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The CRO Perspective: Responding to the ICH M10 BMV Draft Guideline

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Introduction

- The recently issued 2019 ICH M10 BMV draft guideline will be an important step in harmonizing guidances around the world
- Due to the impact this document will have on the bioanalytical industry, there have been numerous meetings dedicated to compiling comments and providing feedback to regulators.
- The aim of this talk is to present the general CRO industry reaction to this guidance and the major changes that we foresee at Alturas as a result of its adoption

Industry Perspective

- General consensus: the ICH M10 draft guidance is a well-written and reasonable representation of current bioanalytical practices
- Outlines the standard for the **minimum requirement**, leaving room for scientifically based additions to, or departures from the guidance
- Several sections of the document have emerged as items for discussion or items that may require updates to current procedures

Assessing Matrix Effects vs Matrix Factor

"The matrix effect should be evaluated by analyzing at least 3 replicates of low and high QCs, each prepared using matrix from at least 6 different sources/lots"

- No need for determination/calculation of matrix factor, as was recommended in CCV
- Industry comments:
  - Propose use of 1 replicate (instead of 3) in 6 lots
  - Remove assessment of HQC, if problems exist it is apparent in the LQC

Dilution QCs in Sample Analysis

"The concentration of the dilution QCs should exceed that of the study samples being diluted (or of the ULOQ) and they should be diluted using the same dilution factor."

- Controversy surrounding the need to assess dilution QCs in sample analysis when an assessment was performed during validation
- GCC recommends adding language to state that it is the dilution **factor** that is being monitored, not the maximum concentration allowable for dilution

Multi-Analyte Stability

"If multiple analytes are present in the study samples (e.g., studies with a fixed combination, or due to a specific drug regimen) the stability test of an analyte in matrix should be conducted with the matrix containing all of the analytes."

- Continues requirement from current FDA guidance
- Lacks clarity around what type of stability test needs to be performed: Benchtop, freeze/thaw, LTS?
- Questions around the scope, is stability testing required for all analytes?
- Industry recommendation: For **fixed dose combination** and specific drug regimen where **primary objective is PK assessment**, the stability test of **an analyte** in matrix should be conducted with the matrix containing all of the dosed compounds

Number of Aliquots Required for Matrix Stability Experiments

"A minimum of three stability QCs should be prepared and analyzed per concentration level storage condition/ time point"

- No mention of the need to use a minimum of 3 tubes, no apparent scientific basis for this requirement
- Nonetheless, industry wide use of n=3 tubes for each assessment has been adopted to meet Health Canada requirements

Selectivity in Lipaemic Matrix

"For the investigation of selectivity in lipaemic matrices at least one source of matrix should be used…Although it is recommended to use lipaemic matrix from donors, if this is difficult to obtain, it is acceptable to spike matrix with triglycerides even though it may not be representative of study samples."

- GCC response:
  - Naturally lipaemic matrix is easy to obtain so spiking plasma is not acceptable
  - Lipaemic matrix should be defined as containing lipid concentration > 300 mg/dL

Assessment of Carryover

"During validation carry-over should be assessed by analyzing blank samples after the calibration standard at the ULOQ"

- More specific than the carryover requirement in the 2018 FDA guidance
- Lacking clarity on how many times (across different runs) this needs to be assessed
- Recommendation from Silver Spring AAPS ICH M10 workshop: assess carryover 3 times during validation, once in each core A & P run

Incurred Sample Reanalysis

"If the total number of study samples is less than 1000, then 10% of the samples should be reanalysed; if the total number of samples is greater than 1000, then 10% of the first 1000 samples (100) plus 5% of the number of samples that exceed 1000 samples should be assessed."

- Similar to current practice and current FDA/EMA guidance
- Industry response:
    - Maximum number of ISR samples should be limited
    - If there is a problem with the assay it is apparent in the first 100 ISR samples assessed

Conclusion

- The guidance outlines reasonable, scientifically sound updates to Bioanalytical Validation and Sample Analysis regulations
- Remains to be seen if the final document will adopt any industry recommendations presented here
- Regardless, the efforts of the regulators to harmonize guidances across regulatory agencies is appreciated and will allow for more efficient processes and submissions

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