Scientific Validation and Fit for Purpose Analysis in support of Clinical Studies @ JRD

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General info

- Application of Scientific Validation (SV) for analysis of parent compound in plasma for FIH studies since 2014
- Also applied to some extra early development studies (e.g. PET-ligand)
- 13 programs supported with SV of parent in plasma, 1 biomarker with SV
- All supported in house
- Only HV studies
- From 2013 to 2016 also SV for urine and CSF samples and for metabolites
  Before 2013 and after 2016: FFP
- All outsourced FIH studies supported with full (BMV) validation (other matrices in house with FFP)

Acceptance

- Discussed with global DMPK Head
  - SV for parent in main matrix only for HV FIH studies
  - Only EU site, US site outsources all FIH studies, and at CRO all with RV

- Discussed with Clinical Pharmacology: “you know what is required for submission, we trust you in doing the right thing’

- Registrations
  - 1 project, 2016: SV described in CTA upon questions from MHRA: no comments
  - 2 projects, 2016/7: IND submission: no comments
  - never comments on FFP analysis of metabolites or parent in other than primary matrices

Value

- We allow (limited) flexibility for selection of the appropriate concentration range for each analytical batch to higher concentrations than tested in SV
  - More measurable time points at lower dose levels without method impact on high dose levels
  - Avoids (excessive) dilution or need for second method

- Time saving
  - Less duplication of experiments between method development and validation
  - One validation batch, more trust in in-study validation P&A
  - Reports reduced to the minimum
  - SV: only few pages (validation and sample analysis)
  - FFP: no reports, but results added to SV sample analysis report

- Bioanalytical lab: Added value to do SV in house: keep internal experience on the analytical method - more efficient partnership with CROs.

Fear/Risks

- Global Head DMPK: if some FIH studies supported by full BMVs, would regulators accept supporting other studies with SV?

- Lab/QC: SV SOP allows much flexibility. Desire for more details/guidance: Interpretation not always straightforward for specific (non-standard) situations. A lot of discussions…need for repeat if no agreement on hindsight => delays

Hurdles

- Within company, regional differences in approach: Some groups tend to stick to full BMVs, even for metabolites and other matrices

- Complicated FIH designs
  - HV and patients in 1 study: SV for HV in house, full BMVs for patients at CRO, cross-validation with QC samples
  - Dose escalation and food effect and/or DDI in 1 study: All SV? All full BMV? Hybrid?

- Combi assay parent +metabolite(s): yes or no all SV?

- Data required for pop-PK: cross validation between SV and subsequent full BMVs

Thank you

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