# CHAPTER 48 – BIORESEARCH MONITORING

| SUBJECT: Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies | IMPLEMENTATION DATE: 03/19/2019 |
|---|---|
| DATA REPORTING | |
| PRODUCT CODES | PRODUCT/ASSIGNMENT CODES |
| eNSpect does not require product codes for Bioresearch Monitoring Inspections | 41807 ANIMAL RULE-SPECIFIC STUDY PROGRM (NONCLNCL LABS) (Biologics-Therapeutics)<br>42807 ANIMAL RULE-SPECIFIC STUDY PROGRM (NONCLNCL LABS) (Biologics-Blood)<br>45807 ANIMAL RULE-SPECIFIC STUDY PROGRM (NONCLNCL LABS) (Biologics-Vaccine)<br>48807 ANIMAL RULE-SPECIFIC STUDY PROGRM (NONCLNCL LABS) (Human Drugs) |

## FIELD REPORTING REQUIREMENTS:

Consult the center point of contact (POC) listed in the assignment memorandum or the Center for Drug Evaluation and Research (CDER), Office of Translational Sciences (OTS), Office of Study Integrity and Surveillance (OSIS) at CDER-OSIS-GLP@fda.hhs.gov and the Center for Biologic Evaluation and Research (CBER), Office of Compliance and Biologic Quality (OCBQ), Division of Inspections and Surveillance, Bioresearch Monitoring Branch at CBERBIMONotification@fda.hhs.gov, if there are questions or concerns prior to documenting any observations on a Form FDA 483.

Copies of all Establishment Inspection Reports (EIRs), including attachments, exhibits, and any related correspondence are to be **submitted** promptly to the Center contact identified in the assignment to meet established deadlines issued by the Center.

All EIRs should be completed in accordance with Field Management Directives (FMD) No. 86, Establishment Inspection Report – Inspection Conclusions and District Decisions (https://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM382035.pdf). When a Form FDA 483, "Inspectional Observations" is issued, a copy should be sent to the Center contact, and the Center's email mailbox, generally no later than three business days following the close of the inspection, or upon return from an international inspection.

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# PART I - BACKGROUND

## 1. Scope of Document

This Compliance Program (CP) outlines procedures for FDA Investigators inspecting domestic and international nonclinical laboratories conducting any portion of Animal Rule-specific studies (defined in the next section) submitted to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) in regulatory applications or FDA's Animal Model Qualification Program (AMQP).

## 2. Introduction

### A. Animal Rule

The regulations at 21 CFR 314.600 through 314.650 (drugs) and 21 CFR 601.90 through 601.95 (biological products) that provide a pathway for approval of drugs and licensure of biological products when human efficacy studies are not ethical or feasible are commonly referred to as the *Animal Rule*. The Animal Rule applies to drugs or biological products developed to reduce or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological or nuclear substances, when human efficacy studies are not ethical and field trials after accidental or deliberate exposure are not feasible. Under the Animal Rule, FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans. The Animal Rule does not address the safety evaluation of the products; thus, the safety of products developed under this pathway should be evaluated under the existing requirements for establishing the safety of new drugs or biological products.

### B. Animal Rule-specific studies

The animal studies that are the subject of this compliance program are referred to as Animal Rule-specific studies.[1] Animal Rule-specific studies are (1) the natural history studies that define the animal model in which efficacy will be tested, (2) the adequate and well-controlled animal efficacy studies intended to provide the primary evidence of effectiveness to support marketing approval, and (3) the pharmacokinetic (PK) and/or pharmacodynamic (PD) studies in animals used to select a dose and regimen in humans.

A unique aspect of Animal Rule-specific studies is the inclusion of a challenge agent (i.e., a chemical, biological, radiological or nuclear substance used to cause the disease or condition of interest in the animal studies).[2] The challenge agent should not be confused with, or referred to as,

[1] The definition of the Animal Rule-specific studies comes from section IV of FDA's guidance *Product Development Under the Animal Rule*.

[2] Although unlikely, there may be studies in which more than one challenge agent is used. In such circumstances, any reference to "challenge agent" used in this compliance program refers to each of the challenge agents individually.

the test article, even in a natural history study in which the only substance "tested" is the challenge agent. In Animal Rule-specific studies, the test article is the investigational drug or biological product.

C. Data quality and integrity and the Animal Rule-specific studies

The Good Laboratory Practice (GLP) regulations (21 CFR part 58) were developed as a quality system for nonclinical safety studies, and, thus, do not address the Animal Rule-specific studies. FDA, however, considers the GLP regulations to be a well-established and relevant framework (e.g., definitions, procedures, roles and responsibilities, and controls) for ensuring data quality and integrity in Animal Rule-specific studies. Currently, FDA recommends the use of the GLP regulations, to the extent practicable, for the adequate and well-controlled animal efficacy studies, and the PK and/or PD studies in animals used to select a dose and regimen in humans, because these studies serve as the basis for a regulatory action. Qualification of an animal model through the AMQP is a regulatory conclusion. Therefore, FDA also recommends the use of the GLP regulations, to the extent practicable, for the model-defining natural history studies submitted to the AMQP to support qualification of an animal model.[3]

There may be justifiable limitations to conducting these studies using GLP regulations, especially for those studies requiring high containment facilities (e.g., biosafety levels 3 and 4 facilities). In such circumstances, sponsors and requestors should propose methods to ensure data quality and integrity for aspects of the studies anticipated to be a challenge with regard to the GLP regulations, and seek concurrence from FDA on the proposed plan prior to the initiation of the studies.

[3] For additional background information on FDA's expectations for data quality and integrity for Animal Rule-specific studies, see section IV.B of FDA's guidance *Product Development Under the Animal Rule*.

## PART II - IMPLEMENTATION

### 1. Objectives

The objective of the Animal Rule-specific studies Bioresearch Monitoring (BIMO) Program is to provide instructions for the inspection of nonclinical laboratories conducting Animal Rule-specific studies. These inspections will be conducted to verify, to the extent practicable, the quality and integrity of the data contained in final reports of Animal Rule-specific studies submitted to FDA.

### 2. Regulated Industry

The regulated industry under this program includes a person who conducts operations to generate data for Animal Rule-specific studies used in support of drug and biological product applications, and in support of qualification of an animal model through FDA's AMQP. *Person* includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

### 3. Inspection Assignments

The CDER Office of Translational Sciences (OTS)/Office of Study Integrity and Surveillance (OSIS) and CBER Office of Compliance and Biologics Quality (OCBQ) receive requests for Animal Rule-specific study inspections from offices that review drug and biologics applications or from the AMQP. As a result of these requests, OSIS and OCBQ may issue directed inspection assignments to ORA. Directed inspection assignments may also be issued based upon complaints received from the public and private sectors, who may report potential misconduct at a nonclinical laboratory, or a nonclinical laboratory's deviations from practices that protect data integrity. For surveillance inspections, the nonclinical laboratories to be inspected are identified based on current surveillance models.

All assignments will be generated by the Center (CDER or CBER, as appropriate) and issued to Office of Regulatory Affairs (ORA) for completion. Center staff may accompany ORA Investigators during inspections as subject matter experts (SMEs).

#### A. Scheduling an Inspection

For domestic and international inspections, if Center staff want to participate, they should follow current procedures to obtain concurrence. Once concurrence is obtained, they should then collaborate with the assigned ORA Investigator to schedule the inspection. ORA and/or Center staff may also participate on international Animal Rule-specific study inspections with non-FDA international regulators.

#### B. Preannounced vs. Unannounced Inspections

Details regarding prior notification of an inspection will be communicated in the assignment. ORA Investigators should contact the Center contact for additional information regarding the need to preannounce an inspection.

C. Roles and Responsibilities While Conducting the Inspection

On inspections that include both Center and ORA staff, the ORA Investigator is the Team Lead in accordance with the Investigations Operations Manual (IOM) Section 5.1.2.5 and the Center staff will:

- Provide on-site support to the ORA Investigator, including coordinating or conducting parts of the inspection, as needed.

- Provide expert technical guidance, advice, information, and support to ORA Investigators prior to, during, and after the inspection, including contacting the ORA Investigator when new information becomes available and writing portions of the Establishment Inspection Report (EIR), as appropriate.

- Attend daily wrap-up meetings held by the inspection Team Lead to discuss findings and status of the inspection and ensure appropriate evidence is collected to document observed deficiencies when warranted.

The Center may arrange for a consultative teleconference immediately prior to an inspection if, for example, there is new information concerning the nonclinical laboratory or the studies assigned, or there are concerns about the data that were not previously conveyed to ORA in the assignment.

## PART III - INSPECTIONAL

This section outlines the minimum components to be included in an Animal Rule-specific study inspection.[4] This is not meant to be an all-inclusive list of components that may be covered during an inspection. Deviations from the minimum components should be documented with appropriate explanation in the EIR.

### 1. Areas of Expertise of the Test Facility

Nonclinical laboratories may conduct more than one type of study, including, but not necessarily limited to, Animal Rule-specific studies. The ORA Investigator should describe in the EIR the types of studies conducted at the nonclinical laboratory using the following broad categories:

- Animal Rule-specific studies[5]
    - Natural history studies
    - Adequate and well-controlled efficacy studies
    - PK and/or PD studies
    - Animal efficacy studies
- Studies with a specific route of exposure for challenge agents (e.g., inhalation studies)
- General toxicology studies
- Specialized toxicology studies (e.g., developmental and reproductive toxicology, carcinogenicity, juvenile toxicology, inhalation toxicology)
- Analytical and clinical chemistry testing
- Other categories of studies for which a list has been requested in the assignment.

### 2. Responsible Persons

- **Identify** the most responsible person at the nonclinical laboratory and those who had leading roles at the time the studies to be inspected were conducted.
- **Issue** the Form FDA 482, "Notice of Inspection" (FDA 482) to the most responsible person upon arrival at the nonclinical laboratory.
- **Issue** the Form FDA 483, "Inspectional Observations" (FDA 483) to the most responsible person at the nonclinical laboratory if significant objectionable conditions were observed during the inspection.

[4] For additional background information, see FDA's guidance *Product Development Under the Animal Rule*.
[5] The Animal Rule-specific studies are defined in greater detail in Part I, Section 2 of this compliance program.

- **Document** the names, titles, duties, roles, and responsibilities of the individuals providing you with information in the EIR as per IOM 5.11.4.3.7.

## 3. Organization and Personnel

- **Obtain** a copy of the organizational chart that lists the most responsible person at the nonclinical laboratory and displays the reporting relationship of all staff. If no organizational chart is available, **obtain** detailed information regarding the lines of authority of management up to the Chief Executive Officer (CEO)/President and include in the EIR.

- **Identify** the person who should receive official correspondence.

- For inspections that involve a Contract Research Organization (CRO), **determine** if there is a written agreement that describes the study activities that the CRO will perform, and **collect** a copy if available.

- **Obtain** the name, physical address, and email address of third parties involved in any aspect of the study.

## 4. Establishment Inspections

The areas listed below should be **evaluated** during the inspection and **described** as appropriate in the EIR. The inspection of certain aspects of Animal Rule-specific studies (e.g., inspection of equipment, reagents, and solutions) may be justifiably limited, especially for those studies requiring high containment facilities (e.g., biosafety level 3 and 4 facilities). Any inspection limitation should be **documented** in the EIR.

In the event that serious deficiencies are noted, the investigator should contact his or her supervisor and the Center contact should be informed to determine the extent to which the scope of the inspection should be expanded.

A. Test Facility Management (TFM)

**Verify** that TFM has defined the roles and responsibilities of specific study personnel by **confirming** the involvement of TFM in the following areas:

- Determining if there are specific phases of a study contracted to a third party, such as histopathology, clinical pathology.

- Assigning and replacing the study point of control (SPOC) (i.e., the person responsible for the overall conduct of the study). That person is commonly referred to as a study director (SD) or principal investigator (PI), but other position titles may be used.

- Managing the SPOC's workload. [**Review** the master schedule to assess the SPOC's workload.]

- Establishing and supporting the Quality Assurance Unit (QAU), including ensuring that the QAU reports deficiencies to the TFM and SPOC.

- Ensuring that deficiencies reported by the QAU are addressed.

- Providing appropriate training to staff for safe handling of challenge agents and any hazardous substances, components, or waste related to the use of the challenge agent in the study.

- Reviewing protocols and standard operating procedures (SOPs).

B. Study Point of Control (SPOC)

- **Verify** that a single person is identified as the SPOC for the conduct of the study.

- **Review** the SOPs and/or the position description that define the qualifications, duties, and responsibilities of the SPOC, and policies related to the replacement of the SPOC.

- **Review** the SPOC's qualifications (e.g., curriculum vitae and training records) and **collect** copies, as necessary, to document cases in which the SPOC's qualifications may not be adequate.

- **Determine** whether the SPOC was kept apprised of any unanticipated study events that may have affected the quality and integrity of the study.

- **Confirm** that the SPOC has:

  - Ensured that study personnel were familiar with and adhered to the study protocol and SOPs.

  - Ensured that data were collected according to the study protocol and SOPs and were accurately recorded and verified.

  - Documented in the final study report any unforeseen circumstances that may have affected the quality and integrity of the study and implemented appropriate corrective actions.

  - Ensured that study materials (including raw data, documentation, protocols, specimens, and final reports) were transferred to the archives during the study or after study completion.

C. Study Personnel

- **Identify** personnel (if any) performing duties at other locations, including their lines of authority.

- **Confirm** that summaries of training and position descriptions are maintained and current for all employees involved in Animal Rule-specific studies.

- **Verify** that study personnel clearly understand the functions they are to perform and are qualified to effectively conduct specific phases of the study to which they are assigned.

- **Determine** whether study personnel are properly trained on study procedures by observing them, to the extent possible, as they perform those procedures.

- **Verify** that study personnel have appropriate education, training, and experience, including training on facility-, study-, and phase-specific SOPs. **Review** training records for personnel observed performing study related procedures and **determine** that personnel have had appropriate training.

- **Verify** that practices are in place to ensure that employees take necessary health precautions, wear appropriate clothing, and report illnesses to prevent contamination of the challenge agent, the test and control articles, and the animals.

- **Verify** that practices are implemented to ensure that study personnel safely handle the challenge agent, animals that have been exposed to the challenge agent, and any hazardous substances, components, or waste related to use of challenge agents.

D. Quality Assurance Unit (QAU)

Because Animal Rule-specific studies do not fall under the scope of GLP regulations, **determine** whether the nonclinical laboratory has a QAU. If the nonclinical laboratory does not have a QAU, **document** how the nonclinical laboratory ensured the quality and integrity of the study data. If the nonclinical laboratory does have a QAU, **confirm** that:

- The QAU is entirely separate from and independent of personnel engaged in the direction and conduct of the study.

- The QAU has scheduled in-process audits and inspections to monitor and document study events and related facility operations.

- The significant study events and facility operations are monitored by QAU staff.

- The QAU audits study records for accuracy.

- The QAU personnel are properly trained to conduct their activities safely and effectively.

- The QAU writes periodic status reports for each study noting any problems and corrective actions taken, and submits the reports to the SPOC and TFM.

E. Facilities

**Verify** that:

- Facilities (including, when appropriate, the specific containment suites) are of adequate size and design, that procedures are in place for environmental controls and monitoring, and that procedures are followed.

- Appropriate areas are designated for the receipt, storage, preparation, and administration of challenge agents, test articles, and control articles.

- Separation of study activities is maintained in rooms to prevent any unanticipated effects on the study.

- Facilities are adequately cleaned and sanitized in accordance with facility-specific SOPs, and the list of cleaning products used is documented.

- Adequate pest control procedures exist throughout the facility (e.g., animal care areas) and are documented.

- Pest control and cleaning materials that would interfere with the study are not used.

- Equipment for facility environmental controls (e.g., heating, ventilation, and air conditioning (HVAC) system) is of adequate design/capacity and is maintained and operated in accordance with established SOPs.

- The HVAC system filters are changed at required intervals, the changes are documented, and that temperature/humidity/air change monitoring is performed in critical areas (e.g., animal rooms) in accordance with established SOPs.

F. Equipment

The inspection of equipment is an aspect of the Animal Rule-specific studies that may be justifiably limited, especially for those studies conducted in high containment facilities. Any inspection limitation should be **documented** in the EIR. **Verify** the following information for equipment used on the study:

- Equipment is in working condition and is appropriately cleaned and/or sanitized.

- Equipment is located where it is intended to be used or is appropriately stored until used.

- Equipment is stored in a controlled environment.

- Equipment is operated (including proper calibration/standardization) in a manner that ensures valid results (e.g., as per SOP/operator's manual).

- SOPs exist and are available for the maintenance, cleaning, calibration, and verification of equipment and reflect the manufacturer's use and maintenance requirements.

- Maintenance schedules are followed, and maintenance logs are maintained.

- Standardization/calibration procedures, schedules, and logs exist. Standards and calibrators used for standardization and calibration are appropriate and not expired.

- Computer systems are properly maintained, validated, and secured (e.g., login required for user identification that ensures restricted access).

- Electronic data is attributable, legible, contemporaneous, original, and accurate (ALCOA).

- The electronic audit trail feature (when present) is turned on and enabled and allows for tracking of any changes to electronically captured and/or electronically stored data.

G. Operations

**Collect** the SOP index and review selected SOPs in detail as inspectional activities dictate. **Verify** that:

- SOPs exist, are available to operations staff, and are followed for critical facility operations.

- Only the most current version of an SOP is available to the operations staff based on examination of representative SOPs in use throughout the facility.

- SOPs represent the actual procedures performed based on observation of personnel performing procedures and comparison with the applicable SOP.

- SOPs are approved by TFM before implementation.

- A historical file of SOPs is maintained by requesting to review the obsolete versions of SOPs from those listed in the SOP index as having previous versions.

- Personnel were trained on and familiar with relevant versions of SOPs (including, but not limited to SOPs specific to study and the challenge agent). [**Verify** this through interview, and review of training records and training materials.]

H. Reagents and Solutions

The inspection of reagents and solutions is an aspect of the Animal Rule-specific studies that may be justifiably limited, especially for those studies conducted in high containment facilities. Any inspection limitation should be **documented** in the EIR.

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

- **Confirm** that storage requirements for reagents and solutions are being followed according to the applicable SOPs and manufacturer specifications, and review temperature logs for those reagents requiring refrigeration or freezing.

- **Confirm** that expired reagents and solutions are clearly marked and separated from those in use.

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

- **Verify** that study records document receipt, storage, handling, and expiration of reagents and solutions used during the conduct of the study.

I. Animal Care and Use

**(1) Facility/Environmental**

- **Verify** that there are SOPs for receiving, housing, feeding, handling, and care of laboratory animals, and that SOPs and protocol-specified instructions for animal care are being followed.

- **Confirm** that the facility has an Institutional Animal Care and Use Committee (IACUC) and SOPs related to the IACUC function, and **review** the most recent committee minutes to **verify** committee operation.

- **Verify** that newly received animals are isolated and identified, as appropriate for the species, and that their health status is evaluated by veterinarians or other trained facility personnel.

- **Confirm** that the environmental control of animal rooms is in accordance with the protocol and SOPs. **Review** temperature, relative humidity, and air change logs for select animal rooms and **determine** that the required conditions are being maintained.

- **Confirm** that water, feed, and bedding for animals are free of substances that may impact the outcome of the study.

- **Verify** that feed and water for animals are periodically analyzed to ensure that substances known to have an adverse effect on the study are not present at levels above those specified in the study protocol or SOPs.

- **Confirm** that animals of different species, or animals of the same species on different projects, are separated as necessary.

- **Verify** that cages, racks, and accessory equipment are cleaned and sanitized, and that bedding and/or resting/sleeping structures appropriate for the species are used.

- **Review** pest control procedures and documentation of the chemicals used. **Identify** individuals responsible for the pest control program.

**(2) Protocol-specific**

**Verify** that:

- Animal records are available for all study animals, including all documentation (e.g., administrative, veterinary, investigational) from the vendor, acquiring facility, pre-protocol periods, and the time on study.

- Animals were appropriately identified by comparing individual animal identification against corresponding housing unit identification and dose group designations.

- Study protocols and/or SOPs have criteria for the use of animal care interventions,[6] that animal care interventions are used in accordance with the protocol and any applicable SOPs, and that the use is documented, including the identity of the authorizing personnel.

- The protocol contains prospectively defined euthanasia criteria for moribund animals, that animals euthanized during the study met the euthanasia criteria, and that deviations from the criteria or in the authorizing individual (if this individual is specified in the protocol) were adequately documented.

- Daily observation logs are accurate (e.g., animals are appropriately noted as dead/moribund/euthanized or having external gross lesions or masses).

- Animal group designations were correct for the test and control articles, and for the challenge agent and its control, when needed.

[6] For the purpose of this compliance program, animal care interventions include any products administered (e.g., anesthesia, analgesia, antimicrobial treatment, intravenous fluid) or procedures carried out (e.g., sutures, wound cleaning, applying heating pads) to provide adequate veterinary care or supportive care to mimic the human clinical scenario. Animal care interventions do not include challenge agent, test article, and controls. See FDA's guidance *Product Development Under the Animal Rule.*

- Animal characteristics (e.g., species, age, source of animals) were in agreement with the protocol.

- Animal instrumentation is documented properly (when applicable), including identification of the instrument and data collected (e.g., telemetry).

- The inclusion and exclusion criteria for acceptance into the study were in agreement with the protocol.

- The size of study groups and the male/female composition of the groups were in agreement with the protocol.

- The randomization procedure(s) used for animal assignment were in agreement with the protocol.

- Blinding procedures used by personnel involved in making decisions regarding animal care interventions and/or euthanasia, and in the collection, assessment, or interpretation of data obtained in the study were performed in agreement with the protocol.

- Clinical observations and monitoring of the animals including frequency, schedule, and parameters evaluated were performed in agreement with the protocol.

J. Test and Control Articles

- **Verify** that the characterization (i.e., identity, strength, purity, and composition or other characteristics which appropriately define the test or control article) of each batch of the test and control article and each batch of the test and control article formulations used in the study meet protocol specifications.

- **Verify** that the stability of test and control articles and mixtures is documented under the conditions of use.

- **Verify** that the concentration and uniformity of test and control article mixtures used during the study are determined and documented in accordance with SOPs.

- **Verify** that when the sponsor performs analytical testing or provides characterization of the test and control articles, the test facility/SPOC receives the results/data in a timely manner for use in generating the final report.

- **Determine** that adequate procedures and documentation exist for the receipt, storage, and distribution of test and control articles, including measures to avoid cross-contamination of the test and control articles.

- **Review** a representative sample of accountability records and, if possible, **verify** their accuracy by **comparing** actual amounts in the inventory.

- **Inspect** test and control article storage areas to **verify** that environmental controls, container labeling, and storage are adequate.

- **Verify** that test and control articles are appropriately labeled and stored separately from each other.

- **Verify** animal group designations for test article and controls. If possible, **observe** test and control article preparation, handling, and identification during distribution and administration to the animals.

- **Verify** that the administration of test or control articles to the animals was initiated in accordance with the protocol.

- **Verify** that the transfer, handling, and storage of samples from the point of collection to the analytical laboratory is documented.

K. Challenge Agents

**Verify** that:

- Study records adequately document, as appropriate, the receipt, storage, preparation, and delivery of the challenge agent.

- The characteristics of the challenge agent and the methods for characterization are in accordance with the protocol and SOPs.

- The preparation and delivery of the challenge agent or challenge agent formulation (and, when needed, its control) were performed according to the protocol or SOPs.

- SOP(s) describe the calibration of instrumentation used to deliver the challenge agent.

    - **Collect** relevant SOPs.

    - **Verify** that instruments used to deliver the challenge agent in the study were calibrated/standardized according to SOPs.

- The methods used for the quantification/verification of exposure to the challenge agent (i.e., determination of the actual dose of challenge agent delivered to the animal) were in accordance with the protocol and SOPs and that the instruments used for the quantification/verification of exposure were calibrated/standardized according to SOPs.

L. Protocol

- **Verify** that SOPs for protocol preparation, amendment, and approval were followed. **Confirm** that all changes, revisions, or amendments to the protocol were authorized, signed, and dated by the SPOC.

- **Collect** the protocol, the final study report, and amendments, if any, to the protocol/final report for each study identified in the assignment, or each study selected for review during the inspection.

- **Verify** that the study was conducted in accordance with the protocol and SOPs, and any changes or deviations were documented per SOP. Study components to be reviewed include, but are not limited to:

  - The statistical analysis plan.

  - Plans for ensuring data quality and integrity.

  - Collection, identification, and handling of specimens.

  - Procedures for recording raw data (manual and automated systems), including procedures for maintaining data quality and integrity if/when the source data cannot leave high containment facilities.

- **Assess** whether the study protocol addresses any unique challenges associated with the conduct of the Animal Rule-specific study (e.g., treatment triggers, euthanasia criteria, and blinding procedures).

M. Records

- **Review** the procedures for storing and retrieving raw data, documentation, protocols, final reports, and specimens.

- **Verify** that raw data, including but not limited to electronic records, are ALCOA.

- **Confirm** that, when circumstances warrant (e.g., original raw data cannot be removed from biocontainment suite) and it is feasible, verified copies of the original raw data are provided for review.

- **Describe** how the nonclinical laboratory stores and retrieves raw data, documentation, protocols, final reports, and specimens.

N. Study Report

**Verify** that:

- The final study report is signed and dated by the SPOC.
- All corrections or additions to the final study report are documented as amendments, and that the final study report amendments include justification for the corrections or additions.
- The study methods described in the final study report agree with the protocol and SOPs.
- The final study report lists all protocol and SOP deviations and discusses the impact of the deviations.
- The final study report submitted to the Agency is supported by the raw data at the nonclinical laboratory.
- Contributing scientist reports are signed, dated, and available for review. **Collect** contributing scientist reports that are not appended to the final study report.
- The final study report identifies any third-party facilities, and the portion(s) of the study performed outside of the nonclinical laboratory.
- The final study report includes a description of any computer program changes.
- The facility prepares a final study report for each study conducted.

O. Archives

- **Confirm** that raw data, electronic data, documentation, protocols, final reports, and specimens (e.g., fixed tissues, paraffin blocks, and slides) are retained and that all of the requested study records are recovered from the archives. **Accompany** facility personnel during the retrieval of the study records from the archives to **evaluate** the facility's archiving procedures.
- **Verify** that archived materials, including computer/electronic data, are stored under appropriate environmental conditions (e.g., protected from heat, water, and electromagnetic forces).
- **Verify** that access to the archives is controlled and limited to authorized personnel.
- **Verify** that SOPs describe the procedures for adding and removing material from the archives.
- **Identify** the individual responsible for the archives and **determine** if duties related to archive maintenance have been delegated to other individuals.

## PART IV - ANALYTICAL

Not applicable to this Compliance Program.

## PART V – REGULATORY/ADMINISTRATIVE STRATEGY

If significant deficiencies are observed during the inspection, prepare a Form FDA 483, Inspectional Observations. Observations included on the Form FDA 483 should be factual statements; the recording of unsupported opinions should be avoided. Observations recorded on a Form FDA 483 should include supporting documentation attached to and discussed within the EIR.

Center reviewers will evaluate the frequency, scope, and severity of Form FDA 483 observations and any discussion items and evidence contained in the EIR and consider the impact of each on the reliability and acceptability of the study data. There are often varying gradations in the severity among similar Form FDA 483 citations. The specific observation(s) and information collected should support the Center's evaluation of the reliability and acceptability of the data for FDA decision-making purposes.

Importantly, as discussed above, the GLP regulations do not include Animal Rule-specific studies. However, the GLP framework allows for evaluation of reliability and acceptability of data, which is critical for the centers. The sponsor or requestor may have discussed aspects of Animal Rule-specific studies anticipated to be a challenge and been granted the ability to deviate from the GLP framework. Ensure this communication is evaluated and documented before citing any Animal Rule-specific studies with deficiencies on the Form FDA 483

## PART VI – REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. **FDA Guidance Documents and References**

A. FDA Laws

Federal Food, Drug, and Cosmetic Act (FFDCA)

B. Relevant Regulations

- 21 CFR Part 314, Subpart I--Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible
- 21 CFR Part 601, Subpart H--Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible
- 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies
- 21 CFR Part 11, Electronic Records; Electronic Signatures

C. Relevant FDA Guidelines, Guidance Documents, and Inspection Guides

- Product Development Under the Animal Rule Guidance for Industry (available through FDA's guidance web page at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm
- List of FDA Guidance Documents: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm
- Investigations Operations Manual
- FMD-86

2. **Program Contacts**

When technical or scientific questions or issues arise from a specific assignment, or if additional information is required about a specific assignment, consult the Center contact identified in the assignment.

For operational questions, contact:

- Office of Regulatory Affairs (ORA)
  - Your Supervisory Consumer Safety Officer (SCSO), or

- Office of Medical Products and Tobacco Operations (OMPTO), Office of Bioresearch Monitoring Operations (OBIMO) – ORABIMOInspectionPOC@fda.hhs.gov

For questions about the Animal Rule-Specific Studies compliance program, contact:

- 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 Biologic Evaluation and Research (CBER)
  - Office of Compliance and Biologic Quality (OCBQ), Division of Inspections and Surveillance, Bioresearch Monitoring Branch – CBERBIMONotification@fda.hhs.gov

## PART VII – CENTER AND ORA HQ RESPONSIBILITIES

1. **CDER Office of Study Integrity and Surveillance (OSIS) and CBER Office of Compliance and Biologics Quality (OCBQ), Division of Inspections and Surveillance (DIS), Bioresearch Monitoring Branch (BMB)**

   For directed inspections, OSIS or OCBQ (BMB) receives an inspection consult from Review Divisions, Center Offices, or the AMQP, and drafts assignments. CBER Review Divisions may request that a BIMO representative join the review committee.

   For surveillance inspections, OSIS or BMB identifies the nonclinical laboratories to be inspected based on the current surveillance model.

   A. OSIS or OCBQ Reviewer

   - Drafts and issues assignments, including contact information for the Center SMEs and documentation regarding any granted deviations from the GLP framework.
   - Provides expert technical guidance, advice, information, and support to Center staff and the ORA Investigator prior to, during, and after inspection.
   - Maintains contact with appropriate SME from Review Division, Center Office, or AMQP as necessary to assist the ORA Investigator with technical questions related to the application prior to, during, and after the inspection.
   - May accompany the ORA Investigator on the inspection and, if so, will participate in drafting the EIR.
   - Reviews the EIR and provides recommendations to the Review Division, Center Office, or the AMQP regarding the reliability and/or acceptability of study data. The Review Division, Center Office, and the AMQP have the ultimate authority to accept or reject study data based on inspectional findings.
   - Consults or communicates with other centers regarding any inspected studies under the purview of that center.
   - Enters the final classification into the appropriate compliance tracking system (e.g., eNSpect).
   - Issues letters to inspected nonclinical laboratories following final classifications, as appropriate.
   - Promptly forwards to the ORA Investigator and any appropriate ORA offices copies of post-inspectional correspondence issued to the inspected party.

2. **Office of Regulatory Affairs (ORA)**

   - Office of Bioresearch Monitoring Operations (OBIMO) receives assignments from centers and assigns the inspection to the appropriate BIMO Division.

     Assignments are addressed to ORABIMOInspectionPOC@fda.hhs.gov.

## ATTACHMENT A – Abbreviations and Acronyms List

**A**

| | |
|---|---|
| ALCOA | attributable, legible, contemporaneous, original, and accurate |
| AMQP | Animal Model Qualification Program |

**B**

| | |
|---|---|
| BIMO | Bioresearch Monitoring |
| BMB | Bioresearch Monitoring Branch |

**C**

| | |
|---|---|
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CEO | Chief Executive Officer |
| CFR | Code of Federal Regulations |
| CP | Compliance Program |
| CRO | Contract research organization |

**D**

| | |
|---|---|
| DIS | Division of Inspections and Surveillance |

**E**

| | |
|---|---|
| EIR | Establishment Inspection Report |
| eNSpect | System used to create, track and finalize EIRs |

**F**

| | |
|---|---|
| FFDCA | Federal Food, Drug and Cosmetic Act |
| FMD | Field Management Directive |
| FDA | Food and Drug Administration |

**G**

| | |
|---|---|
| GLP | Good Laboratory Practice |

**H**

| | |
|---|---|
| HQ | Headquarters |

| | |
|---|---|
| HVAC | Heating, ventilation, and air conditioning |

**I**

| | |
|---|---|
| IACUC | Institutional Animal Care and Use Committee |
| IOM | Investigations Operations Manual |

**O**

| | |
|---|---|
| OBIMO | Office of Bioresearch Monitoring Operations |
| OCBQ | Office of Compliance and Biologics Quality |
| OMPTO | Office of Medical Products and Tobacco Operations |
| ORA | Office of Regulatory Affairs |
| OSI | Office of Scientific Investigations |
| OSIS | Office of Study Integrity and Surveillance |
| OTS | Office of Translational Sciences |

**P**

| | |
|---|---|
| PD | Pharmacodynamic |
| PI | Principal Investigator |
| PK | Pharmacokinetic |

**Q**

| | |
|---|---|
| QAU | Quality Assurance Unit |

**S**

| | |
|---|---|
| SD | Study Director |
| SME | Subject Matter Expert |
| SOP | Standard Operating Procedure |
| SCSO | Supervisory Consumer Safety Officer |
| SPOC | Study point of control |

**T**

| | |
|---|---|
| TFM | Test facility management |

## Change History (optional, choice of one table here, or separate tables in Parts, or no tables)

| Item | Change | Date |
|---|---|---|
| | | |