

Animal Rule Compliance Program

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



Disclaimer

The opinions and information in this presentation are those of the author, and do not necessarily represent the views and/or policies of the U.S. Food and Drug Administration.

Learning Objectives

- Describe the rationale of the Animal Rule (AR) as a drug development pathway
- Summarize the components of the Animal Rule Compliance Program
- Define the goals of the Animal Rule Compliance Program

Animal Rule



- “Product Development Under the Animal Rule, Guidance for Industry” published in October 2015
- Provides information and recommendations on drug and biological product development when human efficacy studies are not ethical or feasible.
- The regulations that set forth the pathway for approval of these products are commonly referred to as the “Animal Rule”
 - 21 CFR 314.600 through 314.650 (drugs)
 - 21 CFR 601.90 through 601.95 (biological products)

CDER Inspections of AR Studies



- Since 2013, inspection of CDER AR studies are conducted as “Data Integrity Audits”
- A new compliance program (CP) for inspecting laboratories conducting Animal Rule-specific studies was finalized on 3/19/2019
 - Compliance Program 7348.007

CDER Inspections of AR Studies



- AR Compliance Program
 - CP 7348.007 Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies
 - Similar components to the compliance program for GLP studies (CP 7348.808)
 - Applies to GLP and non-GLP compliant AR studies

CDER Inspections of AR Studies



- Inspections of Animal Rule studies to verify the quality and integrity of the data
 - Data quality – study conducted in accordance with protocol, SOPs, and applicable standards of research
 - Data integrity – raw data and adequate documentation to reconstruct the study and verify the results

CDER Inspections of AR Studies



- Data Integrity Audits
 - Do not verify compliance with 21 CFR part 58
 - Form FDA 483 may be issued at the close-out meeting
 - Response to FDA Form 483 requested within 15 business days
 - Impact of observations and recommendations (e.g., impact on data reliability) communicated to the review division

CDER Inspections of AR Studies



- Data Integrity Audits evaluate the following areas:

Personnel

Quality Assurance

Facilities

Equipment

Operations

Animal care

Test and control articles

Challenge agents

Protocol and study conduct

Records and reports

Archives

Personnel



Verify:

- Personnel, resources, facilities, equipment, and materials are adequate to conduct the study
- Personnel are adequately trained to perform their functions
- Testing facility has adequate quality oversight
- Study Point of Control (POC) is assigned - Commonly referred to as the Study Director or Principal Investigator
- Study POC approves protocols and amendments and reviews protocol and SOP deviations

Quality Assurance

Verify:

- QA performs inspections to monitor and document study events
- Protocol, amendments, and SOPs were followed by study personnel
- Raw data support the findings in the study reports
- Impact of all protocol and SOP deviations are discussed in the study report

Facilities

Verify:

- Facility is of adequate size and design to successfully conduct the study
- Environmental controls (e.g., handling of biohazardous materials) are adequate for the conduct of the study

Equipment

Verify:

- Equipment is in working condition and appropriately maintained, cleaned and sanitized
- Equipment logs are available for tracking use, scheduling maintenance, and calibration
- SOPs are available for the maintenance, cleaning, and calibration of equipment
- Calibration and verification are performed in accordance with SOPs

Operations



Verify:

- Current version of SOPs are available to study personnel
- Personnel are trained on the study protocol and applicable SOPs

Animal Care

Verify:

- SOPs are available for housing, feeding, handling, and care of laboratory animals
- Facility has an Institutional Animal Care and Use Committee (IACUC) and SOPs related to the IACUC function
- Animals are appropriately identified
- Staff performing clinical observations are blinded to treatment assignment
- Objective criteria exist for the use of animal care interventions and euthanasia of moribund animals

Test and Control Articles



Verify:

- Test and control articles are adequately characterized (i.e., identity, strength, purity, and composition)
- Stability of test and control articles is documented
- Test and control articles are appropriately labeled
- Test and control article mixtures are stable under the conditions of use

Challenge Agents



Verify:

- Challenge agent was adequately documented
 - Chemical and biological: Identity, purity, and concentration or titer
 - Radiological: Instrumentation delivers the desired wavelength and dose
 - Nuclear: Identity, content, and radioactivity of the specific isotope
- Actual dose of challenge agent was in accordance with the protocol

Protocol and Study Conduct



Verify:

- Study personnel followed the protocol, protocol amendments and SOPs
- All changes to the protocol and amendments were authorized by Study POC
- Clear and specific standard for unscheduled euthanasia
 - Criteria for euthanasia clearly stated
- Blinding procedures were maintained throughout the study
 - e.g., personnel performing clinical observations, necropsy and assays
- Impact of supportive care on the outcome of the study was discussed in the final report

Records



Verify:

- Raw data are recorded contemporaneously and legibly
- Entries are identified by the individual's name and date entered
- Computer systems are validated and use an audit trail to document changes to raw data
- Records accurately report the disposition of death (e.g., animal euthanized or found dead)

Final Study Report



Verify:

- Study report is signed by the Study POC
- Corrections to the finalized study report are in the form of an amendment
- Signed contributing scientist reports are available for audit
- Study report lists all protocol and SOP deviations and discusses their impact

Archives



Verify:

- Adequate space is allocated for the storage and retrieval of raw data, records, and specimens
- Access to the archive is limited to authorized personnel
- Raw data, records, and specimens were retained

Record Retention

- No explicit record retention requirement
- 21 CFR 58.195 (Retention of Records) does not apply to Animal Rule-specific studies
- Recommend that raw data and records be retained until no longer needed to support a regulatory action

Summary



FDA expects that AR studies will be conducted in a manner to ensure the quality and integrity of the data to support the product's use in humans for the intended indication

Challenge Question #1

Which of the following statements is true regarding the compliance program for AR studies :

- A. Applies only to GLP compliant AR studies
- B. Verifies compliance with 21 CFR part 58
- C. Form FDA 483 may be issued
- D. Impact of observations are not shared with review division

Challenge Question #2

Which of the following statements is NOT true regarding data integrity audits of AR studies?

- A. Verify that QA performs inspections to monitor and document study events
- B. Verify that study protocols and/or SOPs have criteria for the use of animal care interventions
- C. Verify that the challenge agent was adequately documented
- D. Verify that record retention requirements in 21 CFR 58.195 are met

Resources

- CP 7348.007 Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies
<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs>
- Product Development Under the Animal Rule, Guidance for Industry, October 2015 <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-development-under-animal-rule>

Questions?

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Closing Thought

Remember that the quality and integrity of the nonclinical studies submitted under the Animal Rule have a direct impact on public health as a whole.