Workshop

Towards harmonised implementation of the ICH M10 Guideline

Chapter 6 – Partial and Cross Validation

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on behalf of the EBF

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Flow of the session

- What is in section 6? (focus on cross validation)
- What has been changed compared to the draft?
- Selection of questions-discussion points-concerns from EBF survey & Proposal for implementation
- Panel discussion based on the above selection
- Panel discussion on any other topics raised by the audience
- Follow-up action items

What is in section 6 (on cross validation)?

When?

- Data from different methods or different labs within 1 study
- Data from different methods across studies that will be combined or compared to support special dosing regimens or regulatory decisions re. safety, efficacy, labelling

How?

- QCs L,M,H at least in triplicate and
- Study samples (if available) across study sample concentration range (n≥30)

Bias Assessment?

- Bland-Altman plot
- Deming regression
- Or other methods appropriate for assessment of agreement, e.g. concordance correlation coefficient

Criteria?

- Not specified

What has been removed compared to the draft?

- Cross validation is not generally required to compare data obtained across studies from different laboratories using the same validated method at each site.
- If disproportionate bias is observed between methods, the impact on the clinical data interpretation should be assessed.

Selection of questions-discussion point-concerns from EBF survey (1 x-validation)

- **WHEN** to x-validate?
  - When are 2 methods considered the same/different?
  - Is cross validation needed when the same method is used at different sites for different studies?
  - What does “data…are combined” mean?

Proposal for implementation on the “WHEN”

- When studies are planned or as soon as possible, consult with stakeholders such as Clinical Pharmacology, Regulatory and labeling to understand how the PK data from different studies will be combined and whether the outcome will impact regulatory decisions or dosing regimens

Selection of questions-discussion point-concerns from EBF survey (2; x-validation)

- **HOW** to x-validate?
  - Can we use alternatives to B-A or Deming regression? Eg ISR criteria, R^2…?
  - Why are there no acceptance criteria for cross validation?
  - Using QCs and study samples (if available)? When would QCs suffice?

Proposal for implementation on the “HOW”

- BA is responsible for the accuracy of the data provided by the different methods /different labs
  - If differences between methods/labs are observed -> BA needs to ensure assay was correctly transferred
  - No acceptance criteria to be applied

- Important to discuss the Cross-validation data with end-user of the data,

- Impact assessment to be performed by the Clin. Pharm/stats teams

Next steps

- Value in EBF organizing a Cybermeeting involving stakeholders (e.g. clinical PK) on how to “manage” Cross-validation which is now a shared responsibility

- Spring 2023 ?

Selection of questions-discussion point-concerns from EBF survey (3; partial validation)

- differences between LBAs and chromatography methods ? Eg:
  - change in matrix or species,
  - change in sample volume ?

- change in LBA critical reagents: is bridging also sufficient?

Questions from the audience today

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