Guidance for Industry

Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials

This guidance supercedes the guidance of November 1994. (This document was revised to include the disclaimer in the paragraph below and to add the address to submit comments.)

Guidance #85 entitled "Good Clinical Practices" became final on May 15, 2001. Until the Center revises guidance #56, sponsors should follow the recommendations in guidance #85 when differences among the guidances occur. If you have any questions, please contact Herman Schoenemann (HFV120), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, (240) 276-8302, e-mail: **herman.schoenemann@fda.hhs.gov**.

The purpose of this document is to suggest a uniform system for writing study protocols and to provide a list of essential items that should be included in a study protocol. This guidance represents the agency's current thinking on the preferred system for writing study protocols. It does not 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 as long as it satisfies the requirements of applicable statutes and regulations.

Comments and suggestions regarding this document should be submitted to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulation.gov. For questions regarding this guidance document, contact the Office of New Animal Drug Evaluation, Center for Veterinary Medicine (HFV-100), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, (240) 276-8300.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
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The goals of the Protocol Development Guideline are:

1. To suggest a uniform system for writing study protocols.
2. To provide a reference of essential items that should be considered for inclusion in a study protocol.
3. To facilitate the development of complete study protocol(s) by the author(s).
4. To design more user friendly protocols for investigator(s).
5. To enable FDA reviewers to evaluate study protocols more quickly and convey their comments in terms more easily understood by the sponsor.
6. To reduce the number of essential revisions in study protocols.

On perusal of the contents of the "Protocol Development Guideline," it will become obvious that the contents are neither *all inclusive* nor will *all items listed be applicable* to all study protocols. It is the responsibility of the sponsor to ensure the essential components of a study are included in the study protocol(s). It is requested that effectiveness and target animal safety study protocols follow this suggested format.

In addition to facilitating the development of study protocols, the Center for Veterinary Medicine (CVM) suggests that this format be followed when submitting the final reports of the trials conducted for review by CVM. This format may also be used to prepare the final reports by clinical investigators, study monitors, and the sponsor. More uniform reports should facilitate a systematic, orderly review of the data. This will enhance the efficiency of each CVM reviewer resulting in quicker more complete review of the data.

Regulatory Background:

Guidelines state procedures or practices that may be useful to the persons to whom they are directed, but are not legal requirements. Guidelines represent the agency's position on a procedure or practice at the time of their issuance. A person may follow the guideline or may choose to follow alternative procedures. If a person chooses to use alternate procedures, that person may wish to discuss the matter further with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable to the U.S. Food and Drug Administration (FDA). The guideline does not bind the agency, and it does not create or confer any rights, privileges, immunities, or benefits for or on any person. Where the guideline states a requirement is imposed by statute or regulation, however, the requirement is law and its force and effect are not changed in any way by virtue of its inclusion in the guideline.

This guideline was written in response to a need perceived by the Center for Veterinary Medicine in its work with the animal health industry.

Protocol Format

1 TITLE:

2 PROTOCOL NUMBER:

2.1 Define the type of protocol (i.e. general or site specific)

3 SPONSOR:
- 3.1 Address
- 3.2 Telephone number

4 PROTOCOL OBJECTIVE(S):
- 4.1 Define objective of the protocol (e.g. dose determination, dose confirmation etc.)

5 STUDY OBJECTIVE(S):
- 5.1 Are the studies to be pivotal or non pivotal
- 5.2 Define the standards applied to the conduct of the studies (GLP, investigator, or other)

6 STUDY SCHEDULE:
- 6.1 Proposed date(s) of initiation
- 6.2 Schedule of events
- 6.3 Proposed date(s) of completion

7 STUDY DESIGN:
- 7.1 Treatment Groups
- 7.2 Experimental Design (i.e., cross-over, Latin Square, CRD, RCBD, Split-plots, etc.)
- 7.3 Blocking factor(s)
- 7.4 Randomization Procedures:
- 7.4.1 Allocation of animals to treatment groups
- 7.4.2 Allocation of treatment groups to experimental units

8 STUDY PROCEDURES:
- 8.1 Test Animal(s):
  - 8.1.1 Description:
    - 8.1.1.1 Age (parity if applicable)
    - 8.1.1.2 Sex
    - 8.1.1.3 Breed/Class
    - 8.1.1.4 Initial body weight
    - 8.1.1.5 Physiological State (e.g., Lactating, Pregnant, Estrus)
  - 8.1.2 Number of animals
  - 8.1.3 Source of animals
  - 8.1.4 Identification method (tattoo, neck band, wing band, brand, etc.), if not client-owned companion animals
- 8.2 Inclusion criteria
- 8.3 Exclusion criteria
- 8.4 Acclimation of Test Animals:
  - 8.4.1 Duration
  - 8.4.2 Medication and/or vaccination during acclimation period
  - 8.4.3 Baseline data collected prior to initiating study

8.5 Blinding of study:

- 8.5.1 Extent of blinding, e.g., monitor, investigator, etc.
- 8.5.2 Blinding method(s) and procedure(s)
- 8.5.3 List personnel with access to treatment codes and rationale

8.6 Analytical Methods:

- 8.6.1 Describe the analytical measurement(s) to be made and the relevance to the protocol objectives.
- 8.6.2 Specify the analytical plan to be used for the protocol measurement(s). This should include the following:
  - 8.6.2.1 An abstract of the method(s)
  - 8.6.2.2 Description of procedures for sample selection, preparation, and storage.
  - 8.6.2.3 Evidence of methods validation
  - 8.6.2.4 Description of validation plan when method is being developed for the study
  - 8.6.2.5 Quality control procedures for the method
  - 8.6.2.6 The criteria and procedures used to assess analytical results
- 8.6.3 Relevant scientific literature supporting the use of the analytical method for the intended measurements.
- 8.6.4 Certification that all needed validations will be done before the initiation of the study

8.7 Study Facilities:

- 8.7.1 Containment equipment (cages, pens, runs, stalls, etc.)
- 8.7.2 Lighting equipment (if controlled define photo period)
- 8.7.3 Heating equipment
- 8.7.4 Cooling equipment
- 8.7.5 Feeding equipment
- 8.7.6 Watering equipment
- 8.7.7 Ventilation equipment
- 8.7.8 Space allocation per animal (compare to normal management practices)
- 8.7.9 Pasture description (area, forage, rotation, etc.)
- 8.7.10 Facility diagram:
  - 8.7.10.1 Location of feeding and watering equipment
  - 8.7.10.2 Orientation of building
  - 8.7.10.3 Ventilation
  - 8.7.10.4 Location of lighting
  - 8.7.10.5 Pen/cage dimensions
  - 8.7.10.6 Orientation of blocks
  - 8.7.10.7 Treatment code
  - 8.7.10.8 Environmental/weather recording devices

8.8 Experimental Diet(s) (if applicable):

- 8.8.1 Diet formulation(s):

8.8.1.1 Ingredient list:
8.8.1.1.1 Feedstuffs
8.8.1.1.2 Vitamin premixes
8.8.1.1.3 Mineral premixes
8.8.1.1.4 Feed additives (drugs, antioxidants, pellet binders, copper sulfate, etc.)
8.8.2 Nutrient and drug concentration of experimental diet(s): (Define feed sampling procedure)
8.8.2.1 Calculated nutrient concentration
8.8.2.2 Assayed nutrient concentration
8.8.2.2.1 Assay procedure
8.8.2.2.2 Analytical laboratory:
8.8.2.2.2.1 Address
8.8.2.2.2.2 Telephone number
8.8.2.3 Assayed drug concentration:
8.8.2.3.1 Specify drug(s) that will be assayed in each treatment group for each type of diet
8.8.2.3.2 Anticipated analytical variation and assay limits
8.8.2.3.3 Analytical method
8.8.2.3.4 Analytical laboratory:
8.8.2.3.4.1 Address
8.8.2.3.4.2 Telephone number
8.8.2.3.5 Number of assay replicates
8.8.3 Feed form, (i.e. mash, crumbled, pellets)
8.8.4 Manufacture of experimental diet(s):
8.8.4.1 Procedures
8.8.4.2 Facilities and equipment
8.8.5 Feeding program, (i.e. schedule for feeding experimental diets)
8.8.6 Watering program

8.9 Drug Administration:
8.9.1 Dosing regime (dose(s), frequency, and duration)
8.9.2 Route of administration
8.9.3 Investigational withdrawal period (reference the appropriate CVM authorization letter)
8.9.4 Proposed withdrawal period (anticipated labeled withdrawal period)

8.10 Removal of Subject(s) from the study:
8.10.1 Criteria for removal of subjects from the study
8.10.2 Procedures for removal of subjects from the study
8.10.3 Fate of removed study animals

8.11 Concurrent/Concomitant Medications/Therapies

8.12 General management practices, e.g. frequency of visits to facility site, frequency of checking feeders and waterers, frequency of adding feed to feeders,

frequency of checking for temperature and humidity, distribution of used litter across treatment groups, used or new litter, etc.

8.13 Provisions for necropsy and disposal of expired test subjects

8.14 Owner Consent (if applicable)

9 SPECIFICATION OF VARIABLES:

9.1 Variable(s) to be measured for evaluating labeled claim:
- 9.1.1 When variable(s) will be assessed
- 9.1.2 Procedures for assessing variable
- 9.1.3 Equipment used to assess variable
- 9.1.4 Calculation of derived data
- 9.1.5 Forms for retention of source data
- 9.1.6 Name(s) and address(es) of outside labs used for analysis

9.2 Other variables to be recorded during the study:
- 9.2.1 When variable(s) will be assessed
- 9.2.2 Procedures for assessing variable
- 9.2.3 Equipment used to assess variable
- 9.2.4 Calculation of derived data

10 DATA ANALYSIS (Depends upon protocol design chosen and the variables measured. Details of the analysis procedure should be provided)

10.1 Define the experimental unit

10.2 Define the number of replicates per treatment

10.3 Define statistical methodology, including hypothesis to be tested or parameters to be estimated, assumptions that are being made, and model specification if a model is to be used.

10.4 Define how the statistical results will be used to draw conclusions about the study's objectives

11 STUDY LOCATION(S):

12 PERSONNEL: (Provide debarment statements)

12.1 Investigator(s):
- 12.1.1 Address
- 12.1.2 Telephone number
- 12.1.3 Training and experience of investigator (prefer CVs)

12.2. Study Monitor:
- 12.2.1 Address
- 12.2.2 Telephone number
- 12.2.3 Training and experience of monitor (prefer CVs)

12.3 Consultants (pathologist, statistician, etc.):
- 12.3.1 Address
- 12.3.2 Telephone number

12.3.3 Training and experience of each consultant (prefer CVs)

12.4 Quality Assurance Unit:

12.4.1 Address

12.4.2 Telephone number

12.5 Other personnel involved in study:

12.5.1 Address

12.5.2 Telephone number

12.5.3 Involvement in study

12.5.4 Training and experience of other personnel (prefer CVs)

13 COLLECTION AND RETENTION OF SOURCE DATA:

14 ADDENDUM/DEVIATIONS TO THE PROTOCOL:

15 INVESTIGATIONAL DRUG AND CONTROL:

15.1 Test Substance(s):

15.1.1 Chemical name

15.1.2 Trade name

15.1.3 Active/inactive ingredients (is this the final formula?)

15.1.4 Dosage form (solution, powder, granules, etc.)

15.1.5 Dose(s) to be tested (mg/gram, mg/mL, etc.)

15.1.6 Manufacturing site (name and address)

15.1.7 Lot No.

15.1.8 Packaging

15.1.9 Drug storage during study (define storage environment and drug's stability characteristics in the proposed storage environment)

15.1.10 Material Safety Data Sheet (MSDS)

15.2 Control (placebo, vehicle, positive control, etc.) Identification of applicable items from 11.1

16 DRUG DISPOSITION/ANIMAL ACCOUNTABILITY/FEED DISPOSITION/FEED ACCOUNTABILITY: The accountability and disposition of all unused drug supplies, unused feed, and animals should be documented.

17 PROTOCOL APPROVAL SIGNATURES: Include the appropriate individuals.

17.1 Sponsor Monitor

17.2 Investigator

17.3 Study Monitor

17.4 Quality Assurance

17.5 Consultant

17.6 Others

18 APPENDICES: (such as:)

18.1 Owner Consent Form (if applicable):

18.2 Unexpected or Adverse Reaction Form:

18.3 Description of treatment site preparation:

18.4 Description of sample collections:
18.5 Description of sample preparation for evaluation:
18.6 Description of special equipment: (Validation techniques employed)
18.7 Test organism(s)/include reference strains:
18.8 Assay medium and its preparation:
18.9 Preparation of cultural plates:
18.10 Adjustment of zones of inhibition
18.11 Preparation of standard curve and samples:
18.12 Plating of standards and samples:
18.13 Construction of standard curve:
18.14 Investigator obligations:
18.15 SOPs
18.16 Other: