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

Details from Survey 1

*Presenter: David Higton on behalf of EBF*

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Barcelona

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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

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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 :
     o 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

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Microtracer studies (AMS)

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

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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
     o On-column recovery: 1, Repeatability: 1, Peak separation: 1, Resolution: 1
     o LC retention cfr cold material: 1
     o Specificity as metabolism method: 1
     o Xceleron/Vitalea approaches used: 1
     o 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 & $^{14}$C; 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

<table>
<thead>
<tr>
<th>Is Full validation required?</th>
<th>ED</th>
<th>LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>No, partial validation based on full validation of a method with higher concentration range</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>No, qualified method is sufficient</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Don’t know</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## Poll on microtracer studies (LC+AMS)

<table>
<thead>
<tr>
<th>What type of Validation is required, if study is used for ..</th>
<th>...internal decision?</th>
<th>...filing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Scientific”</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Qualified method (focus on specific AMS parameters &amp; regulated bioanalysis (7))</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>More validation (method validation cf FDA guidance on regulate bioanalysis &amp; qualification of specific AMS parameters)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## 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:

<table>
<thead>
<tr>
<th>Option</th>
<th># answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not needed, AMS is not served by existing guidelines.</td>
<td>2</td>
</tr>
<tr>
<td>Not possible, but needed</td>
<td>6</td>
</tr>
<tr>
<td>Possible but not needed, current guidelines can be adapted</td>
<td>5</td>
</tr>
<tr>
<td>Not needed and not possible</td>
<td>0</td>
</tr>
<tr>
<td>No idea</td>
<td>1</td>
</tr>
<tr>
<td>Possible and needed, current guidelines can be adapted for AMS</td>
<td>1</td>
</tr>
</tbody>
</table>
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)
Acknowledgement

➢ Topic Team 08
  – Philip Timmerman, Janssen
  – Graeme Young, GSK
  – Leif Svensson, Active Biotech
  – Richard Abbott, Shire Pharmaceuticals
  – Magnus Knutsson, Ferring
  – David Higton, AstraZeneca

➢ EBF members for survey data
➢ AMS providers for discussion & survey data