Towards a recommendation of bioanalytical qualification or validation of microdosing and microtracer studies – part 1 : Ideas around Survey 2 and Survey 1 Conclusions

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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

- *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*

Content

- What aspects are needed for validation of LC+AMS – design of Survey 2
- Conclusions of Survey 1
- Breakout session - Part 2
  - Details from survey 1 and discussions

Types of protocols we aim to recommend on

- Microdosing
  - Low dose cold
  - Low dose ^{14}C
- Microtracer
  - Low dose cold isotope
    + anticipated pharmacologic dose (APD) cold
  - Low dose ^{14}C
    + anticipated pharmacologic dose cold

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Types of analytical challenges

- LC-MS/MS
  - Low dose cold.
  - Low dose cold Isotope
    + anticipated pharmacologic dose cold

- AMS
  - Low dose ^{14}C
  - Low dose ^{14}C
    + anticipated pharmacologic dose cold

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When can these studies happen

- Low dose cold.
  - Pre-FIH (first in human)
    = limited tox to support,
    - Rank compounds
    - Learn PK characteristics (half life, clearance, DDI ,…)
- Low dose ^{14}C
  - More likely in Pre-FIH or Early Development
    = pre-phase I (tox data may or may not be available or needed)
    - as above +
      - ADME data
    - Sensitivity problems on low dose cold dosing

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When can these studies happen

- Low dose cold or ^{14}C Isotope + APD
  - Early and late development (ED & LD)
    = pre-phase 1 tox data available and needed
    - o F_{abs}, IV kinetics
    - o ADME data
- Combination protocols needed to anticipate analytical challenges or hurdles, E.g.
  - 10% ^{14}C added to low dose cold (sensitivity problems)
  - Cold added to ^{14}C to prevent phys chem problems (adsorption)

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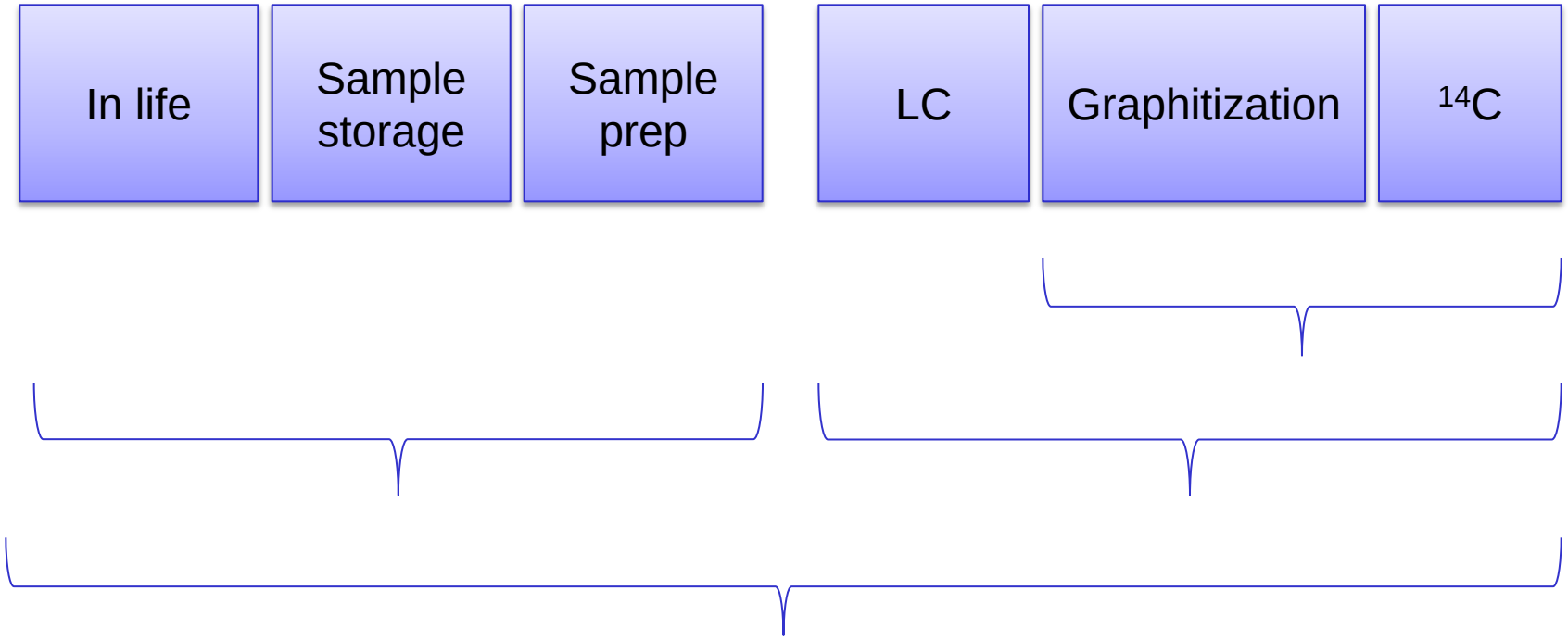
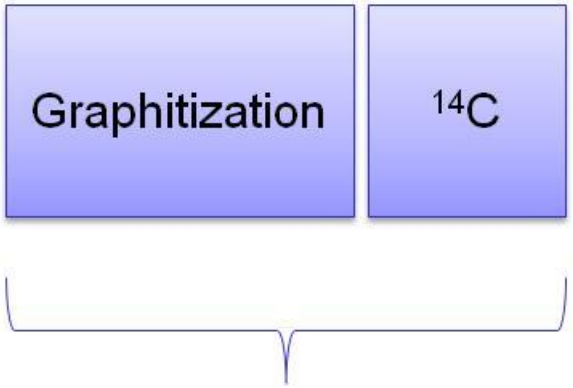
LC+AMS:
Stages of validation reflections



What parameters define quality in AMS



- Inter and intra assay Accuracy
- Inter and intra assay Precision
- Stability
- Selectivity
- Sensitivity, LLOQ
- Matrix effects
- Linearity
  - may not be relevant - is really system suitability (SST)
- Carry over/contamination
- Instrument calibration and SST
- Independent QCs
  - on graphitization, not compound related

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What would these parameters look like

- Instrument qualification questions:
  - Instrument calibration and SST n=3,
  - Independent QCs (on graphitization, not compound related)
  - Software
- Method qualification:
  - Independent QC in target matrix – how many levels, replicates?
    - What is the intended purpose of the QCs
  - Calibration curve in target matrix – how many levels, replicates?
    - What is the intended purpose of the cal curve
  - How to define and determine LLOQ and ULOQ?
  - Selectivity
    - From ^{14}C to chemical structure - how to document?
  - Matrix effects
    - Carbon supplements (enhancement) from solvents, buffers, LC-solvents, other sources

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What would these parameters look like

- Method qualification - continued
  - Carry over
    - What sources of carry over do you recognize above the conventional sources known from LC-MS
  - Storage of LC-fractions prior to graphitization
  - Aliquoting of LC-fractions used in graphitization
    - What are the risks involved in analyzing only an aliquot of the LC-fraction
    - What are the advantages in analyzing only an aliquot of the LC-fraction
  - Considerations for the LC-equipment
    - Is additional validation of LC-equipment required in absence of IS (concentration calculations will be based on volume of injections)
  - Extraction and sample preparation
    - how does your method cope with compound loss during extraction and sample preparation

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What would these parameters look like

- Method qualification - continued:
  - How do you manage non-AMS related criteria or requirements mentioned in regulated BA guidances, e.g.
    - Stability (solution, F/T, LTS, processed sample, LC-fraction…)
    - Instrument qualification/validation, sample logistics

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Running samples

- Instrument qualification questions:
  - SST/pre study qualification prior to sample analysis?
    - what would this look like?
  - Is this different to cold assay SST/pre study qualification?
- Study acceptance:
  - QC in target matrix? – acceptance criteria
  - calibration curve in target matrix? – acceptance criteria
  - What (other) parameters do you include for study acceptance?
    - Related to AMS & graphitization parameters
    - Others
    - ISR
- Individual sample acceptance
  - Which parameters, different from or on top of above study acceptance do you include
    - LC or sample prep-related
    - AMS or graphitization related

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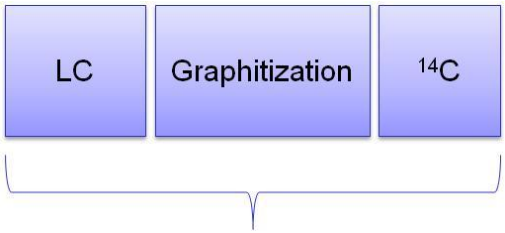
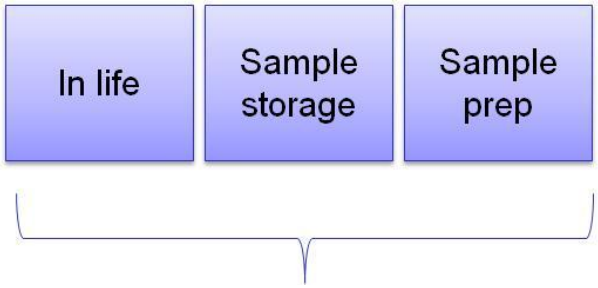
What parameters are added in LC+AMS

- Inter and intra assay Accuracy
  - Storage of LC-fractions prior to graphitization
  - Sampling of LC-fractions prior to graphitization
- Inter and intra assay Precision
- Stability
- Selectivity
  - Retention time drift
  - Retention time window
  - Selectivity of chromatography
- Sensitivity
  - Loss of signal due to adsorption
- Matrix effects
  - Carbon matrix effects from solvents, buffers LC-solvents
- Linearity
  - Assay linearity on top of instrument linearity
- Carry over/contamination
- How to define SST
- Independent QCs (on LC)



What parameters differ for pre LC in case of LC+AMS

- Purity of the radiolabel
- Instability due to radiolysis



- Contaminations of dosed subjects from previous microdosing or ^{14}C studies (selectivity)
- Contamination of stored samples

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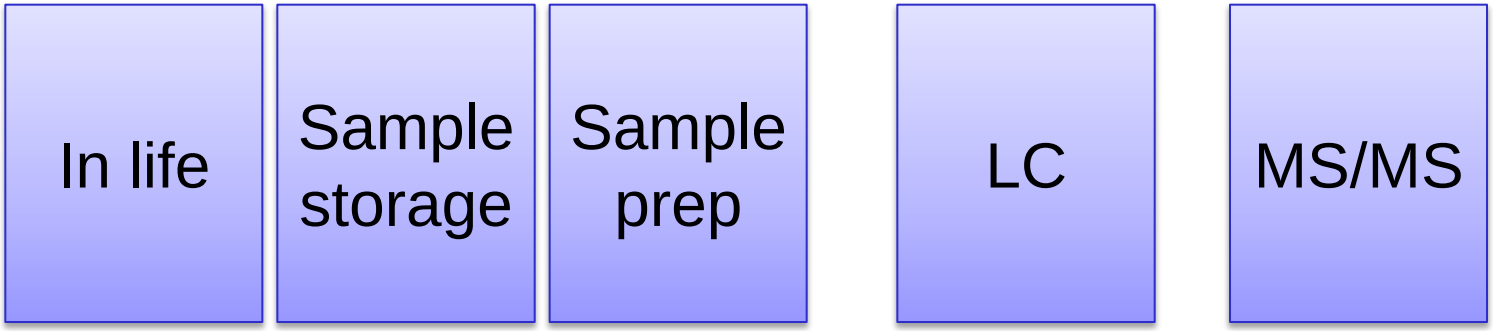
Cold LC-MS/MS

- Survey 2 Questions
  - what is different at lower concentrations?



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Survey 1 Conclusions

- 18 surveys returned – Thank you
  - 5 Cold LC-MS/MS microdosing
  - 9 LC+AMS microtracer

- Everyone performs these type of studies
- Everyone performs validation/qualification for these studies differently
- Potential for discussion and EBF recommendation

- To be continued…….
- Survey 2 replies = 30th November

Acknowledgement

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