Updating Regulated Assays for Implementation of ICH M10

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Session Description and Objectives

- Provide an overview of changes and challenges in implementation of ICH M10 for new and previously validated bioassays

- Discuss main procedural changes based upon ICH M10 guidance
- Discuss what changes need to be considered for previously validated methods
- Discuss how to implement changes from a CRO perspective

Overview

- Minimal changes needed for compliance ICH M10 guidance
- Items that require attention/changes:
  - Dilution QCs
  - QC concentrations
  - Stability QCs
  - Coadministered compound validation
  - Cross validations
  - Internal standard solution stability

Dilution QCs during sample analysis

- Per ICH M10, must be diluted from outside the range and must be prepared at dilution factors that bracket those used for samples
- No additional validation needed to implement in ongoing studies providing dilution QCs at the appropriate dilution factor were previously validated.
- Additional validation needed if increasing dilution factor
- When to add to existing studies?
  - Immediate addition when performing dilutions

Changes in QC concentration

- LQC (3x LLOQ), HQC (75-80% ULOQ) remain the same
- MQC concentration changes from geometric mean (CC III) or “mid-range” (FDA BMV) to 30-50% of ULOQ
- At least 2 QC concentrations should fall in range of sample concentrations
- When to add to existing studies or assays?
  - When to add versus change MQC level
  - Ongoing long-term studies
  - New studies

Multi-aliquot Stability QCs

- Most have implemented based upon Health Canada notice (2015)
- ICH first guidance to specifically call out requirement
- Stability assessments must be performed using a minimum of 3 aliquots per concentration for each assessment
- When and how to add to existing assays?
  - In all cases if data is still pending regulatory approval
  - Short-term stability and a single LTS timepoint

Coadministered Compound Validation

- ICH M10 specifically describes experiments that must be performed for fixed dose combinations
- Selectivity
- Short-term matrix stability and long-term matrix stability
- When to add to existing assays?
  - Many have already implemented
  - Specific guidance allows for ease of creating stability/selectivity assessments

Cross Validations

- Cross validation required when combining data for regulatory submission from two methods or two laboratories
- Analyze the same set of QCs in both methods
- Analyze ≥ 30 incurred samples if feasible
- Per ICH M10, statistical assessment of bias should be performed when comparing two methods
- Previous guidance prescribed ISR criteria or left criteria undefined
- When to perform?
  - Sponsor driven rather than CRO driven

Stability of Internal Standard Solutions

- ICH M10 specifically requires stability of internal standard in stock and working solutions
- Both short and long term stability required for all solutions.
- For stable label compounds, can rely on proven stability for unlabeled reference compound solutions
- For analog internal standards, all stability is required

Summary

- Minimal process changes based upon ICH M10 adoption
- Some SOP and method updates required
- Consider changes to ongoing assays in addition to changes for new assays

Questions??

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