58

Guidance for Industry

GOOD TARGET ANIMAL STUDY PRACTICES:

CLINICAL INVESTIGATORS AND MONITORS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE
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TABLE of CONTENTS

I. FOREWORD

The purpose of this guidance document is to make recommendations to investigators and monitors concerning the conduct of clinical studies evaluating the performance of investigational new animal drugs. The Center for Veterinary Medicine (CVM) has identified an approach to comply with section 512(j) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 511.1. We believe the recommendations of this guidance document should be applicable to the majority of clinical studies, including those studies intended to support a food additive petition for animal use, submitted to CVM. However, we also recognize that, given the diversity and scope of submitted studies, some of these recommendations may not be completely applicable to certain studies. In situations where the present recommendations appear inappropriate for particular circumstances, you may wish to contact CVM prior to conducting the study in question. We welcome discussions of alternative approaches to address specific concerns for individual studies and are open to suggestions that may improve the conduct of all clinical studies.

CVM supports the use of quality assurance (QA) procedures for clinical data. While current regulations do not specifically address or assign responsibility for QA functions in clinical studies, CVM envisions that the sponsor would most likely be the party to execute the QA functions for these studies. CVM believes that this guidance document would be used most effectively within an adequate QA program. CVM encourages all participants in clinical studies to voluntarily adopt and adhere to generally recognized sound QA practices.

This guidance document supersedes the "*Guideline for the Monitoring of Clinical Investigations, January 1988*" as it relates to clinical studies of new animal drugs and replaces CVM's previous guideline, "*Conduct of Clinical Investigations: Responsibilities of Clinical Investigators and Monitors for Investigational New Animal Drug Studies, October 1992.*"

This guidance represents FDA's current thinking on good target animal study practices for clinical investigators and monitors. It does not bind, create, or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the statute, regulations, or both.

When a guidance document states a requirement imposed by statute or regulation, the requirement is law and its force and effect are not changed in any way by virtue of its inclusion in the guidance. If a person chooses to use alternate procedures or practices, that person may wish to discuss the matter with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable to FDA.

FDA may amend this guidance document based upon comments submitted by interested persons or information obtained from agency inspections of sponsors, monitors, and investigators. Submit written comments on the guidance document to the Office of Policy and Regulations (HFV-6), Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

Additional or updated copies of this guidance may be requested from the Communications and Education Team (HFV-12), Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855, telephone (301) 594-1755.

II. GLOSSARY

Adverse Drug Experience

Any adverse event associated with the use of an investigational new animal drug, whether or not considered to be drug related.

Animal Patient Records

Written records of health observations collected by clinical practitioners related to the veterinary care and husbandry of animals. These records are typically the property of the clinical practitioner or veterinary hospital where collected.

Audit (of a study)

A comparison of raw data and associated documentation with the final study report in order to determine whether the raw data have been accurately reported, whether testing was carried out in accordance with the study protocol and SOP's, to obtain additional information not provided in the final study report, and to establish whether practices were employed in the collection of data that would impair their validity.

Case Report Forms

Standardized forms specifically designed to record observations of animals that are participants in a clinical study. These records are not the property of the clinical practitioner or veterinary hospital, but are considered part of the study documentation collected during the conduct of a clinical study.

Clinical Study

A single scientific experiment conducted to test at least one hypothesis relevant to the proposed claim(s) made for a new animal drug under investigation.

Experimental Phase Completion Date

The date the collection of all raw data is complete.

Experimental Phase Initiation Date

The date on which animals are first identified with a treatment.

Final Study Report

The comprehensive description of the study written after its conclusion. This report includes a description of the objective(s), experimental materials and methods, and a presentation and critical scientific evaluation of the results (including statistical analyses where appropriate).

Informed Consent

The written confirmation of an owner's willingness to permit animals to participate in a particular study.

Investigation

All of the studies designed for or conducted as part of a scientific determination of the safety and effectiveness of an investigational new animal drug to support an NADA.

Investigational Animal

Any animal which participates in a study, either as a recipient of the investigational new animal drug or as a control.

Investigator

An individual qualified by training and experience who is entrusted with the implementation of the study protocol, collecting study data, and the overall conduct of the study.

Masking (blinding)

The withholding of the identity of treatments from all appropriate study personnel to reduce bias.

Monitor

An individual qualified by training and experience who represents the sponsor in overseeing the investigator's implementation of a protocol and progress of the study and determines whether the study is conducted in accordance with all applicable requirements.

Protocol

A document signed and dated by the investigator and the sponsor that states the rationale and objectives of the study, and all methods and conditions under which the study is to be performed and managed. A protocol includes all protocol amendments.

Protocol Amendment

A change or modification of the protocol effected prior to the implementation of the protocol or execution of the changed or modified task that is signed and dated by the investigator and sponsor and incorporated into the protocol.

Protocol Deviation

A departure from the procedures delineated in the protocol.

Raw Data

Any worksheets, calibration data, records, memoranda and notes of original observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, computer printouts, magnetic, electronic, or optical media, information recorded from automated instruments, and hand recorded datasheets. Facsimile transmissions and transcribed data are not considered raw data.

Report Amendment

Any addition, deletion, or correction to the final study report. A report amendment clearly identifies that part of the study report that is being added, deleted, or corrected and the reasons for the addition, deletion, or correction, and is signed and dated by the authors.

Standard Operating Procedure (SOP)

Detailed written instructions describing the procedures, test methods, and management operations to be performed or followed, precautions to be taken, and measures to apply for conducting specific tasks.

Study Completion Date

The date the final study report is signed by all authors.

Study Documentation

All records in any form (including documents, magnetic and optical records) describing methods and conduct of the study, factors affecting the study, and any actions taken. These records include, but are not limited to: protocol, raw data, reports, SOP's, reference materials, and specimens.

Study Initiation Date

The date the study protocol is signed by the investigator.

True Copy

A copy (or transcription of an animal patient record to a case report form) which is a complete reflection of the original record that has been verified as accurate and complete in a written statement by the individual(s) making the copy. The statement is signed and dated and indicates the number of pages copied.

III. CLINICAL INVESTIGATORS

A. Investigator Qualifications

Under 21 CFR Part 511, an investigator must be eligible to receive investigational new animal drugs, must be qualified by scientific training and experience to conduct studies to investigate the effectiveness of an investigational new animal drug, and should be knowledgeable about all applicable requirements for conducting clinical studies before receiving an investigational new animal drug.

If a study is conducted by a group of individuals, the investigator is the responsible designated leader of the group. An individual should not be an investigator and perform monitoring functions at any one study site. An investigator may monitor another study site within the same study.

B. Investigator Functions

The investigator should:

(1) Maintain the protocol in the study documentation.

(2) Record, and maintain in the study documentation, any protocol deviation as a signed and dated statement describing the deviation and the reason for its occurrence, and also immediately notify the sponsor of its occurrence.

(3) Conduct the study according to the protocol and all applicable regulations, including any authorization for the use of edible products derived from food-producing animals treated with an investigational new animal drug as regulated by FDA and the U.S. Department of Agriculture.

(4) Collect and report the data in a manner that accurately and completely reflects the observations of the study.

(5) Collect and retain study documentation, and prepare and retain reports of the study as described in the protocol and this guidance document.

(6) Provide sufficient qualified personnel for the timely and proper conduct of the study according to the protocol.

(7) Ensure that all appropriate study personnel are masked to treatment identity. Study personnel who cannot be masked should participate in the conduct of the study only to the minimum extent necessary.

(8) Delegate any authority and work, including any subcontracted work, only to individuals qualified by scientific training and experience to perform the assigned duties.

(9) Utilize only adequate and well-maintained facilities and equipment, whether owned or leased, to conduct the study.

(10) Be responsible for the control, storage, inventory, distribution, and further mixing (if any) of the investigational new animal drug(s) shipped or delivered to the investigator by the sponsor for the conduct of the study, and the documentation of these activities. Storage of the investigational new animal drug should be sufficiently secure to provide controlled access to the investigational new animal drug and be in accordance with the protocol and label specifications.

(11) Not redistribute the investigational new animal drug to any individual not authorized to receive the investigational new animal drug or for purposes other than those specified in the protocol.

(12) Return any unused investigational new animal drug, including animal feed bearing or containing the investigational new animal drug, to the sponsor or otherwise provide for and document the safe disposition of the unused investigational new animal drug or animal feed bearing or containing the investigational new animal drug when the study or investigation is terminated, suspended, discontinued, or completed.

(13) Obtain informed consent from the owner(s) of all investigational animals. A copy of this notification countersigned and dated by the owner should be included in the study documentation. This consent should only be sought after information has been given about the owner's rights and responsibilities, about the risks and inconveniences related to the study, and the objectives and benefits thereof. In the case of food-producing animals, the owner should be informed in writing of the consequences of participating in the study, including the subsequent disposal of investigational animals or the taking of edible tissues from investigational animals.

(14) Supervise the housing of all investigational animals. Animals owned by individuals other than the investigator should be maintained according to the protocol.

(15) Comply with applicable laws and regulations governing the humane care of animals and the proposed use of animals intended for investigational purposes.

(16) Prepare and maintain an accurate and complete record of all contacts (on-site visits, telephonic, written, and electronic) with the monitor or other representatives of the sponsor, and representatives of FDA, concerning the documentation, design, conduct, or reporting of a study. These records may include:

(i) The date and time of each contact.

(ii) The purpose of the contact.

(iii) The name, title, and organizational affiliation of all individuals involved.

(iv) A summary of the contact and findings sufficient to describe the basis for any actions taken by the investigator and/or monitor as a result of the contact.

(17) Promptly report to the sponsor any adverse drug experience associated with the use of the investigational new animal drug.

(18) Permit the monitor (or other authorized representative of the sponsor) and FDA to inspect the facilities used by the investigator for the study and, for the purposes of verifying the validity of the data collected for the sponsor, to inspect and copy all records made or kept by the investigator as part of or pertaining to the study.

IV. MONITORS

A. Monitor Qualifications

A monitor should be qualified by scientific training and experience to oversee the implementation of a study protocol and be trained in quality control techniques. A monitor should understand all applicable study requirements and be able to determine whether the study was conducted in accordance with the protocol.

B. Monitor Functions

The monitor should:

(1) Personally contact each investigator, preferably at the study site, before the initiation of each new study to:

(a) Provide assurance that each investigator understands the investigational status of the new animal drug, the nature and details of the protocol, the conditions of any authorization for the use of edible products derived from food-producing animals treated with an investigational new animal drug or of any restrictions on the disposal of nonfood animals (if applicable), and is willing to perform the functions of an investigator.

(b) Ensure that each investigator has adequate facilities, qualified personnel, and access to appropriate materials, resources, and potentially has an adequate number of suitable animals to conduct the study in accordance with the protocol.

(c) Provide assurance that each investigator understands and agrees to comply with applicable laws and regulations governing the humane care of animals and the proposed use of animals intended for investigational purposes.

(d) Determine that each investigator and any other individual involved in the study will be able to devote appropriate time to the proposed study.

(e) Ensure that any corrective action necessitated by a previous inspection (by FDA or the sponsor) has been taken prior to the initiation of the new study.

(2) Personally contact each investigator, preferably at the study site, with sufficient frequency during the conduct of each study to ensure that the functions of the investigator are being fulfilled. For example, the monitor should:

(a) Ensure that the protocol and applicable requirements are being followed.

(b) Review the study documentation necessary to make a determination that the functions of the investigator are being met for accuracy and completeness of information.

(c) Ensure that illegible or missing data and corrected data entries are fully explained.

(3) Prepare and maintain an accurate and complete record of all contacts (on-site visits, telephonic, written, and electronic) with the investigator or other study personnel concerning the documentation, design, conduct, or reporting of a study. These records may include:

(a) The date and time of each contact.

(b) The purpose of the contact.

(c) The name, title, and organizational affiliation of all individuals involved.

(d) A summary of the contact and findings sufficient to describe the basis for the monitor's evaluation and conclusions and any actions to be taken by the monitor and/or the investigator as a result of the contact.

C. Implementation of Monitor Functions

The "New Animal Drugs for Investigational Use" regulations (511.1(b)(8)(ii)) require current monitoring of clinical studies. The monitoring functions may be fulfilled by one individual or a group of individuals. If the monitoring functions of a study are performed by a group of individuals, the monitor is the designated leader of the group. Individuals to whom monitoring functions have been delegated must (511.1(b)(8)(ii)) be qualified by scientific training and experience to perform their assigned duties.

Individuals performing monitoring functions should never attempt to bias, in any way, the outcome of the study. An individual should not be an investigator and perform monitoring functions at any one study site. CVM may, in rare and limited circumstances, find it acceptable to allow individuals performing monitoring functions to participate in the conduct of a study at a particular study site. Any such potential participation of individuals performing monitoring functions in a study should be discussed with CVM prior to the initiation of the study and be delineated in the protocol.

V. STUDY DOCUMENTATION

All study documentation should be retained, but may not need to be submitted to an application. Study documentation includes, but is not limited to:

A. Protocol

This documentation consists of the original study protocol and all protocol amendments and deviations.

B. Raw data

(1) Classes of raw data. The raw data of a study generally include several classes of study records. Neither the classes listed below nor the examples provided for each class are intended to be all-inclusive.

(a) Animal records. These include all data pertinent to the investigational animals: such as, purchase records, documentation of investigational animal inclusion or exclusion, informed consent agreements, treatment assignment, all recorded observations (including analytical assay results of biological samples), case report forms, adverse drug experiences, animal health observations, and final animal disposition.

(b) Investigational new animal drug records. These include records of the receipt, distribution, drug inventory, results of drug assays, and final disposition of any unused drug or animal feed bearing or containing the drug. Records of the administration of the investigational new animal drug should include, but not be limited to, the documentation of the dosing regimen, including dose, rate, route, and duration of administration.

(c) Contact records. These include the monitor's and the investigator's records of all contacts (on-site visits, telephonic, written, and electronic) concerning the documentation, design, conduct, or reporting of a study.

(d) Facility and equipment records. These include facility descriptions (diagrams, photographs, etc.), equipment identification and specifications, equipment calibration and maintenance records, equipment failure and repair records, meteorological records, and environmental observations.

(2) Valid raw data.

(a) Qualities. *Valid* raw data, whether handwritten or electronic, should be attributable, original, accurate, contemporaneous, and legible. *Attributable* means 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. In automated data collection systems, the individual responsible for data input should be identified. *Original* and *accurate* mean the raw data are the first true observations. *Contemporaneous* means the raw data are recorded at the time of observation. *Legible* means the raw data are readable and recorded in a permanent medium, e.g., ink for written records and electronic records that are unalterable.

(b) Corrections. Any correction should be made so as not to obscure the original entry. The correction should be dated and initialed by the individual(s) making the correction at the time the correction is made and describe the reason for the change.

If a portion of the raw data needs to be copied or transcribed for legibility, a true copy of that portion of raw data should be made. The reason for the copying or transcription should be explained in a dated memorandum, or in a dated notation on the transcribed record, signed by the individual(s) making the copy or transcription. In such a case, the copied raw data, the copy or transcript of the raw data, and the memorandum should be kept together in the study documentation.

(c) Organization. Raw data should be maintained in an organized manner and, where appropriate, be recorded on forms designed specifically for the recording of a particular observation(s).

The initial recording of the observations is raw data. Where both animal patient records and case report forms are used, the case report form is the preferred choice for the initial recording of observations. When the first record of observation is on an animal patient record, that record is considered the raw data and should be handled accordingly. In such a case, the data transcribed from an animal patient record to the case report form, or a true copy of the animal patient record, may be submitted to CVM in support of an NADA *in lieu* of the animal patient record.

C. Reports

(1) Safety reports. The investigator should promptly report to the sponsor, and document for the study records, any adverse drug experience in a signed and dated statement.

(2) Final study report.

(a) Content. A final study report should be written when the collection of all raw data is complete (experimental phase completion date). A study is not considered complete until a final study report is signed by all authors (study completion date). The final study report should include sufficient detail to allow reconstruction or replication of the study and include, but not be limited to, the following:

(i) The name, physical location, and mailing address of each investigator.

(ii) The specific facilities where the study was performed.

(iii) The study and experimental phase initiation and completion dates.

(iv) The objective(s) of the study.

(v) The materials and methods used to conduct the study, including, but not limited to:

(*a*) A copy of the protocol and all protocol deviations.

(*b*) A complete description of the methods used.

(*c*) The number, species, breed or stock, sex, weight, age, and, when applicable, source of supply, physiological state (e.g., lactating, prepubertal), disease state, or other pertinent pathological findings of the animals used, identification procedures, and final disposition records for each animal.

(*d*) The investigational new animal drug identified by name, identity, strength, purity, composition, quantity, and batch or code mark (to the extent known by the investigator).

(*e*) A description of the dosing regimen, including dose, rate, route, and duration of the administration with the investigational new animal drug.

(*f*) A description of the transformations, calculations, or operations performed on the data, and any statistical methods employed to analyze the raw data.

(vi) The results of the study including, but not limited to:

(*a*) A summary and analysis of the data and a statement of the conclusions drawn from the analyses.

(*b*) A description of all adverse drug experiences observed during the study.

(*c*) A description of all circumstances that could have affected the quality or integrity of the data, specifying the time frame and the extent of their occurrence.

(*d*) The location of all study documentation.

(vii) The name of the monitor and the associates, colleagues, and subcontractors of the investigator involved, and the nature and extent of their participation in the study.

(viii) A statement attesting that the final study report is a complete and accurate representation of all study observations.

(b) Authorship. The preparation of this report can be accomplished as follows:

(i) The investigator may prepare a final study report independent of the sponsor; or

(ii) The sponsor and investigator may prepare a final study report through a collaborative effort. All individuals involved in the preparation of the final study report would be considered authors.

An investigator may relinquish authorship of the final study report where the investigator collects information on only a few animals. In such a case, the investigator should provide to the author(s):

(a) all necessary study documentation specific to the site at which the investigator conducted the study, and

(b) a signed and dated document, to be included in the final study report, which adequately describes the study documentation provided to the author(s) and attests to the accuracy and completeness of the documentation provided.

The authors of the final study report should sign and date the report and include in the report a brief statement describing their contributions to the report. Authors of the report should be aware that CVM views these signatures as an affirmation that all statements are accurate and complete representations of study activities and results and are fully supported by raw data.

(c) Amendments. Any addition, deletion, or correction to the final study report should be in the form of an amendment by the authors. The amendment should identify each part of the final study report that is being added, deleted, or corrected and the reason(s) for the addition, deletion, or correction, and should be signed and dated by the authors. Minor errors, e.g., typographical errors, noted after finalization of the final study report may be indicated directly on the final study report when accompanied by the signature or initials of the authors, the date of the change, and the reason for the change.

D. Standard Operating Procedures and Reference Materials

These include any site-specific standard operating procedures and reference materials used in the conduct of the study.

E. Specimens

These include any material derived from a clinical study for examination or analysis.

VI. DOCUMENTATION RETENTION

A. Documents to be Retained

All study documentation (except wet specimens of blood, urine, feces, and biological fluids and specimens of animal feed or water) generated as a result of the study should be retained.

B. Storage of Documents

(1) Conditions. The study documentation should be protected from deterioration, destruction, tampering, or vandalism in accordance with the nature of the records or specimens.

(2) Location. There should be a location for orderly storage and expedient retrieval of retained documents. The documents may be stored at the investigator's site, a designated third-party site, or the sponsor's site. If study documents are transferred from the investigator's site, a true copy of these documents should be maintained at the investigator's site along with documentation identifying the current storage site of the original documents. Upon request, the original documents should be promptly made available for an FDA inspection. If the study documentation is archived at the investigator's site and the investigator retires, relocates, terminates business activity, or for any other reason withdraws from the responsibility for maintaining documents for the period of time requested, custody of all documents should be transferred to the archives of the sponsor.

C. Length of Retention

All study documentation should be retained for a period of two years following the approval of an NADA or termination of the investigation. Specimens should be retained only as long as the quality of preparation affords evaluation, but no longer than the limit stated above.

VII. TEST FACILITY INSPECTION

FDA will not ordinarily accept a study as fulfilling a requirement for approval of an NADA if the investigator who conducted the study refuses to permit an inspection of the ongoing study, any study documentation, or facilities. The determination that a study will not be accepted in support of an NADA does not, however, relieve the sponsor of such a study of any responsibility under any applicable statute or regulation to submit the results of the study to FDA.