In vivo studies – An overview of BA/BE Analytical Compliance Program

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Disclaimer

- This presentation reflects the views of the author. It should not be construed to represent FDA's views or policies.

Learning Objectives

- Learn about the in vivo BA/BE Bioresearch Monitoring (BIMO) Compliance Program (CP)-analytical
- Implementation of the CP during inspection of analytical studies
- How to ensure compliance with applicable FDA regulations and meet the FDA expectations

Outline

- Overview of the FDA BIMO Compliance Program (CP)
- BIMO Compliance Program 7348.004-Analytical
- Inspectional Focus and Expectations
- Challenge Questions

FDA BIMO Compliance Programs

- Comprehensive programs of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated clinical studies.
- Established to assure the quality and integrity of data submitted to the agency in support of new product approvals and marketing applications.
- Established to provide for protection of the rights and welfare of human subjects and animals involved in FDA regulated research.

Program #	Compliance Program Title
7348.003	In Vivo Bioavailability-Bioequivalence Studies - Clinical
7348.004	In Vivo Bioavailability-Bioequivalence Studies - Analytical
7348.007	Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies
7348.808	Good Laboratory Practice (Nonclinical Laboratories)
7348.808A	Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections
7348.809	Institutional Review Board
7348.809A	Radioactive Drug Research Committee
7348.810	Sponsors and Contract Research Organizations
7348.811	Clinical Investigators and Sponsor-Investigators
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections
7353.001C	Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections

FDA BIMO Compliance Programs

The objectives of the in vivo BA/BE Bioresearch Monitoring (BIMO) Program:

- To ensure the protection of the rights, safety, and welfare of human subjects participating in studies
- To ensure the quality, integrity and validity of clinical, analytical, and statistical data from BA/BE studies
- To ensure compliance with applicable FDA regulations and to identify significant deviations.

BIMO Compliance Program 7348.004

CP "Parts" or Sections

- Part I – Background
- Part II – Implementation
- **Part III – Inspectional**
- Part IV – Analytical
- Part V – Regulatory/Administrative Strategy
- Part VI – References, attachments, and Program Contacts
- Part VII – Center and ORA HQ Responsibilities

BIMO Compliance Program 7348.004

Part I - Background

CHAPTER 48 – BIORESEARCH MONITORING

SUBJECT:	IMPLEMENTATION DATE:
Procedures for FDA Staff: In Vivo Bioavailability/Bioequivalence Studies (Analytical)	05/01/2018

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Product coding not required for biopharmaceutical establishments	48004A BIOANALYTICAL IN-VIVO BA/BE (ANDAS) 48004N BIOANALYTICAL IN-VIVO BA/BE (NDAS AND BLAS) 48004P BIOANALYTICAL PEPFAR ANDA BA/BE 48004Q BIOANALYTICAL PEPFAR NDA BA/BE 48004B BIOANALYTICAL BA/BE - BIOSIMILARS

- This Compliance Program (CP) covers the analytical component of BA and BE studies,
- Outlines procedures for FDA investigators to ensure that the analytical portions of in vivo bioavailability (BA), bioequivalence (BE), pharmacokinetic (PK), or pharmacodynamic (PD) studies submitted to CDER are conducted using the highest laboratory standards and in accordance with applicable regulations,
- The studies covered by the FDA BIMO CP are governed by regulations found under 21 CFR 320 and follows the Bioanalytical Method Validation Guidance for Industry published in 2018

Inspectional Focus and Expectations*

PART III – INSPECTIONAL

1. Organization
2. Study Administration and Responsibility
3. Stability
4. Methodology
5. Documentation
6. Analysis of Study Samples

*The CP is based on the Bioanalytical Method Validation Guidance for Industry published in 2018

PART III – INSPECTIONAL

3. Stability: Sample Receipt

- Shipment records and sample conditions
  - temperature monitoring, any temperature excursions?
  - sample condition, any thawed samples?
- Sample accountability logs
  - # shipped, received, vs. analyzed
- Sample queries and resolutions
- Sample custody during normal hours of operation, weekends and holidays.
- Responsibility of sample custodians

PART III – INSPECTIONAL

3. Stability: Sample Handling

- If samples were handled per study protocol
- If samples were protected from light (if applicable)
- The number of instances when samples were retrieved from and restored in storage chambers.
- If number of retrievals supported by validated freeze thaw cycles.

PART III – INSPECTIONAL

3. Stability: Storage

Storage Chambers – Freezers and Cold Rooms

- Access to those who need it
- Sample log sheets with record of sample retrieval and return with date and time
- Functional alarm systems
- Confirm sample integrity during shipping and storage (from receiving to end of analysis)

PART III – INSPECTIONAL

3. Stability: General Considerations for MV Stability Experiments

- Stock solutions not exceeding the period of validated stability
- Experiments include samples prepared from a fresh stock solution of analyte in the appropriate analyte-free, interference free biological matrix
- Stability samples compared to freshly prepared calibrators and/or quality control samples (QCs) or nominal concentration
- Stability samples include at least three replicates of QCs (e.g., low QC (LQC), mid QC (MQC) and high QC (HQC))?
- Results within those recommended in the current BMV guidance?

PART III – INSPECTIONAL

3. Stability: Stability Experiments

- Long Term Stability
  - Cover longest storage duration of each sample from collection to analysis
  - Stability samples stored at same temperature as study samples
  - Stability samples prepared in the same matrix or condition as subject samples
- Freeze-Thaw Stability to cover frequency of sample movement from storage
- Benchtop Matrix Stability to cover maximum time of samples on benchtop/ambient temperature (or any special handling conditions e.g. on wet ice) during sample preparation

PART III – INSPECTIONAL

3. Stability: Stability Experiments

- Processed Sample/Extract Stability to cover
  - duration and the storage conditions prior to sample analysis, including benchtop, refrigerator, and autosampler
- Stock Solution Stability to cover storage duration/condition of master/parent and the working/intermediate stock solutions
- Reference Standard Storage & Procurement
  - Reference standard stock solutions made from reference standard that has not expired
  - Concentrations were adjusted for salts, counter ions, water and impurities
  - Light sensitive analytes and hygroscopic standards were handled and stored accordingly?

PART III – INSPECTIONAL

4. Methodology:

Precision and Accuracy (P&A)

- Inter and intra run assessments including all P&A runs?
- Number of P&A runs, concentration levels, replicates of each concentration used in each run?
- Separate stock solutions for calibrators and QCs?

- P&A evaluation with all valid runs

Recovery

- Extracted samples at three concentrations (low, medium, and high) compared with unextracted standards (analyte in solvent)?
- Should be consistent, precise and reproducible for analyte and IS

PART III – INSPECTIONAL

4. Methodology:

Calibration Curve/Range of Determination

- Made in same biological matrix (and additives) as study samples
- For multiple analytes simultaneous assays, calibration curves include all analytes
- Concentration range includes a blank sample, a zero sample, and at least six non-zero samples covering the expected concentration range in study samples.

Limits of Quantitation (LLOQ & ULOQ)

- LLOQ-analyte response 5x background noise, identifiable, discreet, reproducible
- Demonstrate P&A at LLOQ & ULOQ and sensitivity at LLOQ

PART III – INSPECTIONAL

4. Methodology:

Selectivity/Specificity

- At LLOQ for each analyte using six sources of blank matrix

Matrix Effect

- Evaluate in blank matrix from six sources for both analyte and IS
- Evaluate matrix factor when matrix effect seen

Carryover

Analyte carryover from preceding sample with high analyte concentration

PART III – INSPECTIONAL

4. Methodology:

Dilution

- Use same matrix (and additives) as samples for dilution
- Assess dilution integrity with same dilution factor as used for diluting samples with ULOQ concentration
- Run acceptance criteria based on run QCs and not on dilution QCs

Partial Validation

- evaluate changes made in a validated analytical method

PART III – INSPECTIONAL

5. Documentation

- Information meets ALCOA (accurate legible contemporaneous original attributable)
- Network and computerized systems are safe from inappropriate internal and external access
- All electronic data and computer systems are validated for ‘intended uses’

Refer to 21 CFR part 11 Electronic Records and Electronic Signatures

PART III – INSPECTIONAL

5. Documentation

Laboratory Instruments (used in study)

- Records of qualification, calibration, maintenance up to date per SOP
- Activity logs for instrument usage
- Instrument errors and failure are documented and reported

PART III – INSPECTIONAL

5. Documentation

Source data

- Source records allow reconstruction of study and all study related activities
- Data changes are traceable and documented
- Adequate systems and/or administrative controls exist to prevent deletion or alteration of source data
- An SOP exists to ensure that source data are consistently organized and retrievable
- The site has an SOP and follows it

Re-integration/Re-analysis

- Not selective and justified using SOP driven criteria
- Re-integration of chromatograms for QCs and calibrators should not bias run acceptance

PART III – INSPECTIONAL

5. Documentation

Audits Trails

- Software enabled with audit trails to capture acquiring, integrating, regressing activities for study data
- Adequate control over audit trail functionality
- Audit trail should support reconstruction of sample analysis activities

PART III – INSPECTIONAL

5. Documentation

Data Security

- Specified roles and restricted access for software to acquire, integrate, regress, modify, remove or report study data- unique login and password for individual staff
- Adequate security against unauthorized access to workstations and software used for the study
- SOP driven procedures and requirements for data storage and protection
- Storage, back-up, transfer, and data archival activities are secure

PART III – INSPECTIONAL

5. Documentation

Data Reporting

- Reported data are accurate and consistent with source data
- All (pass/fail) method validation experiments reported
- All sample analysis runs reported with reasons for rejected runs
- All reanalyzed samples and re-assay results reported per SOP
- Failed BE studies are reported to sponsor (and FDA)
- All protocol/SOP deviation are documented with justification

PART III – INSPECTIONAL

5. Documentation

Internal and External Communications

- Communication related to sample analysis between analytical site, clinical site, the sponsor
- Any request from sponsor to change study data or final study report
- Reporting to sponsor and documentation of issues with analytical method or study data and their impact on data quality and integrity

PART III – INSPECTIONAL

6. Analysis of Study Samples

System Suitability (SS)

- Independent of study sample analysis
- Evaluated prior to analytical sample run
- Evaluated prior to resuming a sample analysis run after any instrument malfunction

Run Acceptance

- At least three QC levels in duplicate and LLOQ
- Runs meet acceptance criteria (67% QCs and 50% QC at each level within 15% of nominal) as mentioned in BMV Guidance

PART III – INSPECTIONAL

6. Analysis of Study Samples

Re-injection of Study Samples

- Justified, SOP driven, samples covered by validated processed sample stability
- All reinjected samples reported in study report

Internal Standard (IS) Variability/Drift

- SOP to determine run rejection based on variability or drift in IS response
- IS variability limits pre specified in SOP, QCs and samples with IS variability outside limit re analyzed

PART III – INSPECTIONAL

6. Analysis of Study Samples

PK Anomalies

- PK sample re-assay governed by SOP, potential reason investigated
- Sample repeat request documented with reason
- Anomalous and final concentrations reported with reason for selecting final concentration

Incurred Sample Reproducibility (ISR)

- Samples representing analyte Cmax and elimination half life
- Meet pre-defined acceptance criteria (67% samples values within 20% of original sample values)
- Procedures predefined for investigation of ISR failure

Challenge Question #1

BIMO Compliance Program 7348.004 (analytical) is designed to ensure studies are conducted using the highest laboratory standards and in accordance with applicable regulations. True or False?

A. True

B. False

C. Depends

Challenge Question #2

The following is not a justified reason to re-inject or re-assay subject samples:

1. Sample processing error
2. IS variability
3. PK anomaly
4. Instrument malfunction
5. Poor chromatography
6. None of the above

Challenge Question #3

Security of study data is best achieved by providing unrestricted access for all to analytical software used for acquiring, integrating, regressing, and modifying study data of BE studies. True or False?

A. True

B. False

C. Depends

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References

- Code of Federal Regulations (CFR) Title 21, Part 320 – Bioavailability and Bioequivalence Requirements (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320)
- Code of Federal Regulations (CFR) Title 21, Part 11 – Electronic Records: Electronic Signatures (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11)
- FDA BIMO program www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs
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