Bioanalytical Inspections: Overview and Case Studies

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Learning Objectives

- Understand how FDA conducts analytical inspections of BA/BE* studies
- Understand how FDA evaluates inspectional findings and determines if analytical methods are validated and analyte concentrations from study samples are accurate and precise

* BA/BE (Bioavailability/Bioequivalence)

Outline

- Office of Study Integrity and Surveillance (OSIS) – Introduction
- Bioanalytical Inspections – Overview and BMV Expectations
- Case Studies
- Closing Remarks

OSIS Key Activities

- Conducts inspections of BA/BE studies in collaboration with the Office of Regulatory Affairs
- Reviews inspectional findings and determines regulatory and scientific impact
- Provides study reliability recommendations to CDER review divisions to support regulatory decisions

OSIS Inspections

- Study integrity
  - Evaluate study conduct and completeness of documentation
  - Evaluate scientific approach in method validation and sample analysis
  - Verify on-site records compared to submissions to FDA
  - Assess impact on data reliability and human subject protection
- Surveillance
  - Assess overall quality of firm's operations and compliance to FDA's expectations and regulations (eg., 21 CFR Part 320)
  - Verify corrective actions for previously identified deficiencies

Bioequivalence (BE) Studies

- Typically based on PK endpoint
- Clinical site
  - Site where subjects are screened, enrolled, and dosed with test/reference drug, and blood samples are collected
- Analytical site
  - Site where subject samples are analyzed to determine the concentrations of an analyte

Bioanalytical Inspections

- Method Validation
- Analysis of Study Samples
- Documentation/Re-constructability of Study Conduct
- Facility and Workflow
- Equipment – maintenance and calibrations
- Staff Training Records
- Data Security

Method Validation

- Precision and Accuracy
- Selectivity and Specificity
- Sensitivity
- Matrix effects
- Stability under study sample conditions (e.g., long term storage, number of freeze/thaw cycles, post-processing)
- Partial validation and Cross-validation

Study Sample Analysis

- Study sample receipt and storage
- Sample verification procedures
- Sample movement and check-in/check-out records
- SOPs and pre-established criteria
  - Run acceptance/rejection
  - Chromatography acceptance and reintegration
  - Repeat analysis and data reporting

Study Sample Analysis (Cont'd)

- Appropriate acceptance/rejection of runs
- Reasons for repeat analysis, if any, and adequate documentation
- Audit trail
- Correspondence
- Accuracy of final study reports compared with on-site records
- Goal is to ensure that data supporting regulatory decisions are accurate and reliable

Inspection – What's Involved?

- Evaluation of records and the facility
- Interviews
- Scientific discussions
- Communication of inspectional findings

Expectations in BMV: Documentation

- One of the major clarifications in 2018 BMV Guidance (details in Table 2)
- All relevant documents necessary for reconstruction of a study to be maintained in a secure environment
- Applicable to both paper or electronic records

Expectations in BMV: Documentation

- Includes, but not limited to
  - Source data
  - Experimental records (e.g., processing sheets, lab notebooks, etc)
  - Investigations
  - Correspondence
- Contemporaneous with sufficient details
- Adequate justifications when applicable
- Changes should not obscure original data (i.e., original records should be maintained)

Documentation – Key Reagents/Samples

- Stock solutions, Calibrators, and QC samples
  - Log/records of preparation and usage (e.g., in and out time & dates)
  - Storage location and storage condition
- Blank Matrix
  - Records of receipt, matrix description, and storage
  - Results of interference and matrix effect testing

Documentation – Sample Tracking

- Study sample receipt and sample conditions
- Storage location
- Any temperature deviation during shipping and storage
- Tracking of QCs, calibrators, and study samples
  - E.g., freezer logs, barcode scan, etc.

Documentation – Study Sample Analysis

- System suitability records, if applicable
  - Sample identity, preparations, and data
- Sample extraction/processing records
  - Sample identity, date, time, and initials for each run
- Electronic raw data (chromatograms)
- Justification and mode of re-integration, if any
- Audit trail

Documentation – Repeat Analysis

- SOP for reanalysis
- All repeat values should be documented and available for review (as well as original values)
- Justification for repeats

Documentation – Deviations

- Contemporaneous documentation of deviations or unexpected events
- Documentation of investigations of unexpected events, including ISR failure investigation
- Impact assessment

Case Examples

John Kadavil, Deputy Director, DGDBE

Case #1: Re-injection

- During method validation, analyte's matrix stability (@-70°C) was evaluated
- During inspection, it was found that stability result from an initial run failed to meet the stability acceptance criteria
- Stability samples were re-injected, despite the run meeting the run acceptance criteria
- Results from the re-injected run were reported

Case #1 (Cont'd)

- The firm did not follow the pre-established procedure/criteria in run acceptance
- SOP in place – "*Reinjection at the discretion of the bioanalytical Principal Investigator*"
- Proper justifications for re-injection and contemporaneous documentation were not available

Case #2: Stability

- Long-term stability (LTS) of an analyte was established using a validated method
- Later, additional LTS study was conducted to extend the stability duration
- Extended stability failed to meet the firm's acceptance criteria
- The firm modified sample extraction procedures (i.e., thaw and process samples on ice)
- Repeated stability test and extended LTS duration

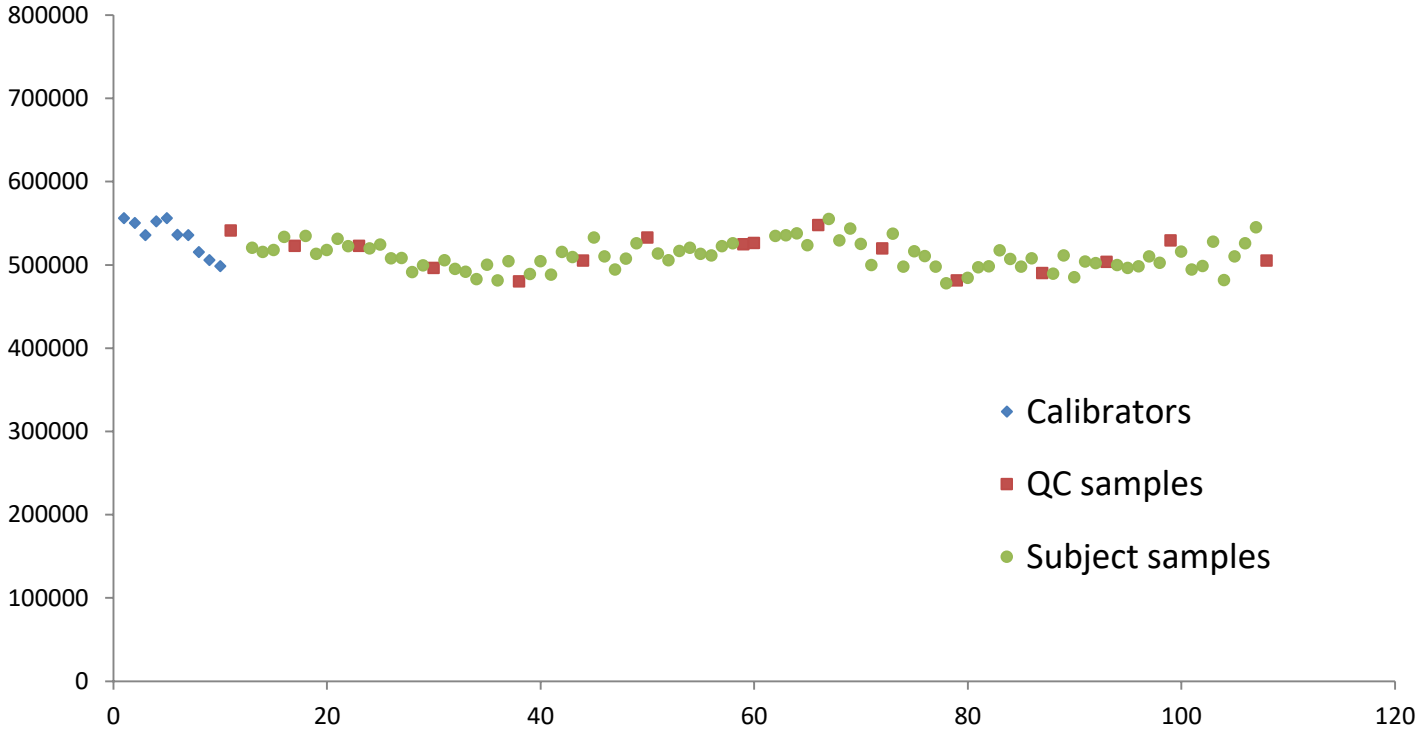
Case #2 (Cont'd)

- Scientific justification as to how the sample processing impacted LTS, while not affecting other stability (e.g., freeze-thaw, benchtop, etc)?
- Accuracy of study sample concentrations for studies conducted prior to the change in the method
- During inspection, the firm provided results of partial validation, evaluating A/P using the revised method

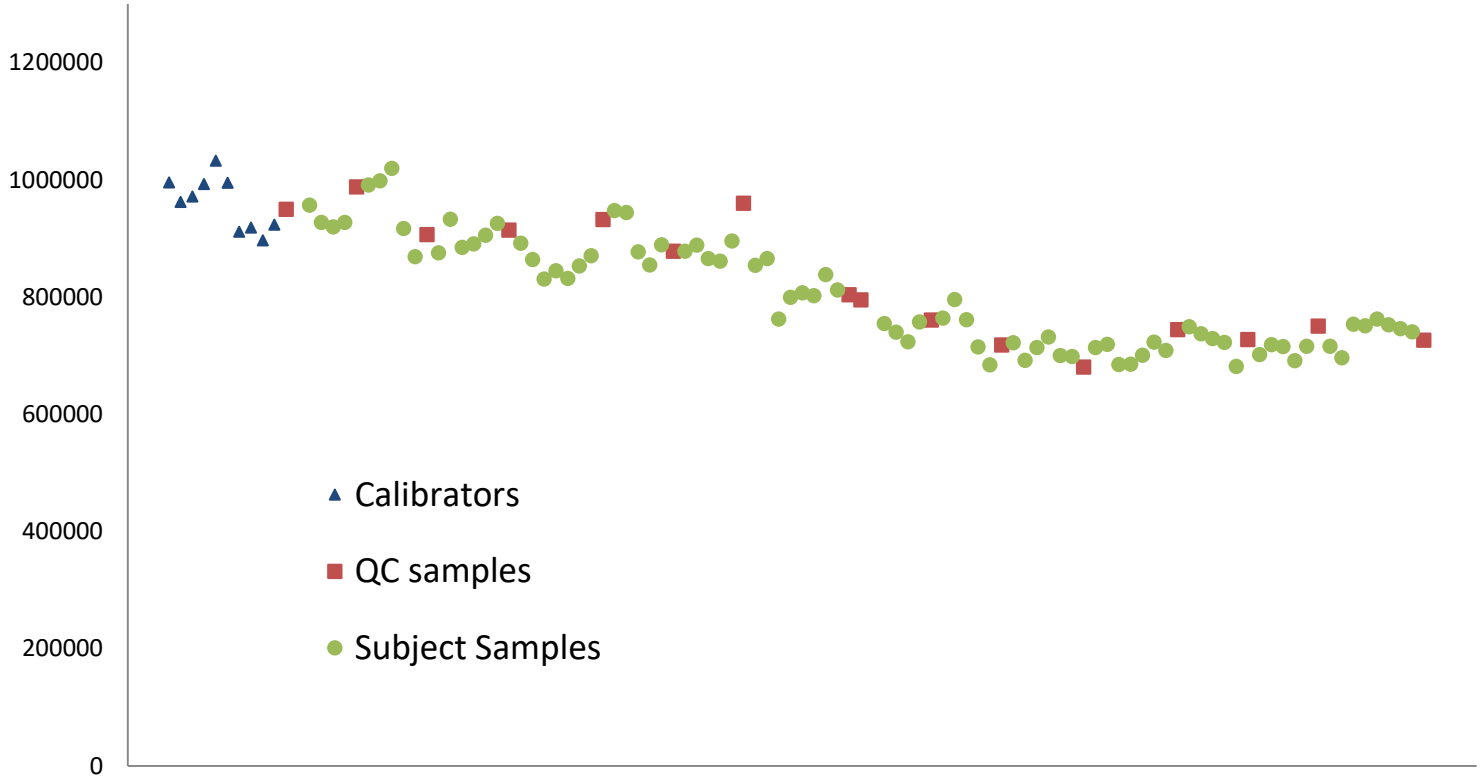
Case #3: Internal Standards (IS)

- For most LC/MS methods, an internal standard is added to all samples to normalize/ correct sample-to-sample variation during an analytical procedure
  - e.g., variability in liquid handling, extraction recovery, injection volume, instrumental conditions, etc.
- Play a critical role in ensuring accuracy and reliability of analyte measurements

Constant IS Responses in a Run/Batch



Drift in IS Responses



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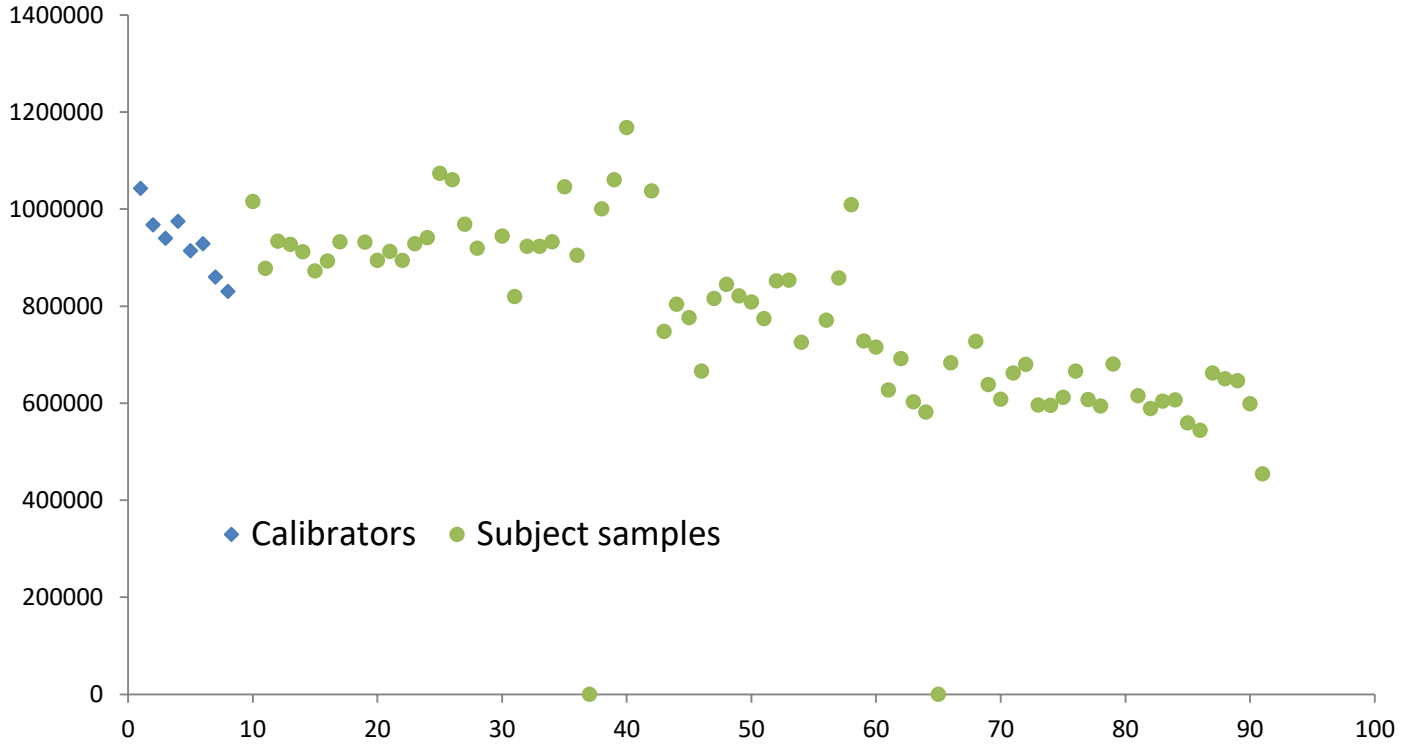

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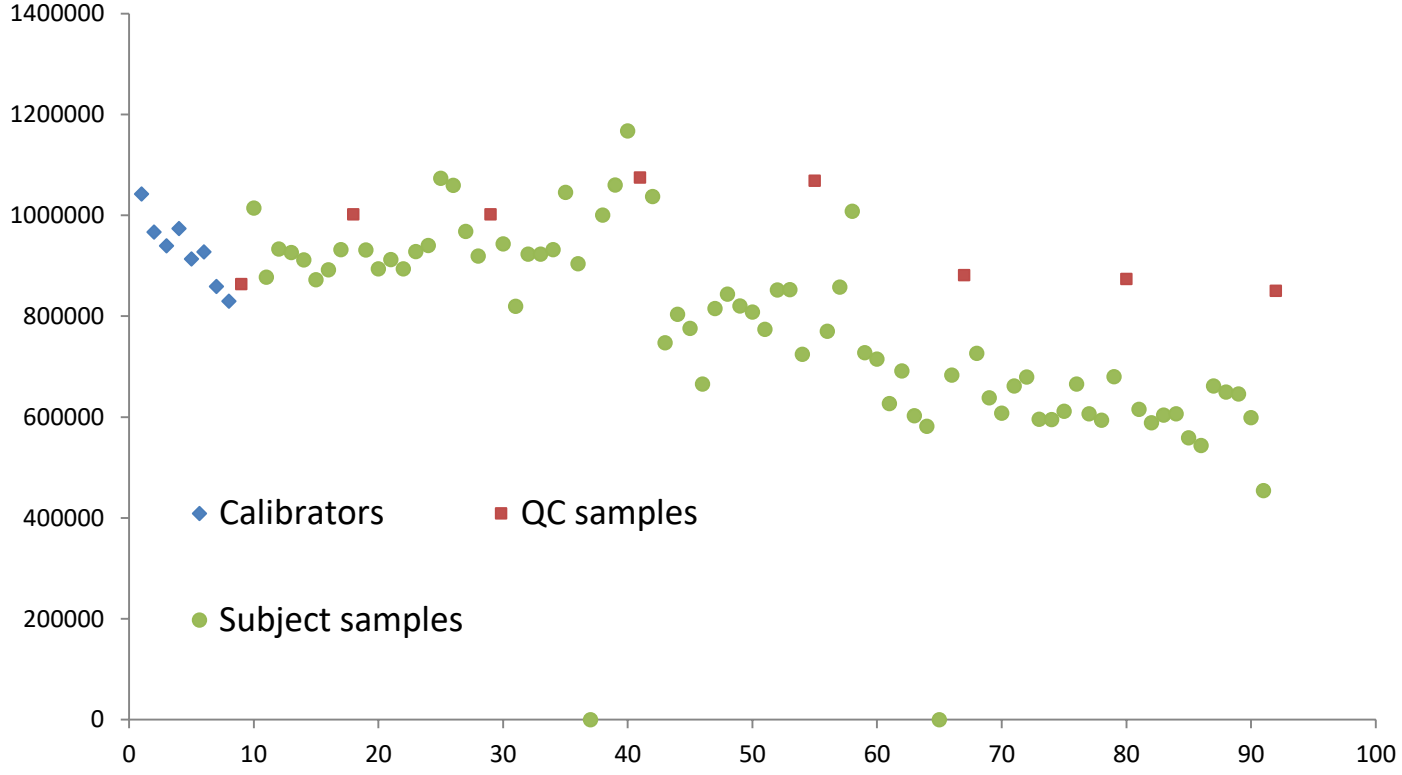
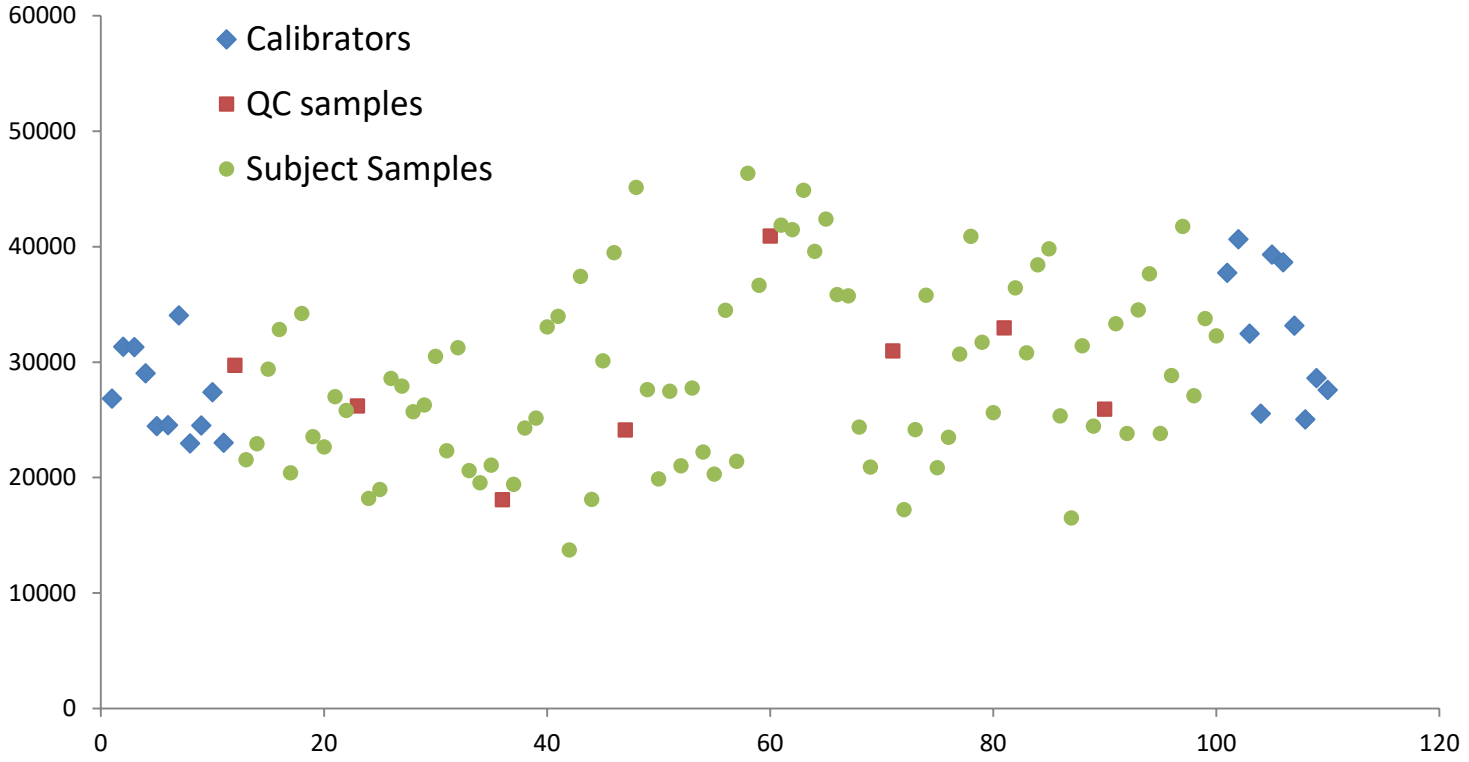


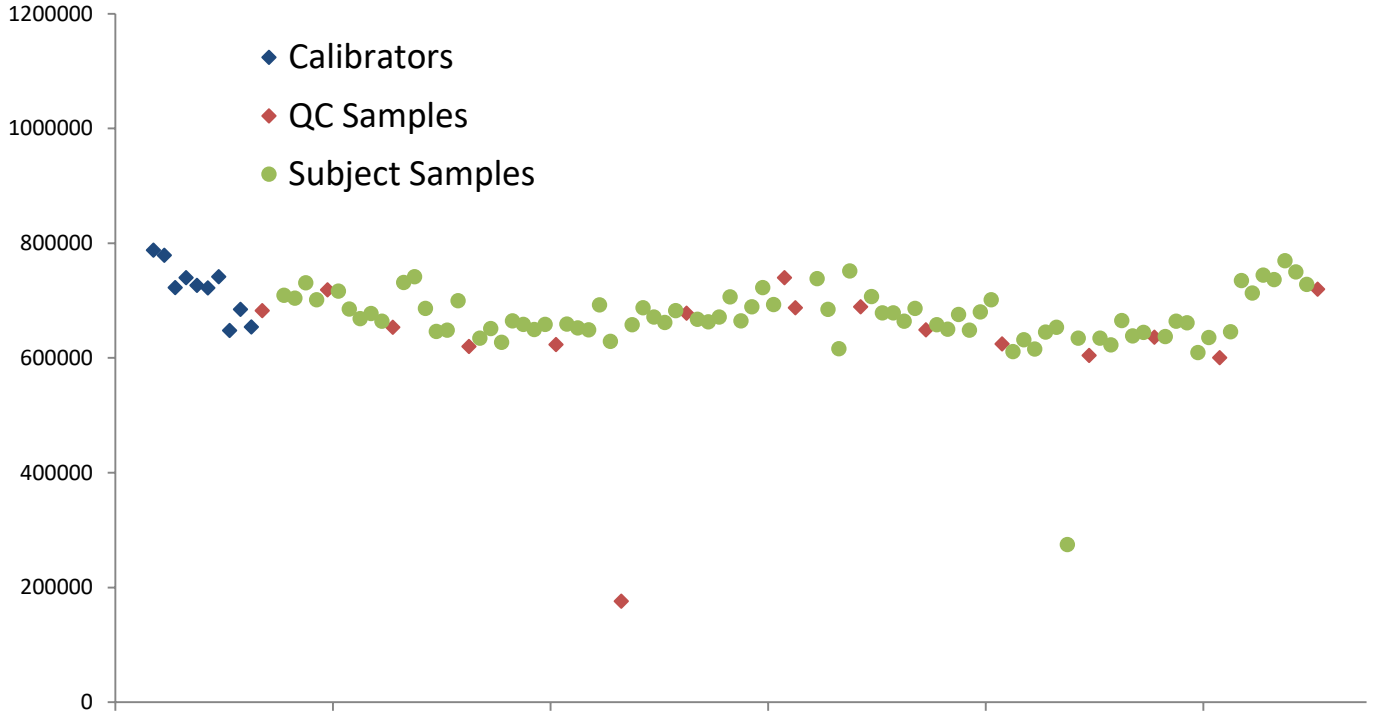
IS Variability

- Why does review of IS responses matter?
- Similar range of IS responses between study samples and calibrators/QCs
- Random/isolated IS variation
- Systematic IS differences between study samples and calibrators/QCs

Comparable IS Variability



Random/Isolated IS Variability

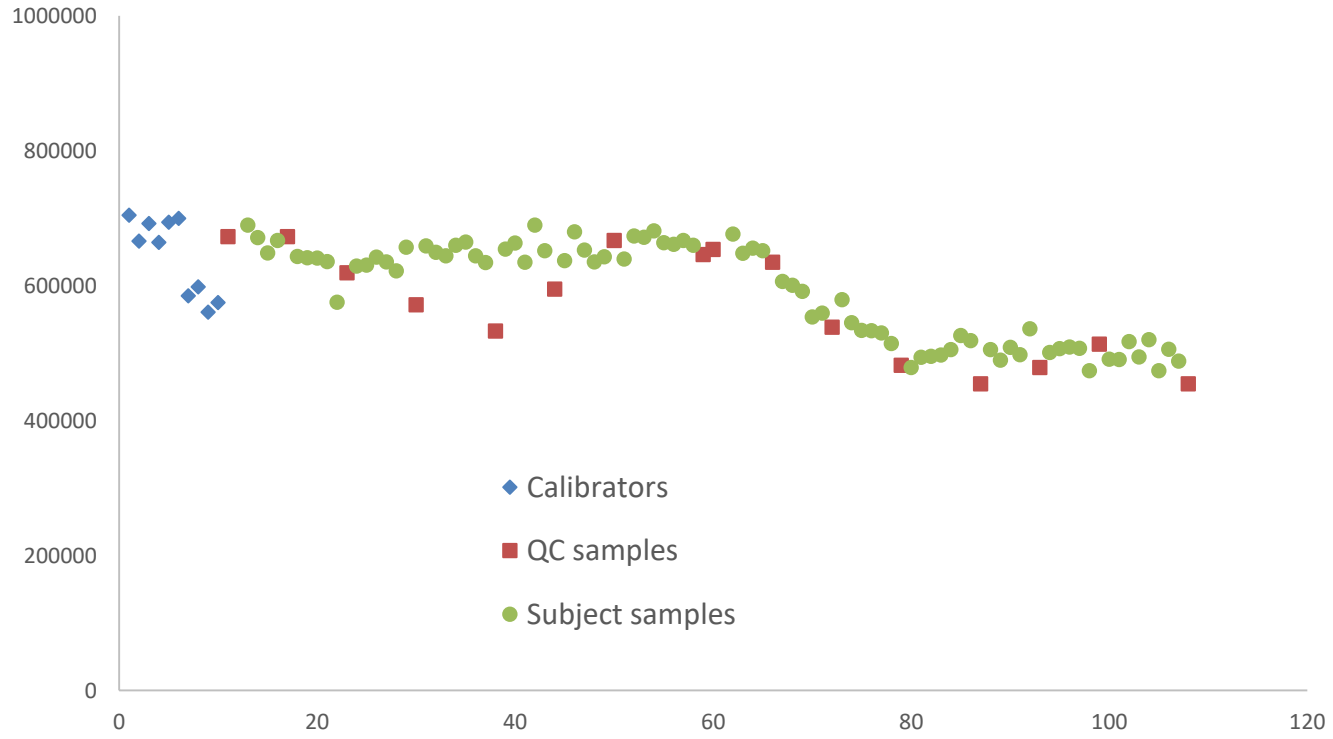


Affected samples should be handled per SOP

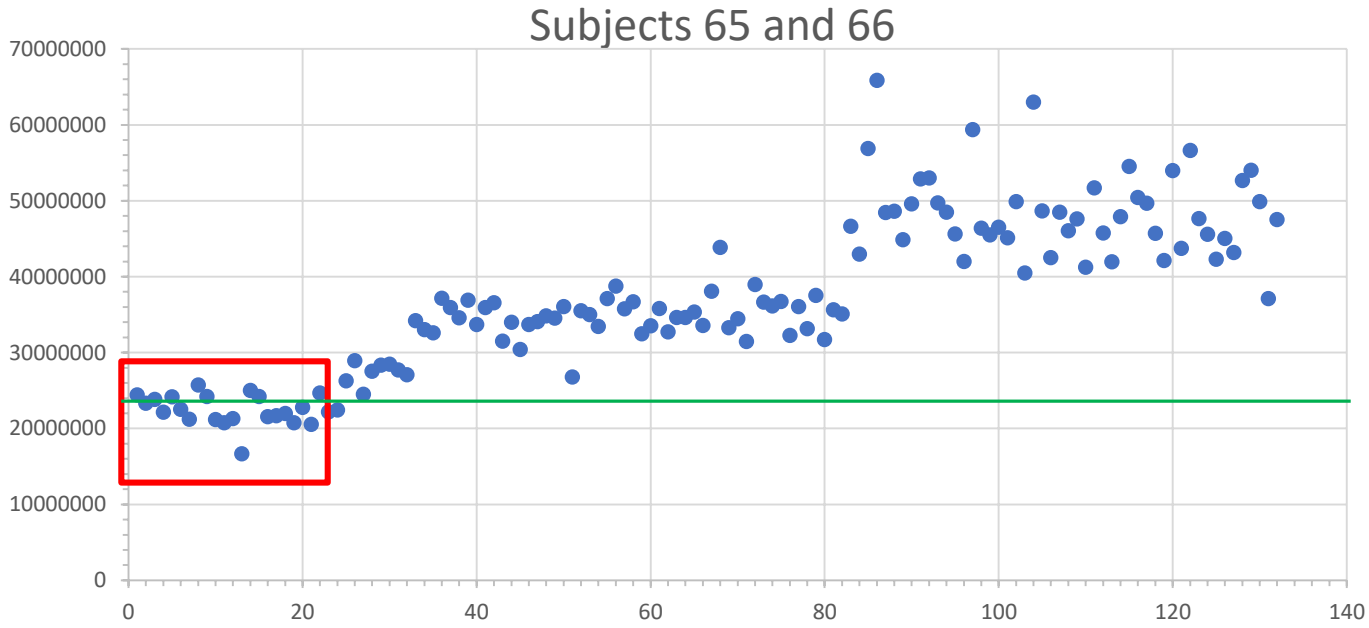
Systematic IS Variability

- IS variations with noticeable patterns
- IS responses from study samples distinctively different from those of CCs/QCs
  - Possible root causes may include
    - Recovery affected by matrix components
    - Detection affected by matrix components (ion suppression/ enhancement)
  - Depending on the extent, SOP criteria may not detect issues

Patterned IS Tracking with CCs/QCs



Distinct IS Responses



Can we be assured that subject sample concentrations are accurate?

IS Variability

- In general, no concerns if variability in IS responses of unknown samples (i.e., study samples) are similar to those of known concentrations (i.e., calibrators/QCs)
- Questions arise if variability in IS responses of study samples are uniquely different from calibrators/QCs
- Investigations/additional information may be needed to verify data accuracy

Conclusions

- OSIS conducts BA/BE bioanalytical inspections to ensure integrity and reliability of data submitted to FDA
- OSIS evaluates findings based on scientific merit and rationales
- Complete documentation to allow study re-construction and contemporaneous records of appropriate scientific justification will help OSIS determine study reliability


Thank
you!!

Challenge Questions

1. For bioanalysis of BA/BE study samples, expectations on contemporaneous documentation and data traceability apply only to electronic records – True or False?

False

Challenge Questions

2. Variability in IS responses of study samples that is uniquely different from calibrators/QCs indicates that the measurements of samples are inaccurate – True or False?

False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