FDA Bioanalytical Method Validation Guidance Update

Chromatographic Assays

Current Status

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Timeline

- Mid 2011 – Intent to issue guidance update announced
- 12th September 2013 – Draft guidance published and open for comments
- 3-5 December 2013 – Joint FDA/AAPS Meeting to discuss guidance held in Baltimore, MD
  - Consensus reached on a number of key issues
- Final guidance (incorporating consensus decisions?) release – to be determined

Feedback to Draft Guidance

- Following publication, draft was open to comment through 12 December 2013
  - according to www.regulations.gov, 62 comments were received before the deadline
    - Comments from individuals /companies, as well as scientific associations
      - GBC, GCC, EBF, AAPS, IQ

Crystal City V Meeting

- Culmination of feedback/comment process
- Baltimore – December 3-5, 2013
- Presentations from FDA and Industry Representatives
  - General Issues
    - Industry position presented by Bob Nicholson (PPD)
  - Chromatographic Assays
    - Industry position presented by Eric Fluhler (Pfizer)
      - Based on input from EBF, IQ, AAPS working groups
  - Ligand Binding Assays
  - Biomarker Assays
- Working dinner meetings following each day to generate consensus on issues discussed following the presentations
  - Dinner meeting on Day 1 lasted from about 6PM to 12:30 AM

FDA general perspective

- Some errors/typos
- Some items intentionally left out to permit flexibility
- Consider PK and biomarker assays have a spectrum of quality and rigor from early development to pivotal studies (e.g., BE)

Guidance Concerns - Chromatography

- Method Development
- Partial and Cross Validations
- Reference Standards
- Matrix Effect Assessment
- Accuracy and Precision
- Number of Validation Runs
- Recovery
- ULOQ
- QCs
- Co-med stability
- System suitability
- Processing batches

Method Development

- Issue: Does FDA consider method development within the scope of regulated BA
  - Guidance references “method development report” for regulatory submission
- Consensus: Narrative of method development (MD) should be included in validation report
  - Pertinent when a-typical approaches to MD are employed
  - Summarized history of method should be included or referenced in section 2.7.1 of the marketing application (CTD)

Partial Validation

- Multiple analysts
  - Issue: Guidance states that partial validation is required for method transfers between analysts
  - Consensus: Expectation that analysts be trained/qualified on technique
    - Documented in training or study file
- Anticoagulant counter-ion changes
  - Consensus that partial validation not required

Cross Validation

- Issue: Guidance calls for conducting cross validation with matrix standards and subject samples
- Consensus:
  - Change matrix standards to “matrix QCs”
  - Incurred samples are required
    - Avoid pooled samples where matrix effects are relevant
      - Ligand binding assays

Reference Standards

- Issue: Guidance extends the documentation and stability requirements of the reference standard to the internal standard (istd) and extends powder expiration date to solutions
- Industry position
  - COA for istd not always possible due to limited material
  - istd stability not critical as long as suitability is demonstrated
  - Follow guidance in Crystal City III whitepaper for istds and solutions
- FDA
  - Prefers COA for istd to be available but realizes that a demonstration of suitability is the critical issue

Stability Experiments

- Issue: Verbiage explaining matrix stability experiments not clear in draft guidance
- Consensus:
  - Stability samples should be compared to freshly made control samples
    - Control samples should be spiked on the day of the stability experiment using a stock solution within demonstrated stability
    - Either matrix standards or QCs can be used for stability assessments
  - 15% criteria applies to matrix stability, not solution stability
  - Stay with minimum of 3 freeze-thaw cycles

Matrix Effects

- Issue: Section on matrix effects does not reflect details of recommendations from previous meetings
- Discussion:
  - Centered around appropriate matrix experiments to perform
    - Ion suppression/enhancement determination
    - Selectivity in 6 individual lots which can include hyperlipemic and hemolyzed samples
    - Consideration should be given to the study population
    - Male/Female testing not required

Number of Validation Runs

- Issue: Guidance specifies 6 validation runs
- Consensus:
  - Less than 6 runs may be sufficient
  - Accuracy & precision (A&P) should be determined using a minimum of 3 runs over at least 2 days
    - 4 QC concentrations should be included in the validation A&P runs with at least 5 replicates per concentration
    - A&P run acceptance based on calibration curve standard (STDs) performance only. The objective being to assess true performance of method from the QCs.
  - Non A&P Validation runs should include 3 levels of run acceptance QCs in duplicate
    - Run acceptance based on STDs and QCs

Recovery

- Issue: approach in guidance confounds recovery and matrix effects
- Consensus:
  - Analyte added to and extracted from matrix should be compared to analyte added to extracted blank matrix (not solvent as in draft Guidance)
  - No specific acceptance criteria

Calibration Curve

- Issue: Guidance calls out ULOQ A&P acceptance criteria separately from other standards
- Consensus: ULOQ should be treated the same as other standards during validation

QC Sample Preparation

- Issue: Guidance calls for at least one demonstration of accuracy and precision using STDs and QCs prepared from separate stock solutions
- Consensus:
  - Agency confirmed this assessment is expected
  - For other runs, the same verified stock may be used for STD and QC preparation

Co-Med Stability

- Issue: Not specifically called for in guidance, yet, in recent years, some inspectors have been asking for this data
- Industry Consensus:
  - Conducting stability experiments in presence of co-meds does not add value
  - Agency still interested in fixed dose combinations, but will consider industry position

System Suitability

- Issue: System suitability mentioned in guidance but unclear if it should be considered as part of run acceptance or included in the actual run sequence of study samples
- Consensus: Not part of run acceptance or formal run sequence; can precede sample run but must be fully independent of STDs, QCs or study samples

Processing Batches

- Issue: if a run is composed of multiple processing batches, each distinct processing batch should possess at least duplicate QCs at all QC levels. Acceptance on the batch as well as run level is required
- Agency Example:
  - Single run contains plates from different days. Overall run passes but middle plate has high percentage of failing QCs
    - Agency questioned acceptability of middle plate
- No consensus on appropriate approach

Adding QC Levels to a Validated Assay

- Issue: If concentrations in study samples are clustered, additional QC levels should be added. A&P of additional QCs should be validated
- Consensus: New QCs do not need to be part of formal validation, but they should be qualified prior to use. Recommend to change verbiage from “validated” to “demonstrated”

Documentation

- Issue: A&P should be provided and tabulated for all runs (passed and failed).
- Consensus: Failed runs during validation need to be documented and reason for failure needs to be reported, but results of the validation runs with failed standards do not have to be incorporated into A&P calculations

Sample Reanalysis

- Issue: Guidance calls for all re-analyses to be done in triplicate
- Consensus:
  - Single reanalysis generally used for re-assay for assignable cause (failed runs, bad chromatography, dilution repeats etc.)
  - Duplicates generally used for confirmatory purposes (anomalous results, ISR investigations etc)

ISR

- Issues:
  - Suggestion to conduct pilot study
  - Total number of samples should be 7% of study
  - Meaning of need to use freshly prepared “calibrators” unclear
  - Assessments around Cmax and elimination phases for all study subjects
- Consensus
  - Pre-clinical pilot study is nice to have but not required
  - Total number of samples should be at least 5% of study
  - Freshly prepared refers to a curve extracted in a run separate from that in which the original samples were analyzed
  - Not necessary for all subjects
    - For subjects chosen, assessment should include samples near -Cmax and in the elimination phase

CRO Unique Topics and Responses

- CROs and Sponsors share the same bioanalytical science
- While the science is not unique, the logistics can be
- Language in the draft Guidance places bioanalytical CROs out of direct control of some specific requirements
- GCC members discussed these items post-CCV and were included in the GCC response to the FDA

Additional Concerns Unique to CROs

- Issue: Guidance calls for pre-study stability evaluations that cover conditions at the clinical site, during shipment and other secondary sites

- GCC Response: CROs are not able to control how clinical sites obtain, process, store, and ship samples.
  - Not appropriate for CROs to be held accountable for such activities
  - Dialogue with associated partners can minimize issues and is encouraged

Additional Concerns Unique to CROs

- Issue: Guidance calls for investigation of stability in a particular container system and this should not be extrapolated to other container systems

- GCC Response: CRO bioanalytical lab typically has little control over the container system used to collect and store study samples.
  - Discussions and early investigations by any bioanalytical lab on issues associated with containers (e.g. NSB) is prudent

Additional Concerns Unique to CROs

- Issue: Guidance refers to addressing unique or disproportionally high concentrations of human metabolites

- GCC Response: Often CROs are not provided with information on the metabolism of the drug, this can make addressing potential metabolite interference difficult.
  - Scientifically this is understood but it requires collaboration with the sponsor to resolve.

Additional Concerns Unique to CROs

- Issue: Guidance proposes conducting pilot studies prior to pivotal studies to obtain ISR samples

- GCC Response: CROs are not in a position to conduct pilot studies to assess ISR in method validation

Additional Concerns Unique to CROs

- Issue: Guidance calls for MV documentation that includes a detailed description of the assay procedure.

- GCC Response: Some CROs consider detailed assay procedures proprietary and are not comfortable including them in regulatory submissions. They are always available for inspection however.

Guidance Finalization

- Time required to finalize guidance is dependent upon whether FDA determines that the suggested edits are “minor” or “major”
  - If minor, potential to finalize guidance within 6 months
  - If major, full re-review required by multiple agency areas
- Recommendation not to alter SOPs until guidance is finalized

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