Cross and Partial Validation

Presenter: Rachel Green
on behalf of EBF

Focus Workshop

(*In collaboration with the AAPS and JBF*)

Industry input into ICH M10: Experimental data as the cornerstone for a science driven bioanalytical guideline

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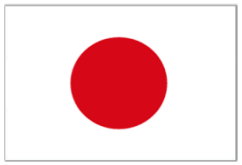
Current Guidelines - Partial Validation






EMA 2011	FDA draft 2013	MHLW 2013	ANVISA 2012
When minor changes are made to an already validated method. Gives some examples of when partial validation may be needed.	When minor changes are made to an already validated method. Gives some examples of when partial validation may be needed.	When minor changes are made to an already validated method. Gives some examples of when partial validation may be needed. Acceptance criteria same as full validation.	Whenever changes occur in a method, full validation or partial validation should be performed, according to the relevance of the modification.

Current Guidelines - Cross Validation

EMA	FDA draft	MHLW	ANVISA
Different methods within and across studies; and different laboratories (same method) within a study. QCs within 15% accuracy; incurred 67% within 20% of mean.	Different methods within and across studies; and different laboratories (same method) within a study. When data generated using different analytical techniques (e.g., LC-MS/MS vs ELISA) in different studies are included in a regulatory submission. Both spiked QCs and incurred samples should be used for inter-laboratory comparisons within a study.	When data are generated in multiple laboratories within a study or when comparing analytical methods used in different studies, after a full or partial validation. Spiked QCs or study samples can be used. Inter-lab, within-study: QCs 3-3-20, incurred 67% within 20% of mean.	Not covered.

Problem statement

Where do we lack clarity/detail?

- Which method parameters to assess during partial validation?
- Considerations for method transfers?
- Use of the term cross validation?
- When to conduct cross validations?
- Design of cross validations – spiked QCs and/or incurred? Acceptance criteria?

Recommendations relate to studies within the scope of ICH M10

Definitions – when, why & how?

Partial Validation

- When a modification is made to an already validated method
- To ensure method performance is not adversely affected by the modification
- Parameters to assess depend upon the nature of the change

Some proposals from TT-53
(chromatographic assays)

Method modification	Extent of partial validation
Change in animal strain Change in anti-coagulant counter-ion Truncated calibration range	None
Change in injection volume Minor change to mobile phase (adjust % organic) Change in MS instrument (same model) Minor change in MS parameters (re-optimisation)	System Suitability Test only
Change in sample volume Change in extraction volumes Change to chromatography conditions Change in MS instrument model Significant change in MS parameters	Intra-run precision & accuracy, selectivity, matrix effect

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Proposals for ligand binding assays

Method modification	Extent of partial validation
Change in animal strain Change in anti-coagulant counter-ion Truncated calibration range	None
Change critical reagents Minor or major change – refer to critical reagent session tomorrow	Precision & Accuracy Or New validation
Change in selectivity Change in disease-state matrix Change to rare matrix Check for interference of co-medication	Intra-run precision & accuracy, selectivity

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Method transfers

- (Almost) full validation for external transfers. Exclude long term stability in frozen matrix if already demonstrated.
- Partial validation for internal transfers. Extent will depend upon closeness of operating processes.

- May be followed by cross validation if necessary

Definition – when, why & how?

Cross Validation

- When data from different methods, or the same method in two different laboratories are used in the same study
- When data from different methods are used in PK modelling across studies and any differences could have a material impact on conclusions drawn
- To determine whether data derived from different sources are comparable
- *Spiked QCs and/or incurred? Number of samples? Acceptance criteria?*

Cross Validation - recommendations

- Perform cross-validation when different laboratories or methods are used within a study
- Cross validations are often being performed when different laboratories (same method) are used across a programme of studies. There is no regulatory requirement to do this.
- Perform cross-validation across studies when different methods are used. *Question* - what constitutes a different 'method'? Comparison of LBA vs LC-MS data is useful scientifically.

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Cross Validation

- Spiked QCs alone are sufficient when comparing the same method in different laboratories. But consider e.g. labile metabolites, use of analogue IS
- Suggest it is beneficial to use incurred samples when comparing different method/technology. However use of incurred samples may be restricted to within the study due to informed consent issues.

- Recommend apply 3-6-15/20 acceptance criteria for spiked QCs
- Recommend incurred samples should be individual, not pooled. Use 20-40 study samples. Apply ISR acceptance criteria; 67% within 20/30% of mean

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Summary

- More detailed guidance on which parameters to assess during Partial Validation would be welcomed by industry
- Cross validate
  - when different methods or labs are used within a study
  - when different technologies are used across studies
- Use incurred samples (where possible) when there could be differences in selectivity/recovery between the methods
- 3 QC levels, 6 replicates, 15/20% accuracy for spiked QCs; 67% of samples within 20/30% for incurred samples (n=20-40)

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Contact: info@europeanbioanalysisforum.eu