U.S. FOOD & DRUG ADMINISTRATION

GLP Compliance Program 7348.808

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CDER Inspections of Good Laboratory Practice, Animal Rule, and Bioavailability/Bioequivalence Study Sites – July 19, 2022

Disclaimer

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

Learning Objectives

- Increase awareness of FDA's BIMO Compliance Programs
- Understand how to apply the inspection elements with CP 7348.808 Good Laboratory Practice (Nonclinical Laboratories)

FDA Compliance Programs

- FDA's Compliance Programs have evolved over the years
- Provide instructions to FDA personnel (ORA and Center staff) for conducting inspections and other compliance activities

FDA Compliance Programs

Organized by the following program areas:

- Biologics (CBER)
- Bioresearch Monitoring (BIMO)
- Devices/Radiological Health (CDRH)
- Drugs (CDER)
- Food and Cosmetics (CFSAN))
- Veterinary Medicine (CVM)

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BIMO Compliance Programs

Compliance Program Manual

Program #	Compliance Program Title	On-line Availability	
7348.003	In Vivo Bioavailability-Bioequivalence Studies - Clinical		PDF
7348.004	In Vivo Bioavailability-Bioequivalence Studies - Analytical		PDF
7348.007	Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies		PDF
7348.808	Good Laboratory Practice (Nonclinical Laboratories)		PDF(117 kb)
7348.808A	Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections	HTML	PDF(38 kb)
7348.809	Institutional Review Board		PDF(293 kb)
7348.809A	Radioactive Drug Research Committee		PDF (155 kb)
7348.810	Sponsors and Contract Research Organizations		PDF
7348.811	Clinical Investigators and Sponsor-Investigators		PDF
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections		PDF (335 kb)
7353.001C	Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections		PDF

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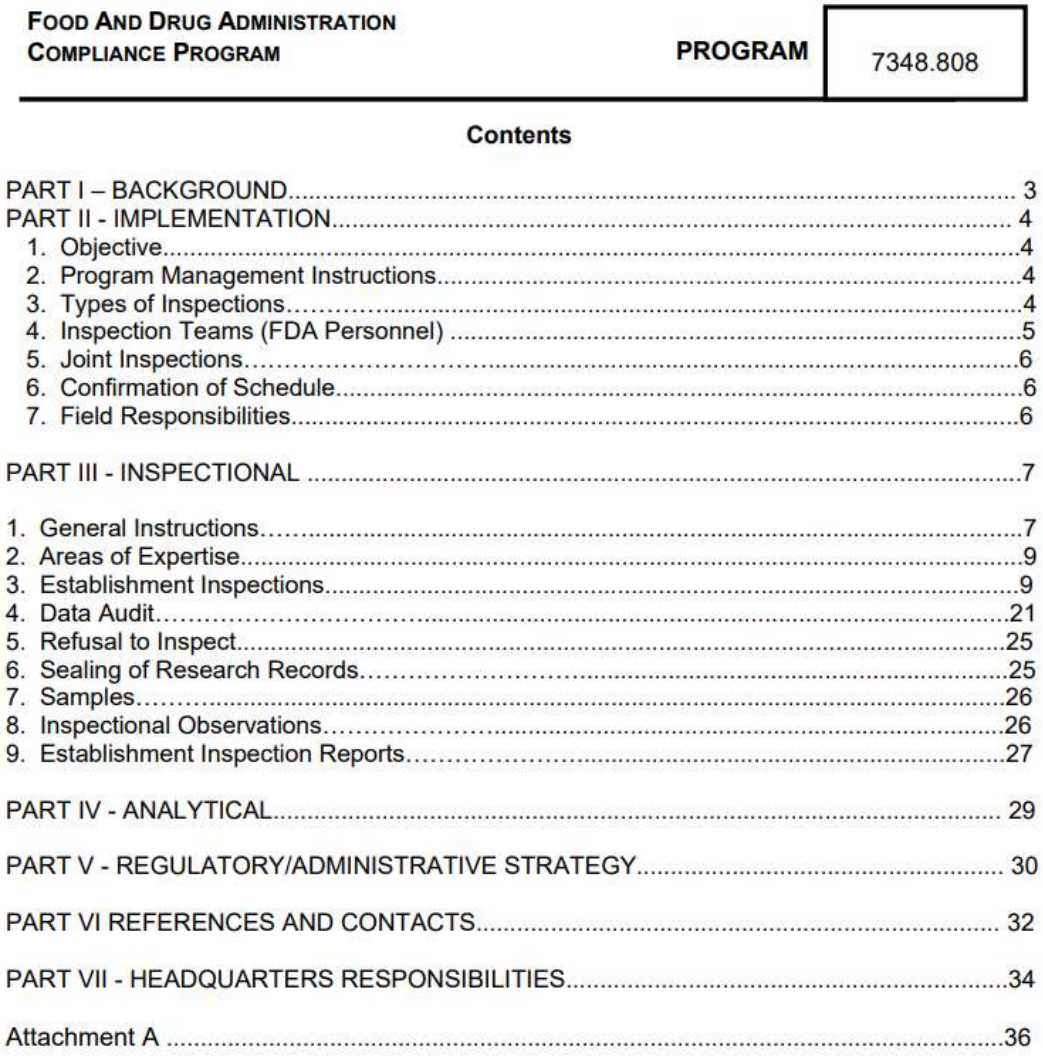
7348.007	Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies		PDF
7348.808	Good Laboratory Practice (Nonclinical Laboratories)		PDF(117 kb)
7348.808A	Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections	HTML	PDF(38 kb)
7348.809	Institutional Review Board		PDF(293 kb)
7348.809A	Radioactive Drug Research Committee		PDF (155 kb)
7348.810	Sponsors and Contract Research Organizations		PDF
7348.811	Clinical Investigators and Sponsor-Investigators		PDF
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections		PDF (335 kb)
7353.001C	Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections		PDF

Importance of GLP Study Data

- The toxicity profile of the test article
- The observed no adverse effect dose level in the test system
- The risks associated with clinical studies
- The potential teratogenic, carcinogenic, or other adverse effects
- The level of use that can be approved

Sections of Compliance Program 7348.808

- Background
- Implementation
- Inspectional
- Analytical
- Regulatory/Administrative
- References/Program Contacts
- HQ Responsibilities



FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM

PROGRAM 7348.808

Contents

Compliance Program Objectives

- To verify the quality and integrity of data
- To inspect (periodically) nonclinical laboratories conducting safety studies
- To audit safety studies and determine the degree of compliance with GLP regulations

Types of Inspections

Surveillance

- Routine, approximately every 2 years
- Verify reliability, integrity & compliance

Directed

- Verify reliability, integrity & compliance
- Investigate issues involving unreliable safety data
- Re-inspection (e.g., OAI case)
- Verify the results of 3rd party audits or sponsor audit
- OECD study data audits

GLP Studies Audited

- Directed inspections: Identified in assignments
- Surveillance inspections:
  - Studies for submission to FDA
    - Initiated/completed since the last GLP inspection
    - Encompass the full scope of laboratory operations
    - Significant for safety assessment (carc/repro/chronic)
    - Different species

Establishment Inspections

- General Instructions
- Areas of Expertise
- Organization/Personnel
- QAU
- Facilities
- Equipment
- Testing Facility Operations
- Reagents and Solutions
- Animal Care
- Test and Control Articles
- Protocol and Conduct of Nonclinical Laboratory Study
- Records and Reports

Inspection Plan

Opening meeting

- Firm’s introduction
- Scope of inspection
- Request organization chart, master schedule, SOP index, floor plan, study materials
- Important to ensure investigator and site staff have clear communication and expectations

Inspection Plan

- Investigators use the CP to conduct the inspection
- Facility tour
- Data auditing
- Interview TFM, Study director, scientists, and lab staff
- Daily wrap up meeting
  - Questions, concerns, progress
  - Plan for following day
- Close out meeting

Organization & Personnel

Goal: To assess that the firm has appropriately trained personnel

- Who - Management, QAU, Study Director, Technicians, etc.
- What - Assess responsibilities and corresponding qualifications
- What records - CVs, training records, protocol, and raw data
- What else - Observe in action, are there enough employees, supplies

Quality Assurance Unit

Function – To ensure firm operates in compliance with all regulatory and firm's requirements

- They are QA and not QC
- Independent of study personnel
- Special Dispensation – We do not audit QA reports
- Required to maintain a copy of the Master Schedule

Facilities

Goal – To assess the adequacy of the facility for its function

- Is there sufficient room?
- Is the temp/ humidity appropriate?
- How well is it maintained?
- Is there specific storage space for specific functions: receipt, storage, housing, cleaning, necropsy, dosing, TA prep, archives?
- What to look at – the room, materials in the room, maintenance, cleaning records, SOPs

Equipment

Goal – To assess the adequacy for its function

- What equipment should be there?
- Is the equipment qualified/ calibrated/ working?
- Is the equipment where it is needed/well maintained?
- Do employees know how to use it?
- Is it used properly?
- What to look at – training records, maintenance/cleaning records, SOPs, user manuals, calibration certificates, etc.

Testing Facility Operation

Goal – To verify that SOPs are established and followed

- Testing facility should have SOPs established and followed
- Required written SOPs – 12 categories listed in 21 CFR 58
- SOPs are adequate to ensure quality and integrity of data
- All deviations must be authorized by the Study Director
- SOPs need to be available for use
- Historical versions maintained

Testing Facility Operation

Goal – To verify that SOPs are established and followed

What to look for:

- TOC for standard operating procedures
- Relevant SOPs related to study or operations being inspected
- Process of how SOPs are reviewed/approved/ distributed/ employees informed of new SOP
- Observe execution of operation and compare with SOP
- Compare SOPs available to employees with versions in the archive

Reagents and Solutions

- All reagents and solutions in the laboratory areas shall be labelled to indicate identity, titer or concentration, storage requirements, and expiration date
- Deteriorated or outdated reagents and solutions shall not be used
- What to look for:
  - Look at storage conditions and labels
  - Are they consistent?
  - Is the fridge/freezer/lighting (yellow) properly maintained?

Animal Care

Goal – To minimize stress and uncontrolled influences that could affect the test systems

- SOP for housing, feeding, handling, and care of animals
- Quarantine/isolation as per acceptable veterinary medical practice
- Health evaluation of animals prior to study initiation
- Treatment of diseased animals shall be isolated/treatments documented
- Identification of individual animals

Animal Care

What to look for:

- Separation of species
- Housing is of appropriate size/construction & clean
- Food & water are analyzed to ensure it doesn't interfere with study
- Bedding not interfere with study
- Pest control – should not interfere with study
- IACUC

Test and Control Article

Goal – Verify that the test article and control article are appropriate/reliable

- The identity, strength, purity, and composition or other characteristics which appropriately define the test or control article
- Label shall include the ID, lot #, expiration, storage requirements
- Formulations: Verify concentration, uniformity, and stability
- If sponsor performs the testing, verify the test facility has documentation

Protocol & Study Conduct

Evaluate the protocol

- Is it properly written and authorized by the Study Director?
- Protocol should contain information required by the regulations:

  Title, test article & control article by name or code, sponsor, testing facility name and address, animals (number, BW, sex, source, species, strain, age), study design, diet, carriers, dose levels, frequency of dosing, analysis, approval date of sponsor, and dated signature of Study Director

- Determine if there were protocol amendments

Protocol & Study Conduct

Verify that the study was conducted according to the study protocol and SOPs

- Protocol vs. Study Conduct
- Check the protocol and final study report has the required elements
- How the test system was monitored
- How raw data were recorded (manual vs. electronic)
- How corrections to raw data is done
- Were animals randomized?
- How samples were collected and identified
- How is access to computer systems limited to authorized personnel

Records and Reports

Verify that the study was conducted as per study protocol and SOPs

- Properties of raw data
    1. Accurate
    2. Legible
    3. Contemporaneous
    4. Original
    5. Attributable

Records and Reports

- Name/Address of facility
- Initiation/completion dates
- Objectives & procedures
- Changes to protocol
- Test/control articles
- Description of quality/integrity issues
- Methods
- Test System
- Dose, Route, duration

- Signed dated scientist reports
- Archive location
- QAU statement
- Record retention:
  - INDs 5 years
  - NDAs 2 years
  - If not submitted, 2 years following end of study
- Data audit:
  - Protocol vs. final report
  - Final report vs. raw data
  - Specimen vs. final report

End of Inspection

- Close-out meeting
  - Inspectional Observations (FDA Form 483)
  - Discussion Items
- Establishment Inspection Reports

Question 1

FDA GLP inspections include

a. Directed Inspections

b. Surveillance Inspections

c. Both

Question 2

FDA GLP CP is numbered

a. 7348.808

b. 7348.807

c. 7348.808A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