Data Integrity Issues from BA/BE Clinical Site Inspections: Case Studies and OSIS Evaluation

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Learning Objectives

- Understand the FDA Bioresearch Monitoring (BIMO) Program
- Understand the documentation expectation specified in BIMO Compliance Program 7348.003
- Understand the potential impact of documentation, or lack thereof, on data integrity of BA/BE clinical studies

Outline

- Overview of the FDA BIMO Program
- BIMO Compliance Program 7348.003 and documentation expectation
- Case studies: Impact of documentation, or lack thereof, on data integrity of BA/BE clinical studies
- Challenge questions

FDA Bioresearch Monitoring (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 research.
- 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

BIMO Compliance Program 7348.003

In Vivo Bioavailability-Bioequivalence Studies - Clinical

CHAPTER 48 – BIORESEARCH MONITORING

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

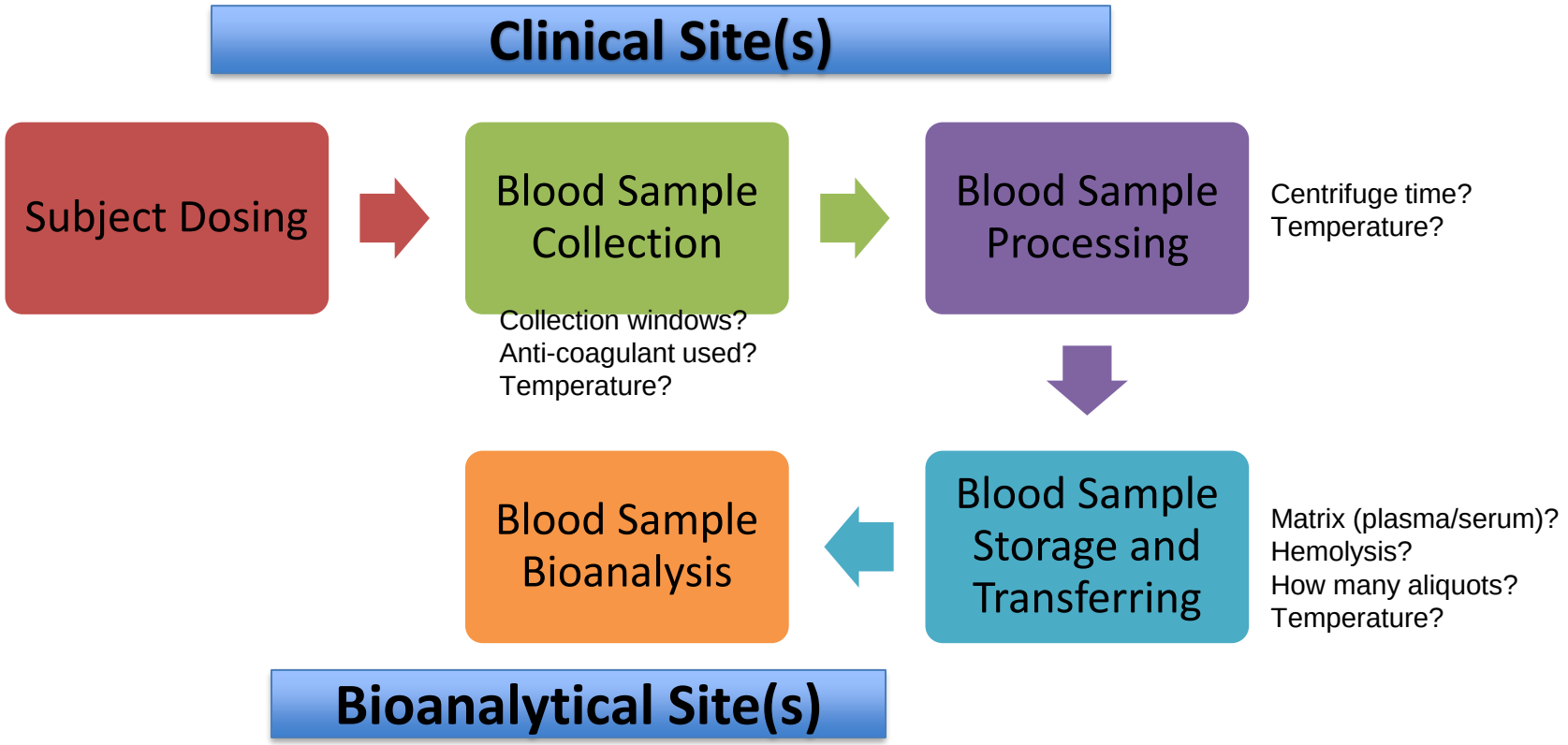
DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Product coding not required for biopharmaceutical establishments	48003A CLINICAL IN-VIVO BA/BE (ANDAS) 48003N CLINICAL IN-VIVO BA/BE (NDAS AND BLAS) 48003P CLINICAL PEPFAR ANDA BA/BE 48003Q CLINICAL IN-VIVO PEPFAR NDA BA/BE 48003B CLINICAL BA/BE - BIOSIMILARS

PART III – INSPECTIONAL

1. Organization
2. Study Administration and Responsibility
3. Subjects' Records and Documentation
4. Test Article Accountability and Disposition
5. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis
6. Randomization
7. Blinding Codes
8. Reserve Samples
9. Review of Electronic Data
10. International Inspections of Clinical BA/BE Study Sites
11. Reporting

www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs

Flow of Subject Samples in BA/BE Studies



BIMO Compliance Program 7348.003

5. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis

- **Review the source documents and determine if sample collection was performed according to the study protocol and the applicable SOPs.**
- **Review the SOPs and source documents for sample collection.**
  - Determine if samples were collected at protocol-specified time points and within allowable time windows.
  - Evaluate if samples collected outside of the protocol-specified range were properly documented and reported in the study report as protocol deviations.
  - Determine if missing samples were clearly documented along with an explanation.
  - Determine if protocol specific “special handling” procedures were followed and documented.
- **Review records for biological sample processing.**
  - Verify if samples were handled per the protocol/SOPs.
  - Evaluate whether critical steps during sample processing were properly documented. For example, evaluate if the duration and settings of sample centrifugation and the time until freezer storage were consistent with specifications in the protocol.
  - Determine if protocol specific “special handling” procedures related to sample processing were performed and documented

BIMO Compliance Program 7348.003

5. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis

- **Review records for sample storage.**
  - Review temperature records for freezer(s) where study samples were stored during the period between the first sample collection and the last sample shipment out to an analytical or other site.
  - Determine if samples were stored under the protocol-specified conditions.

- **Review the records for the total number of samples collected, total number of samples sent, samples that were missing, lost or with an insufficient volume (if any), and shipping records of each shipment in case of multiple aliquots.**

- **Review records for shipping/transfer of biological samples from the clinical site to an analytical lab or other site.**
  - Determine if records were sufficient to track transfer/shipment of samples from the clinical site to an analytical lab, CRO, or another site.
  - Review the correspondence between the clinical site and sample recipient, and the sample shipping records. Verify that date(s) of sample shipment match with those reported in the study report.
  - Review the correspondence, if any, between the clinical site and the sample recipient concerning the conditions of samples upon receipt and/or sample accountability.

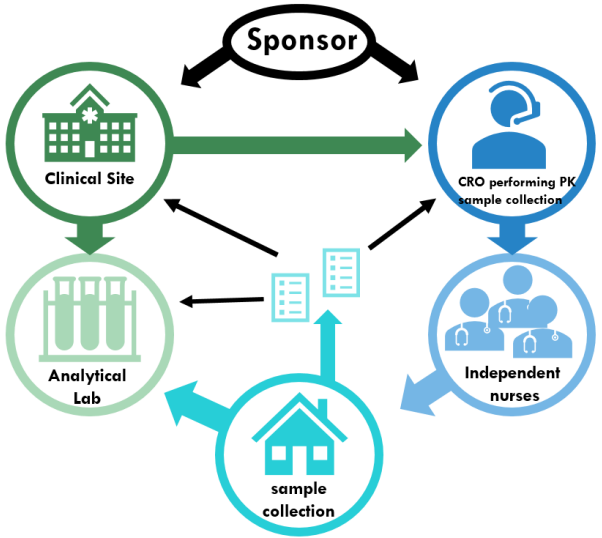
Case Study 1

Study Design:

A randomized, open-label, crossover, multicenter, pivotal in vivo bioavailability (BA) study with PK endpoint.

Sample Collection and Processing:

- The clinical sites were responsible for PK sample collection and processing of the initial timepoints after dosing.
- The sponsor used a CRO for PK sample collection and processing at extended timepoints after dosing.
- Relevant sample collection and processing forms were provided to the clinical sites and the CRO (subsequently further distributed to the independent nurses).



Case Study 1

Objectionable Findings:

Documentation for study subject PK sample collection and/or processing at certain timepoints were missing or inconsistent.

Study Number	123ABC	Subject ID	27
Date of Visit	1/2/2023	Visit Number	3

PK Blood Sample Collection	
Scheduled collection time	15:25
Actual collection time	15:30
Out of Window (±3 min)?	Yes
Comments	

PK Blood Sample Processing and Storage	
Centrifuge start time and condition	17:00, 4°C
Centrifuge stop time and condition	
Number of Aliquots	2
Hemolysis	No
Processed sample transfer time to freezer	16:50

PK Blood Sample Shipping to Central Lab	
Shipping date	1/1/2023
Sample condition	Frozen

** Mock form for illustration purpose only.*

Case Study 1

Evaluation:

- Without accurate documentation, it was impossible to reconstruct the conditions subject samples underwent during collection and processing.
- We concluded that some concentration data of the affected subject samples are not reliable based on the provided information.

Case Study 2

Study Design:

A randomized, open-label, multicenter, pivotal in vivo BA study with PK endpoint.

Drug Product:

Unstable in whole blood and will quickly convert to active moiety depending on storage conditions.

Sample Collection and Processing:

- The clinical sites were responsible for PK sample collection and processing.
- Specific instructions on PK sample collection and processing were provided in the Laboratory Manual; however, no relevant forms were provided to the clinical sites.

Case Study 2

Objectionable Findings:

- There was no written documentation for subject sample collection and processing.
- The clinical site personnel admitted to not completely following the sample collection and/or processing procedures specified in the Laboratory Manual, including the critical steps of temperature control and centrifugation.
- However, these deviations were not documented contemporaneously and were not reported.

Case Study 2

Evaluation:

- Without documentation, it was impossible to reconstruct the conditions subject samples underwent during collection and processing.
- We concluded that the concentration data of the affected subject samples are not reliable based on the available information.

BIMO Compliance Program 7348.003

3. Subjects' Records and Documentation

A. Study Source Records

- Describe the study source data files in terms of their organization, condition, accessibility, and completeness. For example, is the information on study source records attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Determine whether there is adequate documentation that all study subjects were alive and actively participated during the study.
- Determine whether the study subjects met the eligibility criteria (inclusion/exclusion criteria).

C. Other Study Records

- Determine if the site maintains other records pertinent to the study, such as, but not limited to: administrative study files, correspondence files, sign-in logs, financial disclosure records, written agreements (e.g., transfer of obligations), and third-party storage records. Document anything potentially relevant to the study conduct.

Case Study 3

Study Design: A randomized, double blind, placebo-controlled, multicenter, pivotal in vivo BE study with clinical endpoint.

Drug Product: Topical product

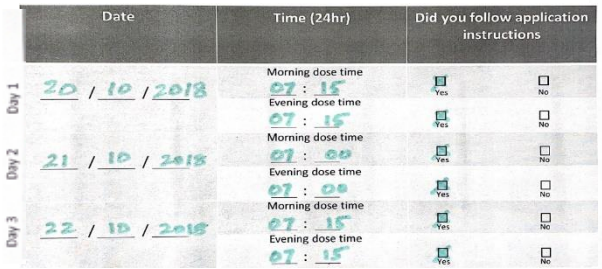
Documentation of dosing:

- Subjects were given a diary card to capture dosing details and to document any changes in skin reactions, AEs and concomitant medications during the study
- Subjects were asked to return the completed diary cards to the clinical site at each visit
- The clinical site staff then verified if the subject complied with the dosing requirements and signed off the completed diary cards.

Case Study 3

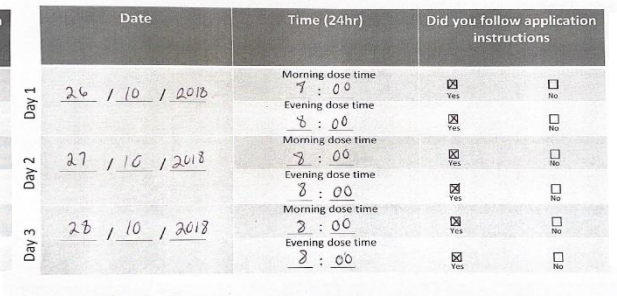
Interesting Findings:

- Similar or identical dosing times of different subjects
- Unique green-inked handwriting of different subjects
- Similar handwriting of different subjects
- Different handwriting of same subject



	Date	Time (24hr)	Did you follow application instructions
Day 1	20 / 10 / 2018	Morning dose time 07 : 15	☒ Yes ☐ No
		Evening dose time 07 : 15	☒ Yes ☐ No
Day 2	21 / 10 / 2018	Morning dose time 07 : 00	☒ Yes ☐ No
		Evening dose time 07 : 00	☒ Yes ☐ No
Day 3	22 / 10 / 2018	Morning dose time 07 : 15	☒ Yes ☐ No
		Evening dose time 07 : 15	☒ Yes ☐ No

Subject A
Period 1, Days 1 - 3



	Date	Time (24hr)	Did you follow application instructions
Day 1	26 / 10 / 2018	Morning dose time 7 : 00	☒ Yes ☐ No
		Evening dose time 8 : 00	☒ Yes ☐ No
Day 2	27 / 10 / 2018	Morning dose time 8 : 00	☒ Yes ☐ No
		Evening dose time 8 : 00	☒ Yes ☐ No
Day 3	28 / 10 / 2018	Morning dose time 8 : 00	☒ Yes ☐ No
		Evening dose time 8 : 00	☒ Yes ☐ No

Subject A
Period 2, Days 1 - 3

	Date	Time (24hr)	Did you follow application instructions
Day 1	20 / 10 / 2018	Morning dose time 07 : 30	☒ Yes ☐ No
		Evening dose time 07 : 30	☒ Yes ☐ No
Day 2	21 / 10 / 2018	Morning dose time 07 : 30	☒ Yes ☐ No
		Evening dose time 07 : 30	☒ Yes ☐ No
Day 3	22 / 10 / 2018	Morning dose time 08 : 00	☒ Yes ☐ No
		Evening dose time 08 : 00	☒ Yes ☐ No

Subject B
Period 1, Days 1 - 3

** Mock form for illustration purpose only.*

Case Study 3

Evaluation:

- Without proper and reliable documentation, it was difficult to reconstruct the self-dosing compliance.
- We concluded that the data generated from the affected study subjects are not reliable.

Summary

- Documentation of study related activities is critical during conduct of clinical BA/BE studies.
- Lack of adequate and/or complete documentation may have negative impact on study data integrity.
- BIMO Compliance Program 7348.003 lists examples of documentation that are expected to be reviewed during the BA/BE clinical inspections.

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)
- FDA BIMO program
  https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/bioresearch-monitoring-program-information
  www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs
- BIMO Compliance Program 7348.003: In Vivo Bioavailability-Bioequivalence Studies – Clinical (www.fda.gov/media/112538/download)
- Draft Guidance for Industry: *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application,* 2021 (https://www.fda.gov/media/87219/download)
- Draft Guidance for Industry: *Bioavailability Studies Submitted in NDAs or INDs – General Considerations,* 2019 (https://www.fda.gov/media/121311/download)

Acknowledgements

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OSIS Management

Challenge Question #1

True or False?

There is no documentation requirement or expectation for in vivo BA/BE studies.

A. True
B. False
C. Depends

Challenge Question #2

According to BIMO Compliance Program 7348.003, which of the following subject sample records would be reviewed during a BIMO BA/BE clinical inspection?

A. Sample collection records
B. Sample processing records
C. Sample storage records
D. Sample transfer and shipping records
E. All of the above


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