Towards a recommendation of bioanalytical qualification or validation of microdosing and microtracer studies – part 2:

Details from Survey 1

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Introduction

- EBF recommendation
  - On appropriate qualification/validation of methods for the quantification of drug and/or metabolites.
  - For clinical microdosing and microtracer studies with a variety of design aims, in a variety of phases of discovery and development.
  - Using LC-MS/MS and LC+AMS
- Details of Survey 1
- *Current slide deck contains EBF work in progress and are consensus ideas of the EBF Topic Team - potentially supplemented with EBF-survey results on the topic*

Cold microdosing studies

1. 5 companies have experience
   - Early development: 4
   - Early and late development: 1
2. Number of studies executed
   - 1 company: 1
   - 2 companies: 1 - 3
   - 2 companies: 3 – 10
3. Purpose of the study
   - Fabs: 3
   - Mass balance: 1
   - Candidate selection: 1
   - PK optimisation: 2

Cold microdosing studies

4. Purpose
   - Mainly decision making
   - One for future filing

5. Bioanalytical quality
   - We apply the same quality standards for ED & LD
     Yes: 4 No: 1
   - Full validation in accordance with guidance for ED studies
     Yes: 3 No: 1
     Only Meth dev, linearity, LLOQ, Acc&Prec for QC
   - Full validation in accordance with guidance for LD studies
     Yes: 1
   - Sensitivity required :
     - 40-100 fold lower (5-25 pg/ml), 10 fold lower (5 pg/ml)

Microtracer studies (AMS)

1. 9 companies have experience
   - ED only: 3
   - LD only: 2
   - ED & LD: 4
2. Number of studies executed
   - 3 companies: 1
   - 2 companies: 1 - 3
   - 4 companies: 3 -10
3. Purpose
   - Fabs: 6
   - Mass balance: 5
   - Metabolite quantification: 3
   - Other : 2

Microtracer studies (AMS)

4. Filing to Health Authorities
   - Yes, following a request for Fabs: 1
   - Not yet, but in future: 6
   - Internal decision making: 2
5. Bioanalysis guided by Regulated Bioanalysis staff
   - No, PK & AMS staff: 4
   - Yes, PK & AMS & Regulated Bioanalysis: 1
   - Other
     - Initially (DM)PK & AMS then Regulated Bioanalysis added: 3
     - BA for cold, metabolism for ^{14}C
     - Regulated Bioanalysis, AMS, pre clin ADME & clinical

Microtracer studies (AMS)

6. We apply the same quality standards for ED & LD

   Yes: 6 No: 2

7. Redevelop sample preparation for AMS

   Yes: 7

   No: 2 (as cold assay)

   Don't know: 1

   Both: Mass Balance different, profiling as pre clin ADME

Microtracer studies (AMS)

8. Sample prep development and validation
   - Partial validation: 1
   - Scientific validation: 5
     - Linearity
     - Selectivity
     - Reproducibility
     - Carbon content
     - Xceleron/Vitalea recommendation
     - AMS is considered as a balance
     - Total ^{14}C recovery from protein pellet
     - Recovery curve of range
     - HPLC recovery of total ^{14}C

Microtracer studies (AMS)

9. LC method development

   Yes: 5 No: Exact copy of cold LC-MS/MS (2)

10. Sample prep development and validation
    - Scientific validation
      - On-column recovery: 1, Repeatability: 1, Peak separation: 1, Resolution: 1
      - LC retention cfr cold material:1
      - Specificity as metabolism method: 1
      - Xceleron/Vitalea approaches used: 1
      - Method is hybrid of cold Bioanalysis & Metabolism: 1

Microtracer studies (AMS)

11. Method qualification parameters and acceptance criteria
    - Accuracy & precision: +/- 15%
    - ^{14}C recovery, repeatability, variability, stability
    - Within run controls (blinds, QC, Cal monitored and discussed in report)
    - Selectivity assessed with carryover, 1 pooled blank
    - Reproducibility, 2 occasions
    - Carryover of IS in LC; LC carryover in UV & 14C; Graphitization carryover
    - Linearity (R^2 >0.99)
    - Prec. & Acc +/- 20% except LOQ +/- 25%: 2
    - Radiochemical purity >95%; impurity <1%
    - Cross reference to validated cold LC-MS/MS for stability, freeze/thaw, processed sample: 2
    - Recovery of cal range

Microtracer studies (AMS)

12. LC+AMS instrument subject to computer system validation (CSV)
    - Yes: 1
    - No, not considered: 1
    - No, not needed: 2
    - No, considered but unable for all aspects relating to AMS: 1

13. Analysis of microtracer samples by LC+AMS needs:
    - “Scientific” validation: 4
    - Method qualification, reflect on guidelines, relate to AMS: 3
    - Partial method validation: 0
    - Full validation, where possible

14. Use of cold microdosing or microtracer for pre-clinical studies
    - Yes, prep for human: 2
    - Yes stand alone: 1
        - Profiling to support safety studies
    - No: 7

Poll on cold microdosing studies

Is Full validation required?	ED	LD
Yes	4	7
No, partial validation based on full validation of a method with higher concentration range	3	7
No, qualified method is sufficient	10	3
Don’t know	0	0

Poll on microtracer studies (LC+AMS)

What type of Validation is required, if study is used for ..	...internal decision?	...filing?
“Scientific”	8	7
Qualified method (focus on specific AMS parameters & regulated bioanalysis (7)	7	7
More validation (method validation cf FDA guidance on regulate bioanalysis & qualification of specific AMS parameters	0	0

Poll on microtracer studies (LC+AMS)

Full or partial validation of a LC+AMS method, as described in the appropriate guidelines on regulated bioanalysis (FDA 2001, EMA 2011) is:	# answers
Not needed, AMS is not served by existing guidelines.	2
Not possible, but needed	6
Possible but not needed, current guidelines can be adapted	5
Not needed and not possible	0
No idea	1
Possible and needed, current guidelines can be adapted for AMS	1

Summary

- People are gaining experience in the field of “cold and hot microdosing”
- People are not sure on what is needed wrt validation and we see all colours of validation being tentatively applied
- Most people are pretty sure of what is not needed (i.e. overdoing validation)
- More discussion is needed and your input is appreciated – Survey 2 (30th Nov)
- EBF will continue the discussion

Towards EBF Recommendation

- Too soon to propose?
  - more discussion needed in TT, EBF community and beyond
- Plan for publication in 1st half of 2012
- Plan to provide input as EBF in GBC discussion (Philip & Graeme)

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- EBF members for survey data
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