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

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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-validation following change in operating conditions
  - Re-validation 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	
Analyte	Specify the analyte(s) (e.g. copper, creatinine, hexavalent chromium).
Measurand	State the measurand (the quantity intended to be measured). E.g. is it the 'total' concentration of the analyte(s) present that is of interest, the 'amount extracted' under specified conditions, or the result obtained from a specified (standard) measurement procedure? State the units in which the measurement results will be reported. State required range (e.g. concentration range in samples).
Matrix and form	State the matrix/matrices of the samples and their physical form.
Purpose of measurement	Specify why the measurements are required (e.g. to check compliance with a particular regulation or a manufacturing specification).

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

Analytical requirement	
Analyte	Specify the analyte(s) (e.g. copper, creatinine, hexavalent chromium).
Measurand	State the measurand (the quantity intended to be measured). E.g. is it the 'total' concentration of the analyte(s) present that is of interest, the 'amount extracted' under specified conditions, or the result obtained from a specified (standard) measurement procedure? State the units in which the measurement results will be reported. State required range (e.g. concentration range in samples).
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Which performance characteristics need to be evaluated?

Performance characteristic	Type of analytical application			
	Identification	Quantitative test for impurity	Limit test for impurity	Quantification of main component
Selectivity	✓	✓	✓	✓
Limit of detection			✓	
Limit of quantitation		✓		
Working range/linearity		✓		✓
Trueness (Bias)		✓		✓
Precision		✓		✓

Plan for each performance parameter

Performance characteristic	
Description:	

Performance criteria	
Experiments	
Evaluation of data	

Notes	
Conclusions	

Specify:

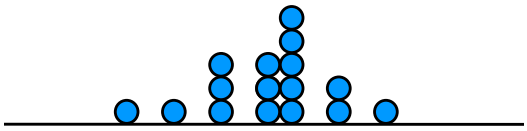
- The performance criteria
- The experiments required
  - Materials to be analysed
  - Number and order of measurements
- Data analysis
  - Appropriate statistics tools
    - Significance tests, analysis of variance, regression
- Assessment of 'fitness-for-purpose'
  - 'Rules' for determining whether 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

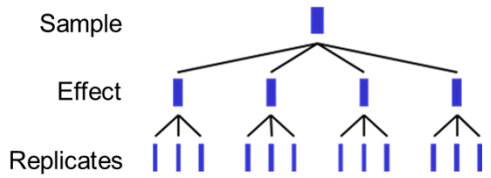
- Repeated measurements on a single material
- Useful for precision studies
  - Especially repeatability
- Can also be used for evaluating bias
  - If a reference value is available (e.g. material is a CRM)



$$s = \sqrt{\frac{\sum (x_i - \bar{x})^2}{n-1}}$$

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)



Source of variation	SS	df	MS
Between groups	…	…	MS_B
Within groups	…	…	MS_W
Total	…	…	…

$$s_{within} = \sqrt{MS_W}$$

$$s_{between} = \sqrt{\frac{MS_B - MS_W}{n}}$$

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.

Experimental parameter	Experiment number							
	1	2	3	4	5	6	7	8
A or a	A	A	A	A	a	a	a	a
B or b	B	B	b	b	B	B	b	b
C or c	C	c	C	c	C	c	C	c
D or d	D	D	d	d	d	d	D	D
E or e	E	e	E	e	e	E	e	E
F or f	F	f	f	F	F	f	f	F
G or g	G	g	g	G	g	G	G	g
Observed result	s	t	u	v	w	x	y	z

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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)?

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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?