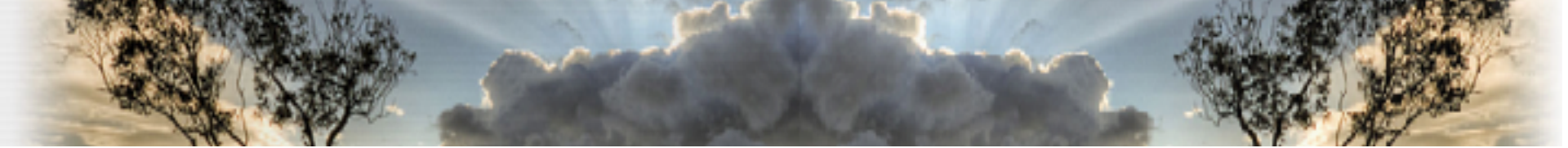

Crossvalidations

Tom Verhaeghe, on behalf of EBF

From the ICH M10 draft Guidance

6.2 Cross Validation

Cross validation is required to compare data under the following situations:

- Data are obtained from different fully validated methods within a study
- Data are obtained from different fully validated methods across studies that are going to be combined or compared to support special dosing regimens, or regulatory decisions regarding safety, efficacy and labelling.
- Data are obtained within a study from different laboratories with the same bioanalytical method.

Cross validation is not generally required to compare data obtained across studies from different laboratories using the same validated method at each site.

Cross validation should be performed in advance of study samples being analysed, if possible.

Cross validation should be assessed by measuring the same set of QCs (low, medium and high) in triplicate and study samples that span the study sample concentration range (if available n≥30) with both assays or in both laboratories.

Bias can be assessed by Bland-Altman plots or Deming regression. Other methods appropriate for assessing agreement between two assays (e.g., concordance correlation coefficient) may be used too. Alternatively, the concentration vs. time curves for incurred samples could be plotted for samples analysed by each method to assess bias. If disproportionate bias is observed between methods, the impact on the clinical data interpretation should be assessed.

The use of multiple bioanalytical methods in the conduct of one comparative BA/BE study is strongly discouraged.

…or summarised

- When?
  - Different methods or different labs within 1 study
  - Different methods across studies
    - PK data compared to support special dosing regimens or
    - PK data compared to support regulatory decisions re. safety, efficacy, labelling
- How?
  - QCs L,M,H in triplicate and
  - Study samples (n≥30) across concentration range
- Assessment?
  - Bland-Altman plot
  - Deming regression
  - Concordance correlation coefficient
- Criteria?
  - None; assess impact on clinical data in case of disproportionate bias

Changes to current (FDA, EMA, MHLW, China)

- FDA:
  - different methods within and across studies; different labs within study
  - QCs and study samples
  - Define criteria *a priori* in SOP

- EMA:
  - different methods within and across studies; different labs within study
  - QCs or study samples
  - QCs (N=?): Average Bias within 15% for each method
  - Study samples (N=?): difference within 20% for 2/3 samples

Feedback from EBF and delegates on

No need to read in detail….take home message is "we are confused and we challenge some parts of the paragraph

A lot of comments were given

Feedback from EBF and delegates on

Data are obtained from different fully validated methods across studies that are going to be combined or compared to support special dosing regimens, or regulatory decisions regarding safety, efficacy and labelling.

This is very controversial. The exercise of comparison of PK results can be done at the end of a dossier, using results from different studies generated with different methods over the years, being impossible for these methods to be cross-validated. If cross validation should be performed in advance of study samples being analysed (line 272 og ICH). This wording induces misunderstandings

proposal: delete this paragraph

Change to: Data are obtained from different fully validated methods obtained with different analytical platforms (eg UV vs. MS) across studies that are going to be combined or compared to support special dosing regimens, or regulatory decisions regarding safety, efficacy and labelling.

Better definition is needed what "different fully validated methods" are. What is a different method?

Needs to define what constitutes different method; MS vs MS, LBA vs LBA or MS vs LBA.

Change to: Data are obtained from different fully validated methods utilizing different detection platforms (LC/MS vs LBA) or sample preparation methods (LLE vs PPT) across studies that are going to be combined or compared to support special dosing regimens, or regulatory decisions regarding safety, efficacy and labelling.

Feedback from EBF and delegates on

Cross validation is not generally required to compare data obtained across studies from different laboratories using a the same validated method with the same analytical platform (eg UV vs. UV or MS vs MS) at each site..

This section contradicts FDA guidance. We suggest deleting this text.

Cross validation should be performed in advance of study samples being analysed, if possible.

This is impossible if study samples have to be included in the cross validation

Cross validation should include study samples and therefore cannot be performed in advance of them

This section contradicts FDA guidance. We suggest deleting this text.

Feedback from EBF and delegates on

Cross validation should be assessed by measuring the same set of QCs (low, medium and high) in triplicate and study samples that span the study sample concentration range (if available n≥30) with both assays or in both laboratories.

...and study samples that span the study sample concentration range. Pooled study samples acceptable?? Informed consent an issue here

at least triplicate?

Cross validation should be assessed by measuring the same set of QCs (low, medium and high) in triplicate and study samples that span the study sample concentration range (if available n≥30) with both assays or in both laboratories. Acceptance of the QCs should be done by ISR-type acceptance limits.

acceptance criteria (deviation from mean +/-15% for LCMS and +/-20 for LBA)

Feedback from EBF and delegates on

Bias can be assessed by Bland-Altman plots or Deming regression. Other methods appropriate for assessing agreement between two assays (e.g., concordance correlation coefficient) may be used too. Alternatively, the concentration vs. time curves for incurred samples could be plotted for samples analysed by each method to assess bias. If disproportionate bias is observed between methods, the impact on the clinical data interpretation should be assessed..

what is "disproportionate bias"?

a clear guidance with acceptance criteria is missing

The proposed assessment may generate controversy in interpretation beyond the demonstration that the cross validation results are accurate according to the standard rules

Proposal : replace the proposed text by the EMA wording (based on criteria of accuracy and ISR concepts): For QC samples, the obtained mean accuracy by the different methods should be within 15% and may be wider, if justified. For study samples, the difference between the two values obtained should be within 20% of the mean for at least 67% of the repeats. The outcome of the cross validation is critical in determining whether the obtained data are reliable and whether they can be compared and used.

Acceptance criteria needed (e.g. difference between the same set of QCs/study sample should be less than 20%.

Feedback from EBF and delegates

No need to read in detail…take home message is "we are confused and we challenge some parts of the paragraph

In summary

A few key questions:

- When is a method considered sufficiently different to trigger cross validation?
- Even though the guideline stipulates “if possible” Cross validation with study samples may become mandatory and will be complicated
  - samples within LTS, current China import/export rules, informed consent, requirement to cross validate prior to the study
- And from which development stage onwards?

EBF position from publications/Lisbon-2017

- Cross validation only mandatory for different methods/different labs within study
- A comparison of two technologies may be performed to build scientific knowledge but should not be subject to any acceptance criteria.
- Incurred samples (check informed consent) are preferred, but spiked QCs are acceptable.
- For spiked QCs: 3-6-15/20 acceptance criteria
- For incurred samples: use 20-40 non-pooled samples; acceptance criteria as ISR, 67% within 20/30% of mean

Feedback from EBF Strategy meeting

- When is a method different;
  - change in range?
  - change in sample prep?
  - change in detection technique?
- Limit to clinical studies only
- Use a simple test with clear acceptance criteria like for ISR

Some reflections

- Within study no discussion; everyone is on the same page: use incurred samples
- Across studies; 2 scenarios:
  - Method Transfer: lab A → lab B without substantial changes: QCs should be sufficient…but not required per draft ICHM10
  - Method Change: use incurred samples for major change with potential impact on results.
  - Impact of major changes should be investigated at the stage of method development before validating the assay. Ideally major changes are made as early as possible in the development program.
  - Leave to scientific judgment of sponsor what is major change and should be cross validated.

And finally….what about acceptance criteria

- From all pre-meeting comments and previous recommendations, have we missed the new philosophy of the draft guideline?

Bias can be assessed by Bland-Altman plots or Deming regression. …..If disproportionate bias is observed between methods, the impact on the clinical data interpretation should be assessed.

Does this mean that, if the run passes, a cross validation cannot fail.

Is the intention to investigate and documents a potential bias across studies?

If so, we are entering into a completely new world (next slide)

And finally….what about acceptance criteria, cntd

Questions that arise include:

- What is *a disproportionate bias*? And who owns *the impact on the clinical data interpretation should be assessed"*?
- Who will decide on actions to be taken?
  - Will the BA scientist provide a new set of corrected concentrations?
  - Or the PK scientist
  - And when, why , how….
- And above all, do we currently have the experience in industry to include this new requirement into a global guideline
  - More context required
  - Intensive training required to manage correct use and documentation and responsibilities

Suggested comment to EMA/EWG

Final recommendation from this presentation, which combines the original recommendation enhanced with the discussions from the panel discussions during the meeting, are captured in the summary slide deck: Recommendations from the EBF Spring FW 2019

Thank you

- EBF community and delegates for providing feedback