Huntingdon Life Sciences
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Fit for Purpose Method Transfer

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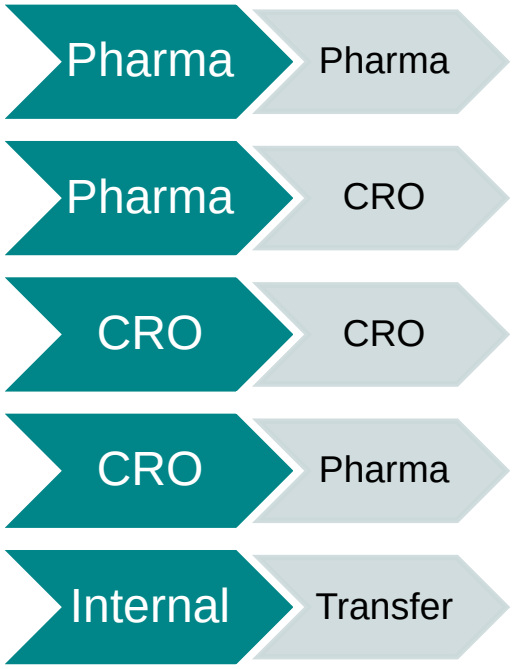
Overview

- What is meant by method transfer
- Why it's important to discuss method transfer
- What the guidelines say
- Current approaches
  - Regulatory bioanalysis
  - Tissue methods
  - Non-regulatory bioanalysis
- Sponsor and CRO requirements
- Summary

What is method transfer?

- A method is available in Lab A and needs to be transferred to Lab B



What is method transfer?

- A method is available in Lab A and needs to be transferred to Lab B
- Regulated bioanalysis
  - Fully validated based on BMV guidance
  - Method developed in Lab A & transferred to Lab B
- For non-regulatory bioanalysis
  - Outline method possibly with supporting data

Why is method transfer important?

- Global nature of drug development means that method transfer is a common activity
- …….but little information on extent of experiments required !
- Guidance documents provide a structured framework for:
  - Key validation experiments
  - Batch acceptability during sample analysis
- Case for best practice approach?

Regulatory

- 2001 FDA Guidance defined different categories of validation:
  - Full validation
  - Partial validation
  - Cross validation

- Concept carried forward to EMA Guideline and 2013 draft FDA Guidance

- Method transfers covered in Partial Validation sections – but no details about extent of experiments required

Considerations

- FDA/EMA guidance - single precision and accuracy batch to almost a full validation
- Overlap with cross-validation
  - "By definition, a method transfer is to cross-validate an intended bioanalytical method in a different laboratory" Lin *et al*, Method Transfer, Handbook of LC-MS Bioanalysis (Wiley, 2013)
- Exchange of QCs and incurred samples between Sending and Receiving labs

Acceptance criteria

- Acceptability of the transfer should be based on:
  - Criteria outlined in FDA and EMA guidelines
  - Other criteria agreed between laboratories
- Quality Controls (method establishment)

QC	LC-MS	LBA
LLOQ	RE ±20%,CV ≤20%	RE ±25%,CV ≤25%
L/M/H	RE ±15%,CV ≤15%	RE ±20%,CV ≤20%
ULOQ	-	RE ±25%,CV ≤25%

- Quality Controls and incurred samples exchanged to confirm transfer

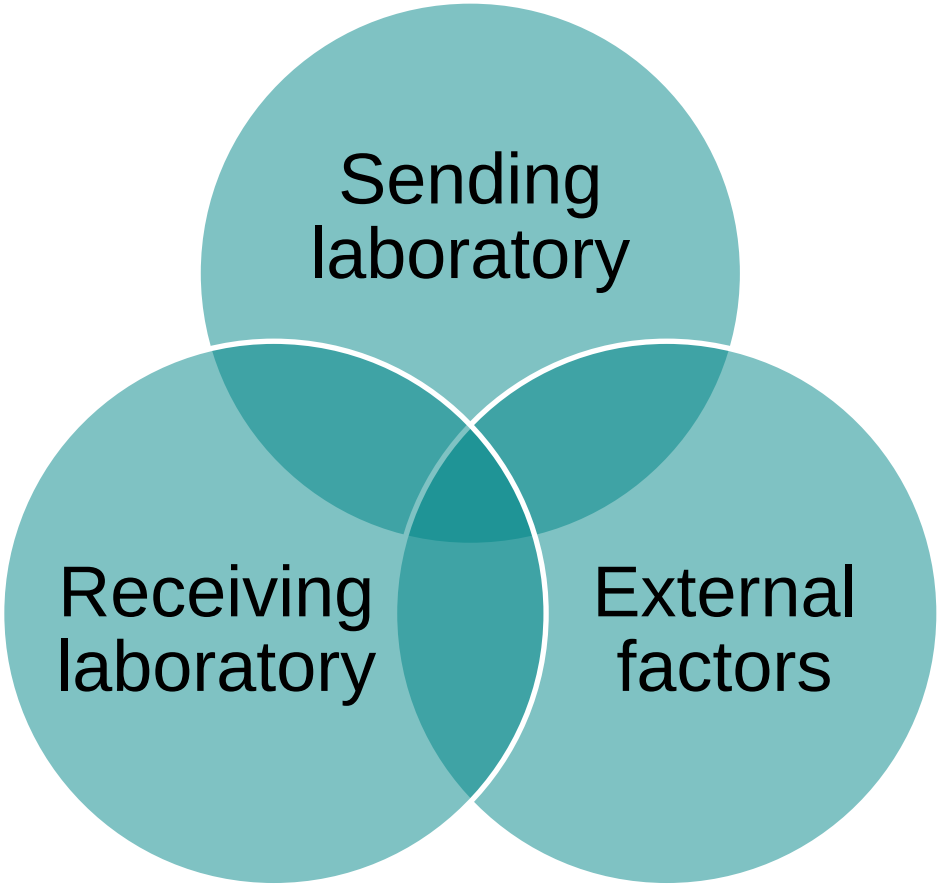
Regulated bioanalysis

- If a validated method is available:
  - Does the transfer require a full validation including stability?

2011 White Paper on Recent Issues in Bioanalysis and Regulatory Findings from Audits and Inspections Garofolo *et al*. *Bioanalysis* (2011) 3(18), 2081-2096

  - Or can a smarter approach be adopted?

Factors affecting transfer



- External or internal transfer
- Method modifications
- Additional stability
- Regulatory
- Objective of the study

LC-MS/MS method transfer

- Selectivity
- Matrix effects
- 1 – 3 precision and accuracy batches
- Use long term frozen and solution stability data from original validation
- Evaluate ambient and freeze-thaw stability
- Method modifications
- Exchange QCs and incurred samples

LBA method transfer

Feasibility experiments – check critical parameters

Tiered validation

Considerations for tissue method transfer

- Tissue methods
  - Hot topic
- Considerations
  - Spiked calibration standards and QCs don’t mimic incurred samples
  - Stability in intact samples versus homogenate?
  - How do you collect representative samples?
  - Sample storage – intact or homogenate?

Qualify or validate?

- Need to understand what the data will be used for
  - Demonstrate presence of drug?
  - Unique end point?
- Flexible tired approach
  - Qualify method with a *priori* agreement on acceptance criteria
- Unique endpoint – validate?

Non-regulated bioanalysis

- Transfer of un-validated/qualified method to support non-regulatory bioanalysis
  - Comprehensive information about method not always available
  - Modifications often requested eg measure a metabolite
- Transfer of validated method to support non-regulatory bioanalysis

Tiered approach

Tier	Calibration standards	QCs	Matrix effects	Stability
1	Yes	No	No	No
2	Yes	4/6/25	No	No
3	Yes	4/6/20	Yes	No
4	Yes	4/6/15	Yes	Yes

Practical considerations

Sponsor (Sending lab)

- Facilities and equipment
- Adequate resources
- Compliance status
- Appropriately trained staff
- Acceptable timeframes
- Provide a robust method

CRO (Receiving lab)

- Adequate transfer time
- Comprehensively documented method
  - Passivation of HPLC columns
  - Centrifuge rpm vs g-force
  - TMB reagents
- Validation data
- Effective communication
- Exchange visits

Summary

- Consider a scientifically driven best practice approach to method transfer in regulatory bioanalysis
  - Common/pivotal procedure
  - Global guidelines open to interpretation
- Non-regulatory bioanalysis
  - Appropriate acceptance criteria agreed between laboratories
- EBF to perform a survey of members and recommend best practice

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QUESTIONS?