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.