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<tr>
<td>Precision</td>
<td></td>
</tr>
</tbody>
</table>
Plan for each performance parameter

Specify:

• The performance criteria
• The experiments required
  – Materials to be analysed
  – Number and order of measurements

• Data analysis
  – Appropriate statistics tools
    • Significance tests, analysis of variance, regression

• Assessment of ‘fitness-for-purpose’
  – ‘Rules’ for determining whether performance targets have been met
Experimental designs

• Choosing a suitable experimental design is a key step
  – Maximise the information obtained from an experiment
• May be possible to obtain information on more than one performance characteristic
• Common designs
  – Simple replication
  – Nested
  – Fractional factorial
  – Linear calibration
Simple replication

• Repeated measurements on a single material
• Useful for precision studies
  – Especially repeatability
• Can also be used for evaluating bias
  – If a reference value is available (e.g. material is a CRM)

\[ s = \sqrt{\frac{\sum (x_i - \bar{x})^2}{n-1}} \]
Nested design

- Each level of a given factor appears in only a single level of any other factor

- Useful for precision studies
  - Replicate measurements obtained in a short period of time are ‘nested’ within days or analytical runs
  - Repeatability and intermediate precision can be evaluated

- Analysed using one-way analysis of variance (ANOVA)

\[
s_{\text{within}} = \sqrt{MS_W} \quad \quad s_{\text{between}} = \sqrt{\frac{MS_B - MS_W}{n}}
\]
Fractional factorial designs

- Factorial design* where carefully chosen combinations of levels have been removed
- Seven factor ‘Plackett-Burman’ design
  - Used in ruggedness studies

*Factorial designs allow the study of multiple parameters at two or more levels. A full factorial design is one in which all combinations of levels are studied.

<table>
<thead>
<tr>
<th>Experimental parameter</th>
<th>Experiment number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>A or a</td>
<td>A</td>
</tr>
<tr>
<td>B or b</td>
<td>B</td>
</tr>
<tr>
<td>C or c</td>
<td>C</td>
</tr>
<tr>
<td>D or d</td>
<td>D</td>
</tr>
<tr>
<td>E or e</td>
<td>E</td>
</tr>
<tr>
<td>F or f</td>
<td>F</td>
</tr>
<tr>
<td>G or g</td>
<td>G</td>
</tr>
<tr>
<td>Observed result</td>
<td>s</td>
</tr>
</tbody>
</table>
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Performance targets

• Performance targets need to be established to assess fitness-for-purpose of the method

• Target values can be:
  – Defined in standards/regulations
  – Specified by the customer
  – Stated in a standard published method (can you match the stated performance?)
  – Based on performance of similar procedures that are known to be fit-for-purpose
  – Defined as the current state-of-the-art (what is the method capable of)?
Content of a validation plan

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Summary and approval

• Validation plan should be approved
• After study is complete
  – Provide a summary of values and other information obtained for each performance characteristic
  – Final statement on whether the aims of the study have been met and whether method is fit-for-purpose
  – Final sign-off of the validation report
Eurachem guidance

• Available from www.eurachem.org
• The Fitness for Purpose of Analytical Methods
• Supplement: Planning and Reporting Method Validation Studies
Summary

• Validation should be a planned and documented activity
• For each performance characteristic specify
  – Materials, number of measurements, order, data analysis, performance criteria
• Planning template recommended
  – Consistent approach
  – Easily converted to a validation report
• Both plan and final report should be signed off
Any questions?