Best practices for reanalysis: from instrument failure to PK outliers

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on behalf of the EBF

Focus Workshop

(*In collaboration with the AAPS and JBF*)

Industry input into ICH M10: Experimental data as the cornerstone for a science driven bioanalytical guideline

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1. Reanalysis due to assignable cause: analytical reason

2. Reanalysis due to incongruous results: PK reason

Reanalysis for analytical reasons

There is an assignable cause:

- instrument failure
- documented dilution error
- poor chromatography
- incongruence of replicate results in LBAs
- failure of run acceptance criteria
- concentration above the Upper Limit of Quantitation (ULOQ)

Assignable cause: What does the guidance/guidelines say?

Requirement	FDA	EMA	MHLW
Acceptable?	Outside assay range. Sample processing error. Equipment failure.		
Replicates	Same as in first analysis		
Acceptance criteria	As defined for other samples		
Reported value	1st valid result		
IS variability	*A priori* (SOP)		
Multi analyte LCMS methods	Repeat failed analyte		

Recommendation

Reanalysis for analytical reasons

- Use the same number of replicates as originally tested
- Use same acceptance criteria as for other results
- Repeat failed analyte only for multi-analyte methods
- Report repeat result, which is the first valid result

Incongruous results for PK reasons - likely obvious to re-analyse

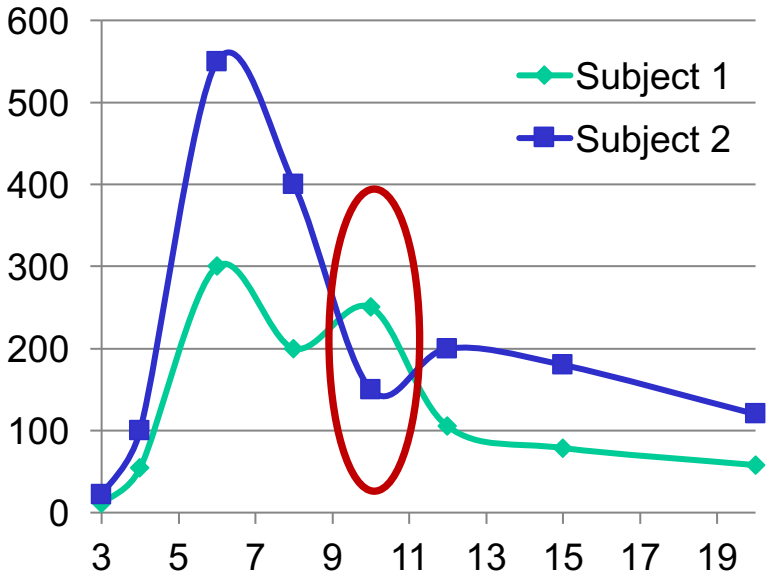
- Quantifiable analyte levels in
  - pre-dose
  - control animal
  - placebo subject samples
- BLQ result in the middle of a concentration-time profile
- Results suggesting an obvious sample switch

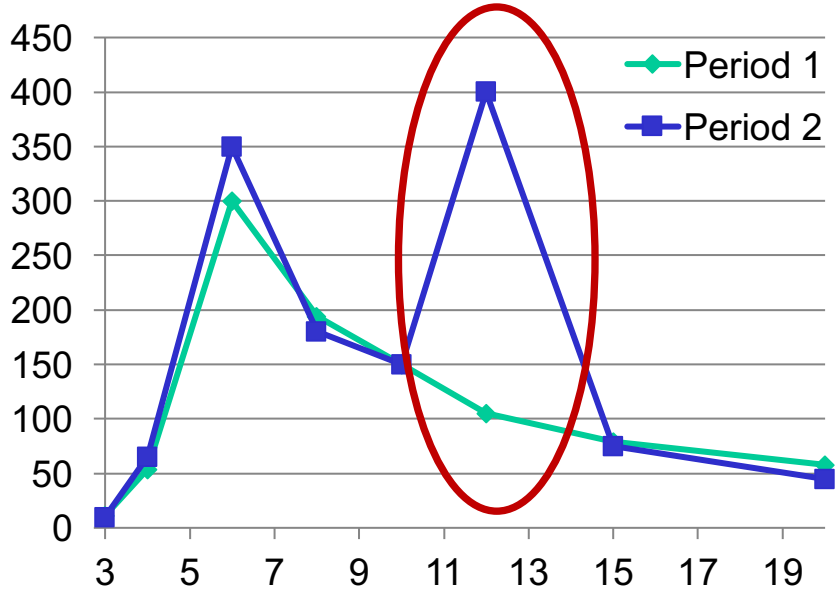
Outliers that require investigation

Documentation and discussion in report

Incongruous results for PK reasons – likely less obvious to just re-analyse

Examples:





Let's discuss how we feel this should be managed

- The FDA guidance provided some clarity on repeat analysis and recommends that reassay for inconsistent PK data be performed in triplicate. At CCIII meeting in 2006 it was clarified to mean duplicate analysis.
- Repeat analysis due to incongruous PK data allowed by the FDA, EMA and MHLW take strong position on stating that normal reanalysis for PK reasons is not acceptable in bioequivalence (BE) studies.

Incongruous result: Current Guidance/Guidelines

Requirement	FDA	EMA	MHLW
Acceptable?	Yes	PK: not in BE. Analyte in pre-dose or placebo samples.	PK: not in BE. Analyte in pre-dose, placebo samples. Causal investigation for abnormal data.
Replicates	Duplicate	-	-
Acceptance criteria	SOP	SOP	SOP
Reported value	SOP	SOP	SOP

Are there any proposals from industry already?

Harmonisation Needed

- Acceptance criteria for replicate repeats when repeat analysis is conducted for PK reasons.
  - 15%, 20%, 30%, 40%?
- Criteria for selecting the reported value after replicate repeat analysis for PK reasons.
  - Decision tree for which result to report
  - Report the original value, median, or mean?
- Number of replicate results
  - Singlicate, duplicate, triplicate?

Industry recommendation (GBC)

- Process should be defined in SOP
  - Do SOPs contain the GBC recommended workflow?
- PK reanalysis – BE discouraged
- PK reanalysis in general
  - Do Investigation
  - Follow SOP
  - Document justification
  - Duplicate or triplicate repeat analysis
  - Acceptance 30% (Chrom) or 40% (LBA)
  - Decision tree for reportable result selection

Should we take a fresh look at the GBC recommendation?

In view of ICH M10, should we focus on BE?

Let's discuss

Starting point for discussion

- Harmonised guideline
  - Decision tree
  - Acceptance criteria
  - Reported value
- Number of repeats
  - Repeat obvious outliers. Does a second or third repeat add knowledge?
- Allow PK re-analysis in BE studies for investigations?
  - What is the advantage of doing so?
  - What is the risk of doing so
- Use same acceptance criteria for Chrom and LBA?

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