TT41:- Processed extract stability recommendations

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on behalf of EBF TT41

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Introduction

- The Original Remit
- Background
  - To address health authority questions
  - Experimental inconsistency across organisations
- Aim
  - To survey the industry on current practice
- Output
  - Consensus recommendation on behalf of EBF

Content

- Definitions
- The Surveys
- Current practice
  - Extract viability
  - Processed sample stability
- Extract storage
- Proposed recommendations
- Summary
- Acknowledgements

Definitions

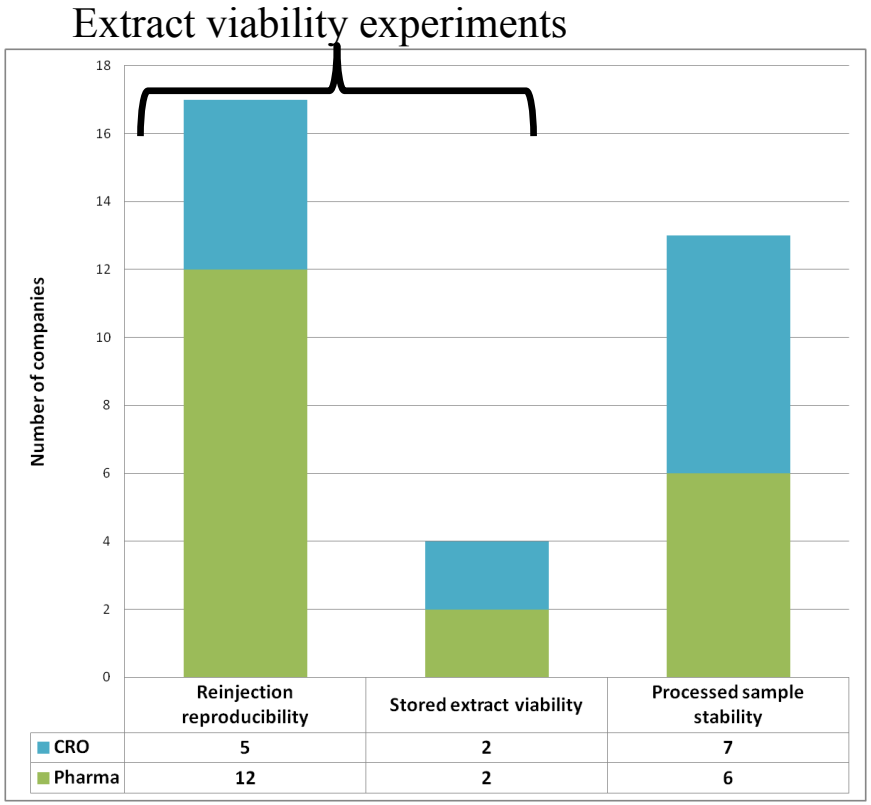
- Extract Viability Experiments (stored vs stored)
  - Re-injection reproducibility – extracts are stored for a defined period prior to re-injection (Stored QCs vs stored calibration standards)
  - Stored extract viability – extracts are stored for a defined period prior to first injection (stored QCs vs stored calibration standards)
- Processed sample stability (Stored vs fresh) – stored quality control sample extracts are analysed against freshly prepared calibration extracts

Source Data

Responses	Survey 1	Survey 2
Total # companies who responded	21	17
# Pharma	13	10
# CRO	8	7

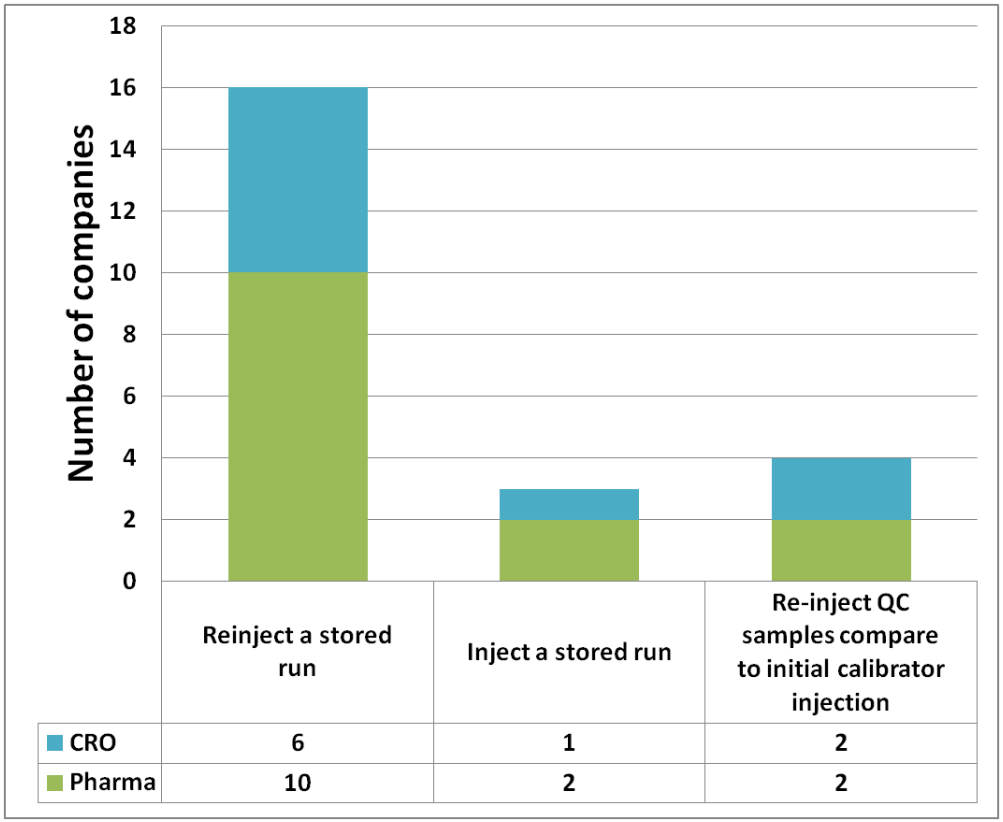
- Good representation from Pharma & CRO

Current practice across EBF community



- 43% extract viability experiment & processed sample stability
- 33% Reinjection reproducibility only
- 14% processed sample stability only
- 5% all experiments
- 5% both extract viability experiments only

Extract viability Experimental approaches

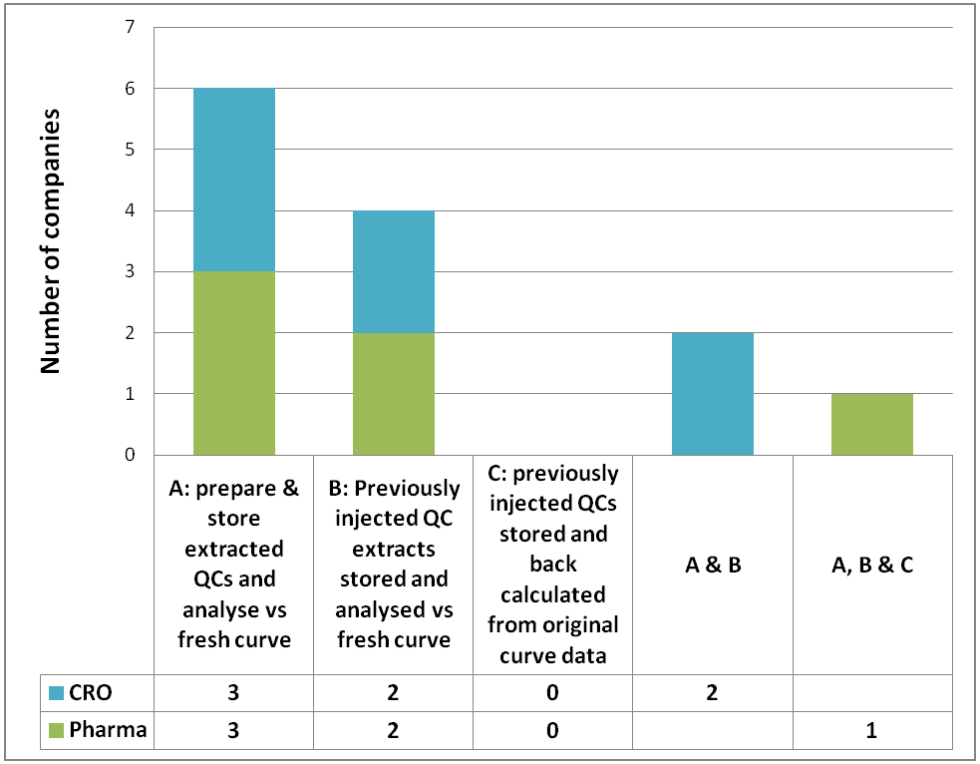


- 50% analyse a selection of QCs (majority use low and high QCs)
- 50% analyse complete A&P run

Why we include this experiment within the validation

- Extract viability
  - Allows injection of a stored analytical batch in the event of.....
    - Instrument stops part way through a run
    - Poor chromatography
    - Instrument availability
    - Change in instrument response

Processed Sample Stability (performed by 13 of 21 respondents)



- Majority use A&P acceptance criteria (n=6)
- 66% Low & high QC only
- 20% Low, medium & high QC
- 14% include either dilution QC or LLOQ QC

For those who perform Processed Sample Stability

- We (13 of 21 respondents) perform the experiment because.....
  - FDA expectation (~60%)
  - We sometimes store sample extracts and analyse with a fresh curve (~40%)

However across the whole community our survey indicates

- 50% think extract viability is enough
- 40% of all respondents think processed sample stability is a pivotal experiment
- 10% think extract viability is enough if you use a labelled internal standard
- Majority find this fails much <10% of the time
  - Causes include adsorption, instability, solubility, evaporation

Extract storage time

- Most popular responses
- First choice
  - End of extraction (for start of storage)
  - Time of last injection / re-injection
- Second choice
  - End of extraction (for start of storage)
  - Time of first injection / re-injection


RECOMMENDED
RECOMMENDED
RECOMMENDED

Proposed recommendation

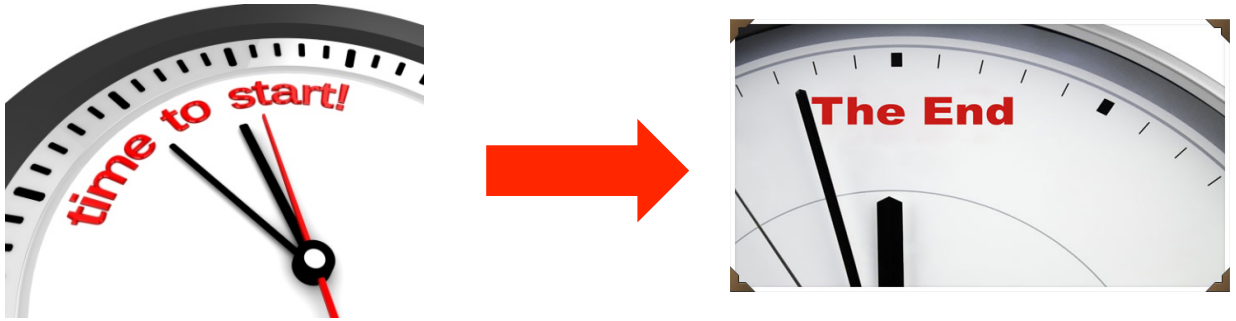
- Extract Viability
  - Re-inject a stored run if you have sufficient extract to do so
  - Minimum n=5 low and high QCs
  - Re-inject stored calibration and QC samples. Read QC results from the re-injected calibration curve
  - Accuracy & precision acceptance criteria

Proposed recommendation

- Processed sample stability
  - Only perform this experiment if there is need to cover a time delay between extraction of QCs/ unknown samples and the extraction of calibration standards
  - Minimum n=5 low and high QCs
  - Accuracy and precision acceptance criteria

Proposed recommendation

- Duration of storage
  - Record the exact time rounded down to the nearest hour
  - Start time = end of extraction time
  - End time = End of the re-injection analysis run
  - Note:- Run must complete within this time period



Summary

Recommend

- Validate exactly what we do
- Use good science as justification

Acknowledgement

- TT41 members
  - Suzanne Barker
  - Ludovicus Staelens
  - Sirpa Laakso
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- EBF community