Chapter 48 – Bioresearch Monitoring

Subject	Implementation Date
GOOD LABORATORY PRACTICE (Nonclinical Laboratories)	5/20/2025

Data Reporting	
Product Codes	Product/Assignment Codes
51Z or 52Z	04808 Chemical Contaminants (EPA)
45Z, 46Z	09808 Foods
57Z, 99Z	41808 Biologics (Therapeutics) 42808 Biologics (Blood) 45808 Biologics (Vaccines)
60Z, 61Z	48808 Human Drugs
68Z, 69Z	68808 Animal Products (Animal Drugs and Food Additives)
73Z, 74Z	83808 Medical and Radiological Devices
94Z or 95Z	98808 Tobacco Products

Field Reporting Requirements

All establishment inspection reports (EIRs), complete with attachments, exhibits, and any post-inspectional correspondence are to be **submitted** promptly to the assigning center. If an FDA-483 is issued, a copy will be emailed or faxed to the center contact identified in the assignment.

If the Office of Inspections and Investigations (OII) Office of Bioresearch Monitoring Inspectorate (OBMI) division becomes aware of any significant adverse inspectional, analytical, or other information which may affect the agency's new product approval decisions with respect to a firm, the OII OBMI division should immediately notify the responsible center program office via electronic mail, or by phone.

If samples are collected for analysis, the analyzing laboratory will **submit** copies of the Collection Report and the Analytical Worksheets to the OII OBMI division and the assigning center.

Contents

Change History

Item	Change	Date
Published	N/A	05/01/2018
Update	Partial revision to include in vivo/vitro practices, update OII reorganization information and minor administrative corrections.	05/20/2025

PART I – BACKGROUND

The Federal Food Drug and Cosmetic Act (FFDCA) and Public Health Service Act require that sponsors of FDA-regulated products submit evidence of their product's safety in research and/or marketing applications. These products include food and color additives, animal drugs, human drugs and biological products, human medical devices, diagnostic products, and electronic products. FDA uses these data to answer questions regarding:

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

The importance of nonclinical laboratory studies to FDA's public health decisions demands that they be conducted according to scientifically sound protocols and with meticulous attention to quality.

In the 1970s, FDA inspections of nonclinical laboratories revealed that some studies submitted in support of the safety of regulated products had not been conducted in accord with acceptable practice, and that accordingly data from such studies was not always of the quality and integrity to assure product safety. As a result of these findings, FDA promulgated the Good Laboratory Practice (GLP) Regulations, 21 CFR Part 58, on December 22, 1978 (43 FR 59986). The regulations became effective June 1979. The regulations establish standards for the conduct and reporting of nonclinical laboratory studies and are intended to assure the quality and integrity of safety data submitted to FDA.

FDA relies on documented adherence to GLP requirements by nonclinical laboratories in judging the acceptability of safety data submitted in support of research and/or marketing permits. FDA has implemented this program of regular inspections and data audits to monitor laboratory compliance with the GLP requirements.

PART II - IMPLEMENTATION

1. Objective

   A. To verify the quality and integrity of data submitted in a research or marketing application.

   B. To inspect (approximately every two years) nonclinical laboratories conducting safety studies that are intended to support applications for research or marketing of regulated products.

   C. To audit safety studies and determine the degree of compliance with GLP regulations.

2. Program Management Instructions

   This program provides for the inspection of public, private, and government nonclinical laboratories that perform testing on food and color additives, animal drugs, human drugs and biological products, human medical devices, diagnostic, and electronic products.

   Details regarding announcing an inspection to a facility will be communicated in the assignment. OII investigators should contact the center contact identified in the assignment for additional information regarding the need to preannounce.

   Consulting laboratories, contractors, and grantees are covered by the GLPs to the degree that they provide data for a nonclinical laboratory study. The sponsor or person contracting the service must notify them that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part. The consulting laboratory, contractor, or grantee is only required to comply with those parts of the GLPs that are appropriate to the nature of their contributions to a study.

   FDA centers initiate nonclinical laboratory inspection assignments.

3. Types of Inspections

   A. Surveillance Inspections

      Surveillance inspections are periodic, routine determinations of a laboratory's compliance with GLP regulations. These inspections include a facility inspection and audits of on-going and/or recently completed studies.

B. Directed Inspections

Directed inspections are assigned to achieve a specific purpose, such as:

i. Verifying the reliability, integrity, and compliance of critical safety studies being reviewed in support of pending applications.

ii. Investigating issues involving potentially unreliable safety data and/or violative conditions brought to FDA's attention.

iii. Re-inspecting laboratories previously classified OAI (official action indicated), usually within 6 months after the firm responds to a Warning Letter.

iv. Verifying the results from third party audits or sponsor audits submitted to FDA for consideration in determining whether to accept or reject questionable or suspect studies.

4. Inspection Teams (FDA Personnel)

Team inspections may be conducted.

A. Team Leader

An OII investigator will serve as team leader and is responsible for the cooperative conduct of the inspection. Responsibilities of the team leader are explained in the Investigations Operations Manual (IOM).

B. Center Participant/Subject Matter Expert (SME)

A center participant/SME will serve as scientific or technical support to the team leader and shall participate in the inspection by:

i. Attending pre-inspection conferences when and if scheduled.

ii. Participating in the entire on-site inspection as permitted by agency priorities.

iii. Providing support, as agreed upon with the team leader, in the preparation of specific sections of the inspection report where the field participant’s expertise is especially useful.

Any difficulties involving center participant/SME in the inspection should be discussed with OII OBMI division management and, if not resolved, immediately referred to the OII OBMI Program Expert Support Branch (OIIBIMOInspectionPOC@fda.hhs.gov).

5. Joint Inspections with Other Government Agency Personnel

Joint inspections with other US government agency personnel may be conducted under this program. In all instances, the FDA OII investigator will serve as the team leader. Specific instructions for conducting Environmental Protection Agency (EPA) data audits are provided in Compliance Program 7348.808A. For joint inspections performed in an Organisation for Economic Co-operation and Development (OECD) member country, the foreign GLP compliance monitoring authority will generally serve as the team leader.

6. Confirmation of Schedule

All inspections of commercial laboratories are to be conducted **without** prior notification unless otherwise instructed by the assigning center.

7. Field Responsibilities

Notify the center contact identified in the assignment when an inspection has been scheduled (preferably a week or more prior to the start of the inspection) or of any significant delay or postponement of an inspection assignment.

Alert center GLP staff of facilities that are becoming operational under GLP.

PART III – INSPECTIONAL

1. General Instructions

A. The OII investigator will **determine** the current state of GLP compliance by evaluating the laboratory facilities, operations, and study performance as outlined in Parts III, C, and D of this program.

B. Organization Chart - If the facility maintains an organization chart, **obtain** a current version of the chart for use during the inspection and **submit** it with the EIR.

C. Facility Floor-plan Diagram – **Obtain** a diagram of the facility. The diagram may identify areas that are not used for GLP activities. If it does not, request that appropriate facility personnel identify any areas that are not used for GLP activities. Use during the inspection and **submit** it with the EIR.

D. Master Schedule - **Obtain** a copy of the firm's master schedule for all studies listed since the last GLP inspection or last two years and select studies as defined in 21 CFR 58.3(d). If the inspection is the first inspection of the facility, review the entire master schedule. If studies are identified as non-GLP, **determine** the nature of several studies to verify the accuracy of this designation. See 21 CFR 58.1 and 58.3(d). In contract laboratories **determine** who decides if a study is a GLP study.

E. Identification of Studies

i. Directed Inspections – Inspection assignments will identify studies to be audited.

ii. Surveillance inspections – Inspection assignments may identify one or more studies to be audited. If the assignment does not identify a study for coverage, or if the referenced study is not suitable to assess all portions of current GLP compliance, the OII investigator will select studies as necessary to evaluate all areas of laboratory operations. When additional studies are selected, first priority should be given to FDA studies for submission to the assigning center.

NOTE: Studies performed for submission to other government agencies, e.g., Environmental Protection Agency, National Toxicology Program, National Cancer Institute, etc., will not be audited without authorization from your OII OBMI Branch Chief in consultation with OII OBMI Program Expert Support Branch (OIIBIMOInpectionPOC@fda.hhs.gov). However, this authorization is not necessary to briefly look at one of these studies to assess the ongoing operations of a portion of the facility.

a) Criteria for selecting on-going and completed studies

1) Safety studies conducted on FDA-regulated products that have been initiated or completed since the last GLP inspection.

2) Safety studies that encompass the full scope of laboratory operations.

3) Studies that are significant to safety assessment, e.g. carcinogenicity, reproductive toxicity, chronic toxicity studies.

4) Studies in several species of animals.

The OII investigator may contact the center for guidance on study selection.

b) Ongoing Studies - **Obtain** a copy of the study protocol and **determine** the schedule of activities that will be underway during the inspection. This information should be used to schedule inspections of on-going laboratory operations, as well as equipment and facilities associated with the study. If there are no activities underway in a given area for the study selected, evaluate the area based on on-going activities.

c) Completed Studies - The data audit should be carried out as outlined in Part III, D. If possible, accompany laboratory personnel when they retrieve the study data to assess the adequacy of data retention, storage, and retrieval as described in Part III, C. 10.

2. Areas of Expertise of the Facility

Testing facilities may conduct one or more types of studies within the scope of GLP regulations. The OII investigator should **identify** in the EIR the types of studies conducted at the facility using the following broad categories:

A. Physical-chemical testing

B. In vivo toxicity studies

C. In vitro toxicity studies

D. Mutagenicity studies

E. Tissue residue depletion studies

F. Clinical pathology testing

G. Test article characterization

H. Analytical testing of test and control article mixtures

I. Bioanalytical testing

J. Histology and histopathology

K. Other studies (specify)

3. Establishment Inspections

The facility inspection should be guided by the GLP regulations. The following areas should be evaluated and described as appropriate.

A. Organization and Personnel (21 CFR 58.29, 58.31, 58.33)

i. Purpose: To determine whether the organizational structure is appropriate to ensure that studies are conducted in compliance with GLP regulations, and to determine whether management, study directors, and laboratory personnel are fulfilling their responsibilities under the GLPs.

ii. Management Responsibilities (21 CFR 58.31) – Identify the various organizational units, their role in carrying out GLP study activities, and the management responsible for these organizational units. This includes identifying personnel who are performing duties at locations other than the test facility and identifying their line of authority. If the facility has an organization chart, much of this information can be determined from the chart.

Determine if management has procedures for assuring that the responsibilities in 58.31 can be carried out. Look for evidence of management involvement, or lack thereof, in the following areas:

a) Assigning and replacing study directors.

b) Control of study director workload (use the Master Schedule to assess workload).

c) Establishment and support of the Quality Assurance Unit (QAU), including assuring that deficiencies reported by the QAU are communicated to the study directors and acted upon.

d) Assuring that test and control articles or mixtures are appropriately tested for identity, strength, purity, stability, and uniformity.

e) Assuring that all study personnel are informed of and follow any special test and control article handling and storage procedures.

f) Providing required study personnel, resources, facilities, equipment, and materials.

g) Reviewing and approving protocols and standard operating procedures (SOPs).

h) Providing GLP or appropriate technical training.

iii. Personnel (21 CFR 58.29) - Identify key laboratory and management personnel, including any consultants or contractors used, and review personnel records, policies, and operations to **determine** if:

a) Summaries of training and position descriptions are maintained and are current for selected employees.

b) Personnel have been adequately trained to carry out the study functions that they perform.

c) Personnel have been trained in GLPs.

d) Practices are in place to ensure that employees take necessary health precautions, wear appropriate clothing, and report illnesses to avoid contamination of the test and control articles and test systems.

If the firm has computerized operations, **determine** the following (see also attachment A):

a) Who was involved in the design, development, and validation of the computer system?

b) Who is responsible for the operation of the computer system, including inputs, processing, and output of data?

c) Whether computer system personnel have training commensurate with their responsibilities, including professional training and training in GLPs?

d) Whether some computer system personnel are contractors who are present on-site full-time, or nearly full-time. The inspection should include these contractors as though they were employees of the firm. Specific inquiry may be needed to identify these contractors, as they may not appear on organization charts.

e) Interview and observe personnel using the computerized systems to assess their training and performance of assigned duties.

iv. Study director (21 CFR 58.33)

a) Assess the extent of the study director's actual involvement and participation in the study. In those instances when the study director is located off-site, review any correspondence/records between the testing facility management and quality assurance unit and the off-site study director. **Determine** whether the study director is being kept immediately apprised of any problems that may affect the quality and integrity of the study.

b) Assess the procedures by which the study director:

1) Assures the protocol and any amendments have been properly approved and are followed.

2) Assures that all data are accurately recorded and verified.

3) Assures that data are collected according to the protocol and SOPs.

4) Documents unforeseen circumstances that may affect the quality and integrity of the study and implements corrective action.

5) Assures that study personnel are familiar with and adhere to the study protocol and SOPs.

6) Assures that study data are transferred to the archives at the close of the study.

v. EIR Documentation and Reporting - Collect exhibits to document deficiencies. This may include SOPs, organizational charts, position descriptions, and curriculum vitae (CV), as well as study-related memos, records, and reports for the studies selected for review. **The use of outside or contract facilities must be noted in the EIR. The assigning center should be contacted for guidance on inspection of these facilities.**

B. Quality Assurance Unit (QAU; 21 CFR 58.35)

i. Purpose: To determine if the test facility has an effective, independent QAU that monitors significant study events and facility operations, reviews records and reports, and assures management of GLP compliance.

ii. QAU Operations - (21 CFR 58.35(b-d)) - Review QAU SOPs to assure that they cover all methods and procedures for carrying out the required QAU functions and confirm that they are being followed. **Verify** that SOPs exist and are being followed for QAU activities including, but not limited to, the following:

a) Maintaining a copy of the master schedule sheet.

b) Maintaining copies of all protocols and amendments.

c) Scheduling of its in-process inspections and audits.

d) Inspection of each nonclinical laboratory study at intervals adequate to assure the integrity of the study, and maintenance of records of each inspection.

e) Immediately notify the study director and management of any problems that are likely to affect the integrity of the study.

f) Submission of periodic status reports on each study to the study director and management.

g) Review of the final study report.

h) Preparation of a statement to be included in the final report that specifies the dates inspections were made and findings reported to management and to the study director.

i) Inspection of computer operations and software validation.

j) Verify that a historical file of outdated or modified computer

programs is maintained. If the firm does not maintain old programs in digital form, ensure that an archived copy of all programs has been made and stored.

Verify that, for any given study, the QAU is entirely separate from and independent of the personnel engaged in the conduct and direction of that study. Evaluate the time QAU personnel spend in performing in-process inspection and final report audits. **Determine** if the time spent is sufficient to detect problems in critical study phases and if there are adequate personnel to perform the required functions.
NOTE: The OII investigator may request the firm's management to certify in writing that inspections are being implemented, performed, documented, and followed-up in accordance with this section (See 58.35(d)).

iii. EIR Documentation and Reporting - **Obtain** a copy of the master schedule covering the last two years or the time span since the date of the last GLP inspection, whichever is shorter. If the master schedule is too voluminous, **obtain** representative pages to permit review. When master schedule entries are coded, **obtain** the code key. Deficiencies should be fully reported and documented in the EIR. Documentation to support deviations may include copies of QAU SOPs, list of QAU personnel, their CV or position descriptions, study-related records, protocols, and final reports.

C. Facilities (21 CFR 58.41 - 51)

i. Purpose: Assess whether the facilities are of adequate size and design.

ii. Facility Inspection

a) Review environmental controls and monitoring procedures for critical areas (e.g., animal rooms, test article storage areas, laboratory areas, handling of bio-hazardous material, etc.) and **determine** if they appear adequate and are being followed.

b) Review the SOPs that identify materials used for cleaning critical areas and equipment. Assess the facility's current cleanliness.

c) **Determine** whether there are appropriate areas for the receipt, storage, mixing, and handling of the test and control articles.

d) **Determine** whether separation is maintained in rooms where two or more functions requiring separation are performed.

e) **Determine** whether computerized operations and archived computer data are housed under appropriate environmental conditions (e.g., protected from heat, water, and electromagnetic forces).

iii. EIR Documentation and Reporting - Identify which facilities, operations, SOPs, etc., were inspected. Only significant changes in the facility from previous inspections need be described. Facility floor plans may be collected to illustrate problems or changes. Document any conditions that would lead to contamination of test articles or to unusual stress of test systems.

D. Equipment (21 CFR 58.61 - 63)

i. Purpose: To assess whether equipment is appropriately designed and of adequate capacity and is maintained and operated in a manner that ensures valid results.

ii. Equipment Inspection - Assess the following:

a) The general condition, cleanliness, and ease of maintenance of equipment in various parts of the facility.

b) The heating, ventilation, and air conditioning system design and maintenance, including documentation of filter changes and temperature/humidity monitoring in critical areas.

c) Whether equipment is located where it is used and that it is located in a controlled environment, when required.

d) Non-dedicated equipment for preparation of test and control article carrier mixtures is cleaned and decontaminated to prevent cross contamination.

e) For representative pieces of equipment check the availability of the following:

1) SOPs and/or operating manuals.

2) Maintenance schedule and log.

3) Standardization/calibration procedure, schedule, and log.

4) Standards used for calibration and standardization.

f) For computer systems, assess whether the following procedures exist and are documented (see also attachment A):

1) Validation study, including validation plan and documentation of the plan's completion.

2) Maintenance of equipment, including storage capacity and back-up procedures.

3) Control measures over changes made to the computer system, which include the evaluation of the change, necessary test design, test data, and final acceptance of the change.

4) Evaluation of test data to assure that data are accurately transmitted and handled properly when analytical equipment is directly interfaced to the computer.

5) Procedures for emergency back-up of the computer system (e.g., back-up battery system and data forms for recording data in the event of a computer failure or power outage).

iii. EIR Documentation and Reporting - The EIR should list which equipment, records, and procedures were inspected and the studies to which they are related. Detail any deficiencies that might result in contamination of test articles, uncontrolled stress to test systems, and/or erroneous test results.

E. Testing Facility Operations (21 CFR 58.81)

i. Purpose: To determine if the facility has established and follows written SOPs necessary to carry out study operations in a manner designed to ensure the quality and integrity of the data.

ii. SOP Evaluation

a) Review the SOP index and representative samples of SOPs to ensure that written procedures exist to cover at least the areas identified in 58.81(b).

b) **Verify** that only current SOPs are available at the personnel

workstations.

c) Review key SOPs in detail and check for proper authorization signatures and dates, and general adequacy with respect to the content (i.e., SOPs are clear, complete, and can be followed by a trained individual).

d) **Verify** that changes to SOPs are properly authorized and dated and that a historical file of SOPs is maintained.

e) Ensure that there are procedures for familiarizing employees with SOPs.

f) **Determine** whether there are SOPs to ensure the quality and integrity of data, including input (data checking and verification), output (data control), and an audit trail covering all data changes.

g) **Verify** that SOPs are periodically reviewed for current applicability and that they are representative of the actual procedures in use.

h) Review selected SOPs and observe employees performing the operation to evaluate SOP adherence and familiarity.

iii. EIR Documentation and Reporting - **Submit** SOPs, data collection forms, and raw data records as exhibits that are necessary to support and illustrate deficiencies.

F. Reagents and Solutions (21 CFR 58.83)

i. Purpose: To determine that the facility ensures the quality of reagents at the time of receipt and subsequent use.

a) Review the procedures used to purchase, receive, label, and **determine** the acceptability of reagents and solutions for use in the studies.

b) **Verify** that reagents and solutions are labeled to indicate identity, titer or concentration, storage requirements, and expiration date.

c) **Verify** that for automated analytical equipment, the profile data accompanying each batch of control reagents are used.

d) Check that storage requirements are being followed.

G. Animal Care (21 CFR 58.90)

i. Purpose: To assess whether animal care and housing is adequate to minimize stress and uncontrolled influences that could alter the response of the test system to the test article.

ii. Inspect the animal room(s) housing the study to observe operations, protocol and SOP adherence, and study records. **Refer to the IOM Safety Chapter prior to inspecting non-human primate facilities.**

Determine whether there are adequate SOPs covering environment, housing, feeding, handling, and care of laboratory animals, and that the SOPs and the protocol instructions are being followed.

a) Review pest-control procedures and documentation of the chemicals used. Identify individuals responsible for the program. When a contractor provides the pest control, **determine** if someone from the laboratory accompanies the contractor at all times.

b) **Determine** whether the facility has an Institutional Animal Care and Use Committee (IACUC). **Obtain and submit** a copy of the committee's SOPs and the most recent committee minutes to **verify** committee operation.

c) **Determine** whether all newly received animals are appropriately isolated, identified, and their health status evaluated.

d) **Verify** that treatment given to animals that become diseased is authorized by the study director and documented.

e) For a representative sample of animals, compare individual animal identification against corresponding housing unit identification and dose group designations to assure that animals are appropriately identified.

f) For a representative sample of animals, review daily observation logs and **verify** their accuracy for animals reported as dead or having external gross lesions or masses.

g) Ensure that animals of different species, or animals of the same species on different projects, are separated as necessary.

h) **Verify** that cages, racks, and accessory equipment are cleaned and sanitized, and that appropriate bedding is used.

i) **Determine** whether feed and water samples are collected at appropriate sources, analyzed periodically, and analytical

documentation is maintained.

iii. EIR Documentation and Reporting - The EIR should identify which areas, operations, SOPs, studies, etc., were inspected and document any deficiencies.

H. Test and Control Articles (21 CFR 58.105 - 113)

i. Purpose: To determine that procedures exist to assure that test and control articles and mixtures of articles with carriers meet protocol specifications throughout the course of the study, and that accountability is maintained.

ii. Characterization and Stability of Test Articles (21 CFR 58.105) - The responsibility for carrying out appropriate characterization and stability testing may be assumed by the facility performing the study or by the study sponsor. **When test article characterization and stability testing is performed by the sponsor, verify that the test facility has received documentation that this testing has been conducted.**

a) **Verify** that procedures are in place to ensure that:

1) The acquisition, receipt, and storage of test articles, and means used to prevent deterioration and contamination are as specified.

2) The identity, strength, purity, and composition, (i.e., characterization) to define the test and control articles are determined for each batch and are documented.

3) The stability of test and control articles is documented.

4) The transfer of samples from the point of collection to the analytical laboratory is documented.

5) Storage containers are appropriately labeled and assigned for the duration of the study.

6) Reserve samples of test and control articles for each batch are retained for studies lasting more than four weeks, from the initial dosing to the final in vivo observations.

iii. Test and Control Article Handling (21 CFR 58.107)

a) **Determine** whether there are adequate procedures for:

1) Documentation for receipt and distribution.

2) Proper identification and storage.

b) Precluding contamination, deterioration, or damage during distribution. Inspect test and control article storage areas to **verify** that environmental controls, container labeling, and storage are adequate.

c) Observe test and control article handling and identification during the distribution and administration to the test system.

d) Review a representative sample of accountability records and, if possible, **verify** their accuracy by comparing actual amounts in the inventory. For completed studies **verify** documentation of final test and control article reconciliation.

iv. Mixtures of Articles with Carriers (58.113) - If possible, observe the preparation, sampling, testing, storage, and administration of mixtures. **Verify** that analytical tests are conducted, as appropriate, to:

a) Determine uniformity of mixtures and to determine periodically the concentration of the test or control article in the mixture.

b) Determine the stability as required under study conditions.

Verify that the results are reported to the study director. When the sponsor performs analytical testing, concentration data may be reported to the study director as absolute or relative (percent of theoretical) values.

v. EIR Documentation and Reporting - Identify the test articles, SOPs, facilities, equipment, operations, etc., inspected. Review the analytical raw data versus the reported results for accuracy of reporting and overall integrity of the data that is being collected.

Where deficiencies or other information suggest a problem with the purity, identity, strength, etc., of the test article or the concentration of test article mixtures, document and **obtain** copies of the analytical raw

data and any related reports. Consideration should be given to collecting a sample as described in Part III, G.

I. Protocol and Conduct of Nonclinical Laboratory Study (21 CFR 58.120 - 130)

i. Purpose: To determine if study protocols are properly written and authorized, and that studies are conducted in accordance with the protocol and SOPs.

ii. Study Protocol (21 CFR 58.120)

a) Review SOPs for protocol preparation and approval and **verify** they are followed.

b) Review the protocol to **determine** if it contains required elements.

c) Review all changes, revisions, or amendments to the protocol to ensure that they are authorized, signed, and dated by the study director.

e) **Verify** that all copies of the approved protocol contain all changes, revisions, or amendments.

iii. Conduct of the Nonclinical Laboratory Study (21 CFR 58.130) - Evaluate the following laboratory operations, facilities, and equipment to **verify** conformity with protocol and SOP requirements for:

a) Test system monitoring.

b) Recording of raw data (manual and automated).

c) Corrections to raw data (corrections must not obscure the original entry and must be dated, initialed, and explained).

d) Randomization of test systems.

e) Collection and identification of specimens.

f) Authorized access to data and computerized systems.

iv. EIR Reporting and Documentation - **Identify** the study(ies) inspected and, if available, the associated FDA research or marketing permit numbers. Report and document any deficiencies observed. **Submit**,

as exhibits, a copy of all protocols and amendments that were reviewed.

J. Records and Reports (21 CFR 58.185 - 195)

i. Purpose: To assess how the test facility stores and retrieves raw data, documentation, protocols, final reports, and specimens.

ii. Reporting of Study Results (21 CFR 58.185) - **Determine** if the facility prepares a final report for each study conducted. For selected studies, **obtain** the final report, and **verify** that it contains the following:

a) The required elements in 21 CFR 58.185(a) (1-14), including the identity (name and address) of any subcontractor facilities and portion of the study contracted, and a description of any computer program changes.

b) Dated signature of the study director (21 CFR 58.185(b)).

c) Corrections or additions to the final report are made in compliance with 21 CFR 58.185(c).

iii. Storage and Retrieval of Records and Data (21 CFR 58.190)

a) **Verify** that raw data, documentation, protocols, final reports, and specimens have been retained.

b) **Identify** the individual responsible for the archives. Determine if delegation of duties to other individuals in maintaining the archives has occurred.

c) **Verify** that archived material retained or referred to in the archives is indexed to permit expedient retrieval. It is not necessary that all data and specimens be in the same archive location. For raw data and specimens retained elsewhere, the archives index must make specific reference to those other locations.

d) **Verify** that access to the archives is controlled and **determine** that environmental controls minimize deterioration.

e) Ensure that there are controlled procedures for adding or removing material. Review archive records for the removal and return of data and specimens. Check for unexplained or prolonged removals.

f) **Determine** how and where computer data and backup copies are stored, that records are indexed in a way to allow access to data stored on electronic media, and that environmental conditions minimize deterioration.

g) **Determine** to what electronic media such as tape cassettes or ultra-high-capacity portable discs the test facility has the capacity of copying records in electronic form. **Report** names and identifying numbers of both copying equipment type and electronic medium type to enable agency personnel to bring electronic media to future inspections for collecting exhibits.

iv. EIR Documentation and Reporting – Provide a brief summary of the facility's report preparation procedures and their retention and retrieval of records, reports, and specimens. If records are archived off-site, **obtain** a copy of documentation of the records which were transferred and where they are located. Describe and document deficiencies.

4. Data Audit

In addition to the procedures outlined above for evaluating the overall GLP compliance of a firm, the inspection should include the audit of at least one completed study. Studies for audit may be assigned by the center or selected by the OII investigator as described in Part III, A. The audit will include a comparison of the protocol (including amendments to the protocol), raw data, records, and specimens against the final report to substantiate that protocol requirements were met and that findings were fully and accurately reported.

A. For each study audited, the study records should be reviewed for quality to ensure that data are:

i. Attributable – the raw data can be traced, by signature or initials and date to the individual observing and recording the data. Should more than one individual observe or record the data, that fact should be reflected in the data.

ii. Legible – the raw data are readable and recorded in a permanent medium. If changes are made to original entries, the changes:

a) Must not obscure the original entry.

b) Indicate the reason for change.

c) Must be signed or initialed and dated by the person making the change.

iii. Contemporaneous – the raw data are recorded at the time of the observation.

iv. Original – the first recording of the data.

v. Accurate – the raw data are true and complete observations. For data entry forms that require the same data to be entered repeatedly, all fields should be completed or a written explanation for any empty fields should be retained with the study records.

B. General

i. **Determine** if there were any significant changes in the facilities, operations, and QAU functions other than those previously reported.

ii. **Determine** whether the equipment used was inspected, standardized, and calibrated prior to, during, and after use in the study. If equipment malfunctioned, review the remedial action, and ensure that the final report addresses whether the malfunction affected the study.

iii. **Determine** if approved SOPs existed during the conduct of the study.

iv. Compare the content of the protocol with the requirements in 21 CFR 58.120.

v. Review the final report for the study director's dated signature and the QAU statement as required in 21 CFR 58.35(b)(7).

C. Protocol vs. Final Report - Study methods described in the final report should be compared against the protocol and the SOPs to confirm those requirements were met. Examples include, but are not limited to, the following:

i. Selection and acquisition of the test system, i.e., species, source, weight range, number, age, date ordered, date received.

ii. Procedure for receipt, examination, and isolation of newly received animals.

iii. Methods of test system identification, housing, and assignment to study.

iv. Types and occurrences of diseases and clinical observations prior to and during the study, as well as any treatments administered.

v. Frequency and methods of sampling and analysis for contaminants in feed and water.

vi. Feed and water contaminant levels did not exceed limits specified in the protocol.

vii. Types of bedding and pest control materials do not interfere with the study.

viii. Preparation and administration of test and/or control articles.

ix. Analysis of test article/test article carrier mixtures.

x. Observation of the test system response to test article.

xi. Handling of dead or moribund animals.

xii. Collection and analysis of specimens and raw data.

xiii. Necropsy, gross pathology, and histopathology.

D. Final Report vs. Raw Data

i. The audit should include a detailed review of records, memorandum, and other raw data to confirm that the findings in the final report completely and accurately reflect the raw data. Representative samples of raw data should be audited against the final report.

For in vivo studies, examples of types of data to be checked include, but are not limited to, the following:

a) Animal body weight records.

b) Food and water consumption records.

c) Test system observation and dosing records.

d) Records for the analysis of uniformity, concentration, and stability of test and control article mixtures.

e) Protocol-required analyses (e.g., urinalysis, hematology, blood chemistry, ophthalmologic exams).

f) Necropsy and gross pathology records.

g) Histopathology, including records for tissue processing and slide preparation.

h) Conformity between "interim" reports (e.g., a report on the first year of a multi-year study) and the final report.

A representative number of animals from selected dose groups (initially the control and high) should be traced from receipt through final histopathologic examination. Evaluate

for the following:

a) The accuracy of individual test system identification.

b) Review trends in each parameter measured or observed and note inconsistencies.

c) Explanations for reported data outliers.

d) Conformity between in vivo test system observations and gross pathology observations.

e) Conformity between gross pathology observations and histopathologic examinations

f) Documentation of unforeseen circumstances that may have affected the quality and integrity of the study.

For in vitro studies, examples of types of data to be checked include, but are not limited to, the following:

a) Maintenance, calibration, and validation records for incubators and pipettors.

b) Review certificates of analysis and assure stability and traceability of materials and reagents. Confirm batch numbers.

c) Verify test article formulation analysis was conducted for each in vitro study.

d) Review SOPs for storage, handling, and authentication of cell systems, and audit current practice against current SOPs.

e) Audit historical control data.

f) If applicable, cell source and medium preparation.

E. Specimens vs. Final Report - The audit should include examination of a representative sample of specimens in the archives for confirmation of the number and identity of specimens in the final report.

F. EIR Documentation and Reporting

i. All studies audited should be identified by:

a) Sponsor's name.

b) Study title (and any study numbers).

c) Study director's name.

d) Test article name and/or code.

e) Test system.

f) The date the protocol was signed by the study director.

g) In-life starting and ending dates.

h) The date the study director signed the final report.

i) If available, the FDA research or marketing application number.

ii. Describe and document any significant deficiencies in the conduct or reporting of the study. **Obtain** a copy of the narrative study report and protocol.

5. Refusal to Permit Inspection

OII investigators should refer to the IOM for general guidance on dealing with refusal to permit inspection. Test facility management should be advised that the agency will not consider a nonclinical laboratory study in support of a research or marketing permit if the testing facility refuses to permit inspection (58.15(b)).

REFUSAL TO PERMIT INSPECTION OF FACILITIES OR STUDIES SHOULD BE REPORTED IMMEDIATELY TO YOUR OII OBMI BRANCH CHIEF, DIVISION DIRECTOR, AND THE ASSIGNING CENTER POC.

Under this program, partial refusals, including refusal to permit access to, and copying of the master schedule (including any code sheets), SOPs, and other documents pertaining to the inspection will be treated as a **"total"** refusal to permit inspection.

6. Sealing of Research Records

Whenever an OII investigator encounters questionable or suspicious records under any Bioresearch Monitoring Program, and is unable to copy or review them immediately, and has reason for preserving the integrity of those records, **the OII investigator may officially seal the records using an FDA 415a seal. The OII investigator should immediately contact** their OII OBMI Branch Chief, the Center POC and the OII OBMI Program Expert Support Branch at OIIBIMOInspectionPOC@fda.hhs.gov for instructions**.**

7. Samples

   A. Collection of samples should be considered when the situation under audit or surveillance suggests that the facility had, or is having, problems in the area of characterization, stability, storage, contamination, or dosage preparation.

      The OII investigator should contact the assigning center and appropriate FDA laboratory office, either the Human Foods Program Office of Regulatory Testing and Surveillance (ORTS) or Office of the Chief Scientist Office of Analytical and Regulatory Laboratories (OARL), before samples are collected.

      If the OII investigator collects a sample, a copy of the methodology and reference samples from the sponsor or the testing facility must also be **obtained**. The copy will be sent to the appropriate FDA laboratory office for designation of a laboratory to perform the sample analysis according to instrument capabilities and the availability of the selected FDA laboratory. The OII investigator should contact the laboratory office for specific disposition/handling instructions. The OII investigator must use the appropriate 7-digit code for product collected and provide complete documentation with each sample for possible legal/administrative actions.

   B. Samples may include physical samples of:

      i. Carrier.

      ii. Test article.

      iii. Control article.

      iv. Mixtures of test or control articles with carriers.

      v. Specimens including wet tissues, tissue blocks, and slides (see above regarding center, ORTS, and OARL authorization and instructions).

8. Inspectional Observations

   An FDA 483 listing inspectional observations may be issued under this program. Findings should not be listed on the FDA 483 if in the opinion of the OII investigator:

   A. The findings are problems that have been observed and corrected by the firm through its internal procedures.

B. The findings are minor and are one-time occurrences that have no impact on the firm's operations, study conduct, or data integrity.

Findings that are not considered significant enough to be listed on the FDA 483 may be discussed with the firm's management. Such discussions must be reported in the EIR.

9. Establishment Inspection Reports

Because the centers are solely responsible for issuing post-inspection correspondence, each EIR must include the full name, title, academic degree(s), and mailing address of the most responsible person at the test facility. For universities the most responsible person would typically be a member of the administration (e.g., department chair, dean).

Documentation necessary to support the observations listed on the FDA 483 should be collected, **submitted**, and referenced in the EIR narrative. Suspected violations under Title 21 must be documented sufficiently to form the basis for legal or administrative action. Discuss potential violations under Title 18 with your branch chief and division director prior to extensive documentation.

A. Full Reporting

A full report will be **prepared** and **submitted** in the following situations:

i. The initial GLP inspection of a facility.

ii. All inspections that may result in an OAI classification.

iii. Any assignment specifically requesting a full report.

The EIR should contain the headings described in IOM Chapter 5, in addition to the headings outlined in Part III, C, and D. The report must always include sufficient information and documentation to support the recommended classification.

B. Summary of Findings

i. OII investigators may use Summary of Findings reports for the following types of assignments:

a) Surveillance inspections (except for initial inspections) of a facility when it is apparent from the findings that the inspection may result in a final classification of no action indicated (NAI) or voluntary action indicated (VAI). These reports must include enough documented information to support the final

classification.

b) Directed inspections and data audits, provided the report fully covers all aspects of the specific topic of the inspection (i.e., operations, past deficiencies, assigned studies, etc.) and documents significant adverse findings to support the final classification.

ii. Format

a) **The EIR should be clearly identified as a Summary of Findings report.**

b) The report should include all the headings described in IOM Chapter 5 and include:

1) The identity of the studies selected for audit and review

2) Identification of the areas, operations, and amount of data that were inspected (e.g., identity and percent of records reviewed in a specific area, number of animals tracked, percent of slides checked for accountability, etc.).

3) All adverse observations will be fully discussed in the EIR and documented to permit assessment of their impact on the quality and integrity of the studies.

If the center review reveals that a Summary of Findings report is inadequate, the center will notify the appropriate OII OBMI Division Director.

PART IV - ANALYTICAL

1. Analyzing Laboratories

   Human Food Program laboratories or Office of the Chief Scientist laboratories based upon the category of the sample(s) to be analyzed.

2. Analysis

   Samples of test or control articles, or mixtures thereof, may be submitted for a determination for identity, strength, potency, purity, or composition. Sample analysis will follow the exact methodology of the sponsor or the testing facility. If the methodology is available at the testing facility, the OII investigator must **submit** the methodology with the sample. In those cases where a contract testing facility does not have the methodology, the OII investigator should direct the facility to request the method be provided to the FDA laboratory by the sponsor.

3. Identification of Appropriate FDA Laboratory

   For medical and tobacco product sample analysis contact:
   Office of the Chief Scientist (OCS)
   Office of Analytical and Regulatory Laboratories (OARL)
   OCOCSOARLProgramCoordinators@fda.hhs.gov

   For human and animal food sample analysis contact:
   Human Foods Program (HFP)
   Office of Laboratory Operations and Applied Science (OLOAS)
   hfp-oloas-orts-io-management@fda.hhs.gov

4. Reporting

   The analyzing laboratory will **submit** copies of the Collection Report and the Analytical Worksheets to the originating OII OBMI division and to the center with reference to the EIR.

PART V - REGULATORY / ADMINISTRATIVE STRATEGY

1. OII OBMI Division EIR Classification Authority

   The OII OBMI division is encouraged to review and initially recommend a classification of EIRs under this compliance program.

2. Center EIR Classification Authority

   The Center has the final classification authority for all Bioresearch Monitoring Program inspection reports. The center will provide to the appropriate OII OBMI division copies of final classifications, including any reason for changes from the recommended classification.

3. EIR Classifications

   The following guidance is to be used in conjunction with the instructions in FMD-86 for the recommended OII OBMI division and center classification of EIRs generated under this compliance program:

   - NAI - No objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action).
   - VAI - Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action.
   - OAI - Regulatory and/or administrative actions will be recommended.

4. Post-Inspectional Correspondence

   Under the BIMO program the centers are responsible for administrative or regulatory follow-up. The OII OBMI division should advise the center of any response to the FDA 483 or any other communication (written or oral) with the facility concerning the inspection. Similarly, if the center has communication with the facility following the inspection the OII OBMI division should be advised of such communication.

5. OII OBMI Division Follow-up

   All OII OBMI division follow-up action, including re-inspection, will be made at the request of the center.

6. Regulatory/Administrative Actions

The regulatory/administrative actions that can be used under this compliance program are not mutually exclusive. Follow-up of an OAI inspection may involve the use of one or more of the following:

- Warning Letter
- Re-inspection
- Informal conference
- Third party validation of a nonclinical study or studies
- Rejection of a nonclinical study or studies
- Disqualification of the facility
- Injunction/prosecution
- Withholding or revocation of marketing permit
- Termination of a research permit
- Application integrity policy

PART VI – REFERENCES. ATTACHMENTS, AND PROGRAM CONTACTS

1. References

A. Guidance for Industry, FDA reviewers, and Compliance on Off-the-shelf software use in Medical Devices, issued 9/9/99
B. General Principles of Software Validation; Final Guidance for Industry and FDA Staff, issued 1/11/02
C. Guidance for Industry, Computerized Systems Used in Clinical Trials, issued May 2007
D. Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application, issued 8/03
E. Food and Drug Administration [Docket No. 99D-1458] Enforcement Policy: Electronic Records; Electronic Signatures-- Compliance Policy Guide; Guidance for FDA Personnel, [Federal Register: July 21, 1999 (Volume 64, Number 139)]
F. Guidance for Industry, S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, issued June 2012

2. Program Contacts

Questions regarding the interpretation of the regulations or agency policy should be addressed to your OII OBMI Branch Chief or OII OBMI Program Expert Support Branch (OIIBIMOInspectionPOC@fda.hhs.gov). When technical questions arise on a specific assignment, or when additional information or guidance is required, contact the assigning center POC.

A. Specific Contacts:

Office of Inspections and Investigations (OII)
Office of Bioresearch Monitoring Inspectorate (OBMI)
Division of Bioresearch Monitoring Global Operations

Domestic:
OII OBMI Program Expert Support Branch
OIIBIMOInspectionPOC@fda.hhs.gov
Foreign:
OII OBMI Foreign Inspections
FDAInternationalBIMO@fda.hhs.gov

Center for Drug Evaluation and Research (CDER)
Office of Compliance (OC)

Office of Scientific Investigations (OSI)
BIMO-CDEROSI@fda.hhs.gov

Center for Drug Evaluation and Research (CDER)
Office of Translational Sciences (OTS)
Office of Study Integrity and Surveillance (OSIS)
CDER-OSIS-GLP@fda.hhs.gov

Center for Biologics Evaluation and Research (CBER)
Office of Compliance and Biologics Quality (OCBQ)
CBERBIMONotification@fda.hhs.gov

Center for Veterinary Medicine (CVM)
Office of Surveillance and Compliance
CVMBIMORequests@fda.hhs.gov

Center for Devices and Radiological Health (CDRH)
Office of Clinical Evidence and Analysis
Division of Clinical Policy and Quality
BIMO-CDRH@fda.hhs.gov

Human Foods Program (HFP)
Office of Quality Assessment and Management
Human Foods BIMO Program
HFP-BIMO@fda.hhs.gov

Center for Tobacco Products (CTP)
Office of Compliance and Enforcement (OCE)
CTP-BIMO@fda.hhs.gov

PART VII – FDA CENTER AND OFFICE RESPONSIBILITIES

1. Center
   - A. Reviews EIRs and regulatory/administrative recommendations forwarded by the OII OBMI divisions.
   - B. Provides OII OBMI Program Expert Support Branch with a list of facilities on a yearly/quarterly basis, or as other priorities dictate, to be scheduled for inspection.
   - C. Issues all assignments to the OII OBMI Program Expert Support Branch at OIIBIMOInspectionPOC@fda.hhs.gov.
   - D. Selects studies to be audited and provides necessary support documents.
   - E. Prepares letters for issuance by the center, OII, or Commissioner as appropriate.
   - F. Recommends compliance program changes to BIMO Compliance Program Committee (BCPC).
   - G. Distributes copies of inspectional correspondence, to include final classification decisions, to the appropriate OII OBMI division correspondence email address or OII OBMI Foreign Inspections (FDAInternationalBIMO@fda.hhs.gov).
   - H. Provides inspectional support to the field by direct participation and in consultant capacity.
   - I. Copies all centers whenever a Warning Letter has issued to a specific laboratory.

2. Office of Inspections and Investigations (OII)
   - A. Office of Bioresearch Monitoring Inspectorate (OBMI)
     - i. Provides inspection quality assurance, training of field personnel, and operational guidance.
     - ii. Maintains liaison with centers and resolves operational questions.
     - iii. Coordinates and schedules joint center and multi-OII OBMI division inspections.

3. FDA Laboratory
   - A. Human Foods Program (HFP) Office of Laboratory Operations and Applied Science (OLOAS)

i. Assigns laboratories for human and animal food sample analysis and responds to method inquiries.

B. Office of the Chief Scientist (OCS) Office of Analytical and Regulatory Laboratories (OARL)

i. Assigns laboratories for medical product and tobacco product sample analysis and responds to method inquiries.

ATTACHMENT A

Computerized Systems

The intent of this attachment is to collect, in one place, references to computer systems found throughout Part III. Computer systems and operations should be thoroughly covered during inspection of any facility. No additional reporting is required under this Attachment.

In August 1997, the Agency's regulation on electronic signatures and electronic recordkeeping became effective. The regulation, at 21 CFR Part 11, describes the technical and procedural requirements that must be met if a firm chooses to maintain records electronically and/or use electronic signatures. Part 11 works in conjunction with other FDA regulations and laws that require recordkeeping. Those regulations and laws ("predicate rules") establish requirements for record content, signing, and retention.

Certain older electronic systems may not have been in full compliance with Part 11 by August 1997 and modification to these so called "legacy systems" may take more time. Part 11 does not grandfather legacy systems and FDA expects that firms using legacy systems are taking steps to achieve full compliance with Part 11.

If a firm is keeping electronic records or using electronic signatures, **determine** if they are in compliance with 21 CFR Part 11. **Determine** the depth of part 11 coverage on a case-by-case basis, in light of initial findings and program resources. At a minimum ensure that: (1) the firm has prepared a corrective action plan for achieving full compliance with part 11 requirements and is making progress toward completing that plan in a timely manner; (2) accurate and complete electronic and human readable copies of electronic records, suitable for review, are made available; and (3) employees are held accountable and responsible for actions taken under their electronic signatures. If initial findings indicate the firm's electronic records and/or electronic signatures may not be trustworthy and reliable, or when electronic recordkeeping systems inhibit meaningful FDA inspection, a more detailed evaluation may be warranted. OII OBMI divisions should consult with center POC and the OII OBMI Program Expert Support Branch (OIIBIMOInspectionPOC@fda.hhs.gov) in assessing the need for, and potential depth of, more detailed part 11 coverage. When substantial and significant part 11 deviations exist, FDA will not accept use of electronic records and electronic signatures to meet the requirements of the applicable predicate rule.

See IOM Chapter 5 for procedures for collecting and identifying electronic data.

Personnel - Part III, C.1.c. (21 CFR 58.29)

Determine the following:

- ☒ Who was involved in the design, development, and validation of the computer system?

- ☒ Who is responsible for the operation of the computer system, including inputs, processing, and output of data?
- ☒ Whether computer system personnel have training commensurate with their responsibilities, including professional training and training in GLPs.
- ☒ Whether some computer system personnel are contractors who are present on-site full-time, or nearly full-time. The investigation should include these contractors as though they were employees of the firm. Specific inquiry may be needed to identify these contractors, as they may not appear on organization charts.

QAU Operations - Part III, C.2 (21 CFR 58.35(b-d))

- ☒ **Verify** SOPs exist and are being followed for QAU inspections of computer operations.

Facilities - Part III, C.3 (21 CFR 58.41 - 51)

- ☒ **Determine** that computerized operations and archived computer data are housed under appropriate environmental conditions.

Equipment - Part III, C.4 (21 CFR 58.61 - 63)

For computer systems, check that the following procedures exist and are documented:

- ☒ Validation study, including validation plan and documentation of the plan's completion.
- ☒ Maintenance of equipment, including storage capacity and back-up procedures.
- ☒ Control measures over changes made to the computer system, which include the evaluation of the change, necessary test design, test data, and final acceptance of the change.
- ☒ Evaluation of test data to assure that data is accurately transmitted and handled properly when analytical equipment is directly interfaced to the computer.
- ☒ Procedures for emergency back-up of the computer system, (e.g., back-up battery system and data forms for recording data in case of a computer failure or power outage).

Testing Facility Operations - Part III, C.5 (21 CFR 58.81)

- ☒ **Verify** that a historical file of outdated or modified computer programs is maintained.

Records and Reports (21 CFR 58.185 - 195) (PART III C.10.b.)

- ☒ **Verify** that the final report contains the required elements in 58.185(a) (1-14), including a description of any computer program changes.

Storage and Retrieval of Records and Data - Part III, C.10.c. (21 CFR 58.190)

- ☒ Assess archive facilities for degree of controlled access and adequacy of environmental controls with respect to computer media storage conditions.
- ☒ **Determine** how and where computer data and backup copies are stored, that records are indexed in a way to allow access to data stored on electronic media, and that environmental conditions minimize deterioration.
- ☒ **Determine** how and where original computer data and backup copies are stored.