Common Deficiencies for Study Sample Reanalysis in Pharmacokinetic Bioequivalence Studies Submitted in Abbreviated New Drug Applications (ANDAs)

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Learning Objectives

- Summarize common reasons/codes of study sample reanalysis in pharmacokinetic (PK) studies
- Understand common deficiencies for study sample reanalysis in PK studies
- Identify ways to avoid some of these deficiencies

Study Sample Reanalysis

- Study sample reanalyses are commonly observed in PK studies in ANDAs.

Table 9 Reanalysis of Study Samples[7]

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[8]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

[7] Provide a separate table for each analyte measured for each in vivo study.
[8] If no repeats were performed for pharmacokinetic reasons, insert "0.0."

https://www.fda.gov/media/75081/download

- Many deficiencies related to study sample reanalyses can be avoided.

Examples of Common Reasons/Codes of Study Sample Reanalysis

- Internal standard (IS) variation
- Incomplete analysis (e.g., instrument malfunction and lost sample during analysis)
- Above upper limit of quantification (ULOQ)
- Poor chromatogram
- PK repeat
- Positive pre-dose
- Truncated calibration curve (CC)
- Rejected runs

Common Deficiencies for Study Sample Reanalysis

- General deficiencies (i.e., not specific to a repeat code)
- Code-specific deficiencies

Common Study Sample Reanalysis Deficiencies – General Deficiencies

- Incomplete or no numerical raw data
- Standard Operating Procedure (SOP) related deficiencies
  - Missing or incomplete study sample reanalysis-related SOP(s)
  - SOP(s) provided not current at the time of study sample reanalysis
  - SOP effective date not specified
  - Missing guideline for how final values should be reported for reanalyzed samples
  - SOP has discrepancies

Common Study Sample Reanalysis Deficiencies – General Deficiencies (cont'd)

- Missing information on whether rejected samples were reanalyzed or reinjected
- Inconsistencies between
  - Study sample reanalysis summary table
  - Study report
  - Bioanalytical report
  - SAS dataset
  - Repeat criteria in SOP(s)

Common Deficiencies for Study Sample Reanalysis

- General deficiencies (i.e., not specific to a repeat code)
- Code-specific deficiencies

Some repeat codes are more deficiency-prone compared to others

Common Deficiencies Related to Poor Chromatograms

- Missing rejected and/or accepted chromatograms
- Chromatograms provided not legible
- Missing detailed reasons for poor chromatograms

Common Deficiencies Related to Incomplete Analysis

- Examples of incomplete analysis
  - instrument malfunction, lost sample during analysis
- No detailed reason or supporting documentation for reanalysis
- Repeat criteria not objective or clear

Common Deficiencies Related to Sample Concentration Above ULOQ

- Reported sample concentration not supported by the dilution integrity validated in the pre-study method validation
- Missing information on dilution factor and/or dilution medium
- Missing explanation when reanalyzed sample concentration (after correcting for dilution factor) was markedly lower than ULOQ

Common Deficiencies Related to PK Repeat

- Sometimes reported as, for example,
  - *"anomalous value"*
  - *"unexpected value"*
  - *"confirming value"*
  - *"investigational report"*
  - *"sponsor-requested sample reanalysis"*
- Repeat criteria not pre-defined or not objective

Common Deficiencies Related to Rejected Runs

- Missing detailed reason or supporting information for run rejection
- Run rejection criteria not clearly defined or not objective
- Did not provide chromatograms for runs that were rejected due to e.g.
  - Gradual deterioration in analyte and IS peak
  - Poor chromatograms

Common Deficiencies Related to IS Variation and Positive Pre-Dose

- IS Variation
  - Lack of a list of original IS response together with mean IS response
- Positive Pre-Dose
  - Missing explanation for presence of positive pre-dose in Period 1

Deficiencies related to truncated CC are uncommon.

Summary

- Study sample reanalysis accounts for an important portion of the bioanalytical section in ANDAs.
- Deficiencies related to study sample reanalysis are commonly identified.
- Many of these deficiencies can be avoided.
  - Provide complete information
  - Clearly and objectively pre-define the repeat criteria under each repeat code in the SOP(s)

Challenge Question #1

Which of the following statements is true:

A. Only accepted chromatograms need to be submitted.

B. For samples reanalyzed due to concentration above ULOQ, dilution factor and dilution medium used should be specified in the bioanalytical report.

C. If there is no study sample reanalysis, then raw data does not need to be submitted.

D. Study sample repeat criteria should all be specified in one SOP.

Challenge Question #2

Which of the following statements is NOT true?

A. The study sample reanalysis-related SOP(s) provided should be the version current at the time of study sample reanalysis.

B. The repeat criteria under each repeat code should be clearly and objectively pre-defined in the SOP(s).

C. For above ULOQ samples, the reported sample concentration should be supported by the dilution integrity validated in the pre-study method validation.

D. As long as I do not report a sample reanalysis as “PK repeat” in the ANDA submission, then it will never be considered as a PK repeat.

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