Clinical Inspections for Bioavailability/Bioequivalence Studies

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OSIS Workshop: CDER Bioavailability/Bioequivalence Study Sites and Inspections of Good Laboratory Practice – June 13, 2024

Disclaimer

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

Learning Objectives

- Understand OSIS's collaboration with the Office of Regulatory Affairs (ORA) on clinical inspections for bioavailability/bioequivalence (BA/BE) studies
- Describe clinical inspections
- Identify common issues (case studies)

BA/BE Clinical Work in OSIS

BIMO Compliance Program

7348.003 - In Vivo Bioavailability-Bioequivalence Studies - Clinical

FOOD AND DRUG ADMINISTRATION

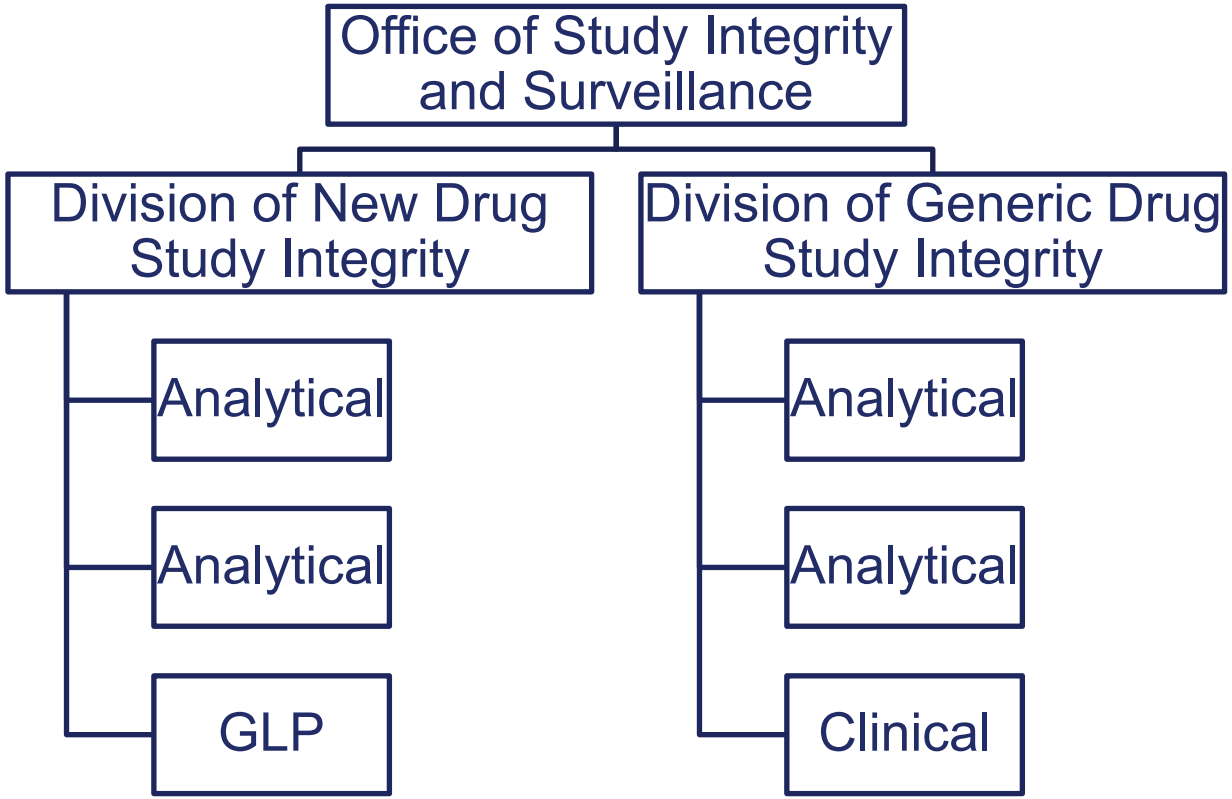
COMPLIANCE PROGRAM PROGRAM 7348.003

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

https://www.fda.gov/media/112538/download


Office of Study Integrity and Surveillance
Division of New Drug Study Integrity
Division of Generic Drug Study Integrity
Analytical
Analytical
GLP
Analytical
Analytical
Clinical

Assignment Workflow

- OSIS selects the sites for inspection
- OSIS sends inspection assignment to ORA
- ORA conducts inspection
- ORA prepares report

Assignment Workflow

- OSIS reviews ORA's report and associated exhibits
  - Form 483, site response
- OSIS prepares OSIS Review
  - Summarize inspection or RRA
  - Provide recommendations to the Review Division(s)
- OSIS issues Close Out Letter

Clinical Inspections

FDA's Bioresearch Monitoring Program

- FDA's Bioresearch Monitoring (BIMO) Program ensures
  - the information submitted to FDA are scientifically valid and reliable
  - the rights, welfare, and safety of human subjects have been protected
- FDA conducts inspections to verify the reliability, integrity and compliance of clinical and non-clinical research being reviewed in support of pending applications.

Clinical Inspections

- ORA conducts an inspection at the clinical site
  - May be announced or unannounced
  - Domestic: FDA Form 482

Clinical Inspections

- Tour of the clinical facilities
- Interviews with study personnel
- Protocols and amendments, IRB/IEC approvals
- Protocol deviations
- Informed consent forms
- Source records, CRFs, and eCRFs
  - Screening and eligibility
  - Meal-related records
  - Pharmacokinetic (PK) sampling times
  - Laboratory test results
- Adverse and serious adverse events

Clinical Inspections

- Randomization
- Blinding
- Drug administration, accountability records
- Reserve samples

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=320.38 and https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=320.63

- SOPs
- Temperature, calibration, maintenance records
- And more!

What happens at the end of an inspection?

- Close out meeting
  - Observations: FDA Form 483, 15 business days to respond
  - Discussion items: Verbal
- An ‘Establishment Inspection Report’ (EIR) is prepared
- OSIS reviews the EIR, exhibits, site response (if applicable) and prepares the OSIS Review, providing a recommendation to the Review Division(s)

What happens at the end of an inspection?

- Classifications (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-basics/inspection-classifications)
  - **No Action Indicated (NAI)** which means no objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action),
  - **Voluntary Action Indicated (VAI)** which means objectionable conditions or practices were found but the agency is not prepared to take or recommend any administrative or regulatory action, or
  - **Official Action Indicated (OAI)** which means regulatory and/or administrative actions will be recommended.

Common Issues and Case Examples

Common Issues

- Protocol adherence
- Recordkeeping
- FDA Inspection Dashboard: https://datadashboard.fda.gov/ora/cd/inspections.htm (overview of all inspections)

Protocol Adherence

- What does the protocol entail?
- What site activities does the protocol inform?

Case Study 1: Protocol Adherence

- Food effect study
- Protocol stated drug should be administered 30 minutes **after** the start of the meal
- 14/15 subjects received drug before 30 minutes elapsed
- OSIS recommended the Review Division determine the impact of the protocol deviation on PK data

Recordkeeping

- Broad category, including, but not limited to
  - Failure to retain records
  - Discrepancy between records
  - Illegible records
- Proper recordkeeping helps ensure data integrity and study reconstruction

Case Study 2: Recordkeeping

- Freezer records
  - More samples noted for storage/retrieval on log than were collected
  - Aliquots logged for storage on one shelf but retrieved on another shelf, no record of sample movement during storage
  - Sample returns not documented after retrieval
- Systemic issue, not isolated to study

Challenge Questions and Resources

Challenge Question #1

Which of the following statements is NOT true?

A. OSIS's clinical BIMO program falls under Compliance Program 7348.003 - In Vivo Bioavailability-Bioequivalence Studies – Clinical.

B. ORA provides the final inspection classification.

C. OSIS sends the Inspection Assignment Memorandum to ORA.

D. ORA writes the Establishment Inspection Report following an inspection.

Challenge Question #2

Which of the following study components could FDA inspect?

A. Adverse events

B. Drug accountability

C. IRB/IEC approvals

D. All of the above

Some Regulations Relating to Good Clinical Practice and Clinical Trials

- Electronic Records; Electronic Signatures (21 CFR Part 11)
- Regulatory Hearing Before the Food and Drug Administration (21 CFR Part 16)
- Protection of Human Subjects (Informed Consent) (21 CFR Part 50)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Institutional Review Boards (21 CFR Part 56)
- Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR Part 58)
- Investigational New Drug Application (21 CFR Part 312)
- Applications for FDA Approval to Market a New Drug (21 CFR Part 314)
- Bioavailability and Bioequivalence Requirements (21 CFR Part 320)
- Applications for FDA Approval of a Biologic License (21 CFR Part 601)

https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

Helpful Information

- https://www.fda.gov/training-and-continuing-education
- Guidance documents (https://www.fda.gov/regulatory-information/search-fda-guidance-documents, e.g., August 2023 Guidance Document on Informed Consent https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent)
- FDA Clinical Investigator Training Course (link to 2023 training: https://www.fda.gov/drugs/news-events-human-drugs/fda-clinical-investigator-training-course-citc-2023-12062023
- Good Clinical Practice Training (https://www.fda.gov/science-research/good-clinical-practice-educational-materials/good-clinical-practice-training)
- Sign up for the SBIA Webinars (many helpful ones https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/sbia-webinars
- Division of Drug Information webinars (https://www.fda.gov/about-fda/fda-pharmacy-student-experiential-program/division-drug-information-webinars)
- CDERLearn (https://www.fda.gov/training-and-continuing-education/cderlearn-training-and-education)

Good Clinical Practice Inquiries

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FDA oversees clinical trials to ensure they are designed, conducted, analyzed and reported according to federal law and FDA's regulations. The agency's oversight of clinical trials protects the rights, safety, and welfare of people participating in clinical trials, and supports the development of safe and effective medical products. The agency addresses inquiries related to good clinical practice and human subject protection policies on an ongoing basis. The downloadable spreadsheet below includes inquiries that have been submitted to the FDA as well as the agency's replies to each inquiry and is searchable by different fields such as topic, date, etc.

See the FDA archive for inquiries from 2013 to 2017 and inquiries prior to 2013. Contact gcpquestions@fda.hhs.gov with questions.

Good clinical practice inquiries and responses 2018 - 2022

Summary

- OSIS collaborates with ORA for clinical BA/BE inspections
- OSIS provides recommendations to the Review Divisions based on evaluation of inspection findings

Closing Thought

Questions?

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