

Chapter 48 – Bioresearch Monitoring

Subject  GOOD LABORATORY PRACTICE PROGRAM (Nonclinical Laboratories) EPA DATA AUDIT INSPECTIONS	Implementation Date  October 1, 2000
	Completion Date  September 30, 2003
Data Reporting	
Product Codes	Product/Assignment Codes
52Y	04808A - Chemical Contaminants

Field Reporting Requirements

Inspections covered by this compliance program involve facility inspections and data audits conducted under Food and Drug Administration (FDA) authority and data audits conducted under authority delegated to FDA by the Environmental Protection Agency (EPA). Separate establishment inspection reports (EIR) should be prepared for the FDA and EPA components of the inspection. For the FDA component of the inspection, the EIR including attachments and exhibits, will be sent to the assigning center bioresearch monitoring program unit. For the EPA component, the EIR including attachments and exhibits, and inspectional support documents provided by EPA prior to the inspection, will be sent to the Office of Enforcement, Division of Compliance Policy (HFC-230). The District Office should NOT retain any records or documents related to EPA component of the inspection.

For data reporting purposes, all manpower expenditures on EPA assignments by FDA investigators; such as pre-inspection activities, on-site time, and report writing, should be fully reported as EPA time expenditures under 7348.808A on the same cover sheet as the FDA component of the inspection under 7348.808.

## PART I - BACKGROUND

An Interagency Agreement between the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) provides for FDA auditing of selected health-related toxicological test reports and related laboratory records in order for EPA to determine, (1) whether the testing was performed in accordance with the test protocols, (2) whether any reported deviations may have affected the reliability of the test results, and (3) whether the test reports fully and accurately reflected the test procedures and results. These audits will be performed by making on-site visits of the toxicological laboratories that conducted the tests. The agreement is limited to coverage of laboratories within the United States.

EPA is responsible for setting tolerances for pesticide residues in or on raw agricultural commodities and processed foods under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346 and 348) and for registering pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 *et seq.*). In addition, EPA has the mandated task under the Toxic Substances Control Act (TSCA) (15 U.S.C. 2601) to assure that no chemical will present an unreasonable risk of injury to health or the environment. EPA regulatory decisions on such matters are based in part on the results of toxicological testing performed by or for registration applicants, tolerance petitioners, and chemical manufacturers. Therefore, it is essential that such testing provide an objective and reliable basis for decision-making. An EPA determination that testing was deficient or that a test report was inadequate, may lead to regulatory and/or enforcement action; accordingly, such determinations must be well founded and fully documented.

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PART II - IMPLEMENTATION

Objective

This program is designed to provide specific instructions regarding the conduct of EPA data audit inspections under the Good Laboratory Practice Program (CP 7348.808).

Program Management Instructions

A. Kinds of Laboratories to be Inspected

1. See CP 7348.808
2. FDA may perform data audit inspections for EPA at facilities which test pesticides or toxic substances not regulated by FDA.

B. Frequency and Type of Inspection

1. The laboratories identified by EPA for coverage under this program will be inspected in accordance with assignments issued to FDA district offices by HFC-230.
2. Each inspection may include a detailed audit of one or more studies to determine whether: (1) the final laboratory report(s) submitted to EPA, accurately reflects the raw data, (2) the testing was performed in a manner that did not involve errors or practices that may have adversely affected the validity of the study, and (3) the testing was performed in accordance with the protocol submitted to EPA.

C. Inspection Team

EPA may provide a staff scientist or regional inspector to accompany the FDA investigator. EPA may waive this whenever scientific support is not deemed necessary for carrying out the objectives of an audit.

1. Team Leader: The FDA investigator, as team leader, has the prime responsibility for the accomplishment and the conduct of joint inspections involving EPA agency personnel. Additional FDA field investigators may participate at the discretion of the district.
2. EPA Participant: EPA personnel will serve in a scientific advisory capacity to the team leader and shall specifically participate in the inspection by:
  - a. attending any scheduled pre-inspection conferences, and

- b. participating in the on-site inspection and remaining on-site with the FDA investigator for as long as necessary to complete the audit of studies being examined.

Written signed observations of the EPA participants regarding this data audit inspection must be included in the report submitted to EPA. It is important that the EPA participant provide the FDA investigator with all comments or observations on the inspection before his/her departure from the district.

4. Should the EPA scientist depart and, in the judgment of the FDA investigator, the data audit inspection cannot be continued without the aid of the scientist, the district will immediately inform the HFC-230 contact. If the inspection is terminated, the district will prepare an inspection report encompassing only those studies audited prior to termination.
5. Disagreements between FDA investigators and EPA staff regarding conduct of inspection should be discussed off-site and if not resolved, should be immediately referred to the HFC-230 contact.

#### D. Confirmation of Schedule

After the district has scheduled a tentative inspection date, the district will advise the EPA contact of the anticipated date of inspection.

If EPA is to participate in the data audit inspection, the district will inform the EPA contact as soon as possible to permit the coordination of schedules. Joint inspection arrangements should be agreeable to both parties, with no undue delays by either party.

#### E. Prior Notification of the Facility to be Inspected

EPA may notify the sponsor of the study to be audited in order to request that the sponsor provide test substance characterization data to the nonclinical laboratory.

FDA prior notification of the laboratory facility will be done in accordance with CP 7348.808.

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PART III - INSPECTIONAL

Establishment Inspections

A. Authority to Audit EPA Studies

FDA investigators will be delegated the authority to review records under Sections 8 and 22 of FIFRA and/or Sections 9 and 11 of TSCA. The delegation of authority will be documented in a "Letter of Entry" provided to the investigator(s) by the EPA contact.

B. Inspectional Procedures for EPA Data Audits

After displaying FDA credentials and issuing a Form FDA-482, the lead investigator should inform testing facility management of the reason for and the intended scope of the inspection. This will include information that the inspection will include the physical facility, if applicable, a data audit of FDA selected studies, and under the authority of the EPA Letter of Entry, will also include a data audit of EPA selected studies. The EPA Letter of Entry will include a statement that confidential commercial or trade secret, or other non-public information that the facility provides to FDA during the data audit of EPA studies will be given by FDA to EPA. The lead investigator should also advise the testing facility management that any study records copied from an EPA study and any written report of any observations made during the EPA data audit portion of the inspection including confidential commercial, trade secret, or other non-public information, will be submitted directly to EPA for appropriate review and follow-up by that agency. It is suggested that the EPA data audit portion of the inspection should be conducted after the inspectional operations for FDA regulated studies and facilities under CP 7348.808 are completed. The data audit procedures found in CP 7348.808, Part III-Inspectional, D. Data Audit, may be useful guidance for conducting the EPA requested data audit portion of the inspection under CP 7348.808A.

C. Issuance of an FDA-483

1. Inspectional observations under FDA authority

An FDA-483 will be issued under this program when noncompliance with FDA GLP regulations is observed and the laboratory is or has worked on FDA-regulated products

2. Data audit observations under EPA delegated authority

Inspectional observations during the EPA data audit portion of the inspection should be recorded separately from observations related to noncompliance with FDA GLP regulations. The observations may be listed on a Form FDA-483

provided that the references to FDA laws on the back of the Form FDA-483 are omitted or crossed through. It should be noted on the Form FDA-483 that the observations are being provided under authority delegated from EPA to FDA in the EPA Letter of Entry.

D. Refusal to Permit Inspection

Refusal to permit inspection or copying of records should be reported immediately to HFC-230, telephone 301-827-0420.

E. Confidentiality

Under various provisions of the FD&C Act, FIFRA, and TSCA, data submitted in support of tolerance petitions and registration applications may be considered trade secrets or confidential business information entitled to protection from unauthorized public disclosure.

FDA will maintain the confidentiality of all data received as a result of an inspection conducted for EPA. The FDA district office will NOT retain a copy of the EPA audit report. Any requests for disclosure of such information received by the FDA under the Freedom of Information Act or other non-EPA requester will be referred to EPA for processing and response. All documents provided to FDA by EPA for the conduct of the audits will be returned to EPA along with the audit report.

F. Report Format

Follow the report format outlined in CP 7348.808.

PART IV - ANALYTICAL

No samples are to be collected under this program circular.

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PART V – REGULATORY / ADMINISTRATIVE STRATEGY

FDA Inspection

See CP 7348.808

EPA Data Audit

EPA will determine whether discrepancies listed in reports submitted by FDA investigators impact on the validity of the audited studies. Any administrative or regulatory actions resulting from EPA audit reports will be the responsibility of EPA and will be consistent with TSCA or FIFRA regulations.

Exchange of Information

Each agency will exchange information and coordinate actions concerning active investigations, regulatory correspondence and legal or administrative action being considered against any laboratory covered under this agreement. In addition to the provisions of III. E., FDA will disclose information from its records to EPA according to FDA's procedures to implement 21 CFR § 20.85.

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PART VI - REFERENCES AND CONTACTS

References

1. 40 CFR Part 792, Toxic Substances Control; Good Laboratory Practices Standards.
2. 40 CFR Part 160, Pesticide Programs, Good Laboratory Practice Standards.
3. 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.
4. 21 CFR § 20.85, Disclosure to other Federal government departments and agencies.
5. Compliance Program Guidance Manual 7348.808; Chapter 48 - Bioresearch Monitoring, Good Laboratory Practice.

Program Contacts

When technical questions arise on a specific assignment, or when additional information or guidance is required, contact the assigning Center. Operational questions should be addressed to HFC-130.

Specific Contacts

Office of the Associate Commissioner for Regulatory Affairs

Office of Enforcement, Division of Compliance Policy:  
Dr. James F. McCormack, HFC-230, 301-827-0425, FAX 301-827-0482.

Office of Regional Operations, Division of Emergency and Investigational Operations: Dr. Thaddeus Sze, HFC-130, 301-827-5649, FAX 301-443-6919.

EPA

Office of Compliance, Laboratory Data Integrity Branch (2225A), Ariel Rios Building 1200 Pennsylvania Avenue, N.W., Washington, D.C. 20460 (when sending documents via an express service use the ZIP code 20004 and list the room number as 5109), Ms. Francisca Liem, 202-564-2365, FAX 202-564-0029.

Center for Drug Evaluation and Research (CDER)

Division of Scientific Investigations, Good Laboratory Practices and Bioequivalence Investigations Branch: Mr. Ty Fujiwara, HFD-48, 301-827-7287, FAX 301-594-1204.

Center for Biologics Evaluation and Research (CBER)

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Bioresearch Monitoring Staff: Dr. Patricia Hasemann, HFM-650, 301-594-1077, FAX 301-827-6221.

Center for Veterinary Medicine (CVM)

Bioresearch Monitoring Staff: Ms. Dorothy Pocrull, HFV-234, 301-594-1785, FAX 301-827-6664.

Center for Devices and Radiological Health (CDRH)

Division of Bioresearch Monitoring: Mr. Rodney Allnutt, HFZ-312, 301-594-4723, FAX 301-594-4731.

Center for Food Safety and Applied Nutrition (CFSAN)

Division of Product Policy: Dr. John Welsh, HFS-207, 202-418-3057, FAX 202-418-3126.

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PART VII – HEADQUARTER’S RESPONSIBILITIES

Office of Regulatory Affairs

Office of Enforcement, Division of Compliance Policy (HFC-230)

1. Is the liaison with EPA concerning the nonclinical laboratory compliance program.
2. Conducts periodic meetings with EPA and FDA centers to identify facilities requiring a coordinated inspection under the interagency agreement.
3. Following consultation with EPA, issue assignments to the district offices with copies to HFC-130 and the appropriate center for inspections coordinated under the interagency agreement.
4. Receives and reviews EIRs of EPA data audits and approves the forwarding of the documents to the EPA contact.
5. Reviews and resolves pertinent differences in the classification of the EPA data audit and the FDA inspection.
6. Notifies EPA whenever FDA approves a regulatory action against a specific laboratory.
7. Advises district offices in managing refusals to permit inspection.

Office of Regional Operations, Division of Emergency and Investigational Operations (HFC-130)

1. Monitors inspectional operations.

Centers

1. Attend periodic meetings with EPA to identify facilities requiring coordinated inspection under the interagency agreement.
2. Communicate final inspection classification of the FDA inspection to HFC-230 and the EPA contact.

EPA Contact Responsibilities

1. Is the liaison with FDA concerning the nonclinical laboratory compliance program.

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2. Attends periodic meetings with FDA representatives to identify facilities requiring a coordinated inspection under the interagency agreement.
  3. Following consultation with FDA, provides FDA liaison with pre-inspectional documents to be used in conducting EPA data audits.
  4. Provides investigators with a letter of entry delegating authority to FDA to audit test data submitted to EPA.
  5. Communicates final inspection classification of the EPA data audit to FDA liaison.
  6. Reviews and resolves pertinent differences in the classification of the EPA data audit and the FDA inspection.
  7. Notifies FDA whenever EPA approves a regulatory action against a laboratory.
  8. Provides information for updating the FDA's list of GLP Inspections.