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Guidance for Industry

Target Animal Safety and Effectiveness Protocol Development and Submission

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments on the guidance at http://www.regulations.gov. All written comments should be identified with the Docket No. FDA-2011-D-0023.

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Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
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Contains Nonbinding Recommendations

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

To facilitate the drug development process, the Center for Veterinary Medicine (CVM) recommends that sponsors submit protocols to CVM's Office of New Animal Drug Evaluation's (ONADE) Division of Therapeutic Drugs for Non-Food Animals, Division of Production Drugs, or Division of Therapeutic Drugs for Food Animals to review study designs before initiating a study to support substantial evidence of effectiveness or target animal safety. This guidance makes recommendations to aid in the preparation of protocols used to generate data to support new animal drug applications, specifically target animal safety and substantial evidence of effectiveness. The recommendations are intended to reduce the time to protocol concurrence by:

- Recommending a path to protocol concurrence,
- Enhancing quality of protocol submissions by focusing on agreements on study design and statistical analysis, and
- Making use of opportunities to meet with CVM before and during protocol development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Protocol Development and Review Process

Protocol submission and CVM concurrence are not required before conducting studies intended to support substantial evidence of effectiveness or target animal safety.[1] However, if a sponsor conducts a study using a protocol that did not receive CVM concurrence, the study design may not be adequate to collect appropriate data to support substantial evidence of effectiveness or target animal safety. FDA recommends that sponsors meet with the appropriate ONADE division (i.e., Division of Therapeutic Drugs for Non-Food Animals, Division of Production Drugs, or Division of Therapeutic Drugs for Food Animals) to discuss their study designs before initiating a study to support substantial evidence of effectiveness or target animal safety.

A. Meetings Surrounding Protocol Development

CVM encourages sponsors to have frequent and early contact with CVM, through both formal meetings and informal communication, as they are developing their study protocols. When requesting a formal meeting with an ONADE division, the sponsor should articulate the intended purpose and expected outcome of the meeting. CVM recommends that a sponsor schedule a presubmission conference to discuss the development plan for the drug product. A protocol development meeting may be scheduled to discuss the protocol design in greater detail.

1. Presubmission Conference(s)

After the investigational new animal drug (INAD) file is established, the sponsor should request a presubmission conference with the appropriate ONADE division to discuss the general development plan, intended indication(s), and proposed studies to support approval of the new animal drug. A presubmission conference enables two-way communication between the sponsor and CVM regarding the development of the product. The purpose of this conference is for the sponsor and CVM to come to agreement on the number, types, and general design of studies that are necessary to demonstrate the safety and effectiveness of a new animal drug (21 CFR 514.5(e)).

To facilitate the discussion, the sponsor should provide background information specific to the product to allow CVM to obtain knowledge about the product and to understand the concepts proposed for product development. Sufficient time should be allotted between the submission of background material and the meeting to enable complete review of the material by CVM. CVM must receive the meeting request with the following items at least 30 days in advance of the conference date (21 CFR 514.5):

- A detailed agenda that clearly outlines the scope, purpose, and objectives of the meeting,
- A copy of any materials to be presented at the meeting,
- A list of proposed indications,
- A copy of the proposed labeling (if available) for the product under consideration,

[1] See Animal Drug User Fee Act (ADUFA) Reauthorization Performance Goals and Procedures, (http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm044941.htm).

- Copies of materials evaluated or referenced relative to issues listed in the agenda, and
- A list of names and positions of the representatives who are expected to attend.

Outcomes of this conference will be documented in a memorandum of conference (MOC) as specified in 21 CFR 514.5.

2. Protocol Development Meetings

Sponsors can request the scheduling of a protocol development meeting to discuss the specific details of a protocol. CVM strongly encourages a protocol development meeting for novel indication(s), novel products, and complex study designs. When requesting a protocol development meeting, sponsors should consider the timing of the meeting in relation to the submission of the protocol and any additional supportive information that may be needed (H submission[2]).

The sponsor's request for a formal protocol development meeting should provide a detailed agenda, objectives, and a list of participants, including their expertise. CVM will not review or provide concurrence on a protocol during the meeting. However, CVM will provide feedback on the proposed study design.

The purpose of this meeting is to discuss specific details of the proposed study design including, but not limited to, the following:

- The proposed indication,
- Issues that are unique to the study design,
- The impact of initial supportive data or literature on the study design, and
- Previously identified areas of concern with related protocols.

B. Protocol Development and Submission

The following guidances should be used for general protocol development and design, as applicable, for the specific study:

- CVM Guidance for Industry 56: Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials
- CVM Guidance for Industry 85: Good Clinical Practices: (VICH GL9)
- CVM Guidance for Industry 185: Target Animal Safety for Veterinary Pharmaceutical Products (VICH GL43).

[2] CVM will code the submission of data that support a protocol as an H submission. The H submission has a 100-day review time and should be submitted before the protocol to allow sufficient time for review of the supporting data.

Additionally, the following should be considered when developing a protocol.

Issues pertinent to study design, as stated in the presubmission conference MOC, should be incorporated into the protocol. Protocol non-concurrence may occur if issues that were discussed in previous meeting(s) are not addressed in the protocol.

Protocols should be well-written, clear, concise, and consistent across all sections so the investigator has a document outlining the study methodology and procedures. Data collection forms (e.g., case report forms, owner consent forms) should be included with the protocol and referenced in the section of the protocol where they are discussed. Relevant standard operating procedures (SOPs) for laboratory studies related to the collection of data should be appended to the protocol or an adequate description of the procedure should be incorporated into the protocol (for example, SOPs for describing parasite collection for anthelmintic studies or SOPs for culture and sensitivity microbiological procedures). If unsure, the sponsor should contact CVM to discuss which, if any, SOPs should be included with the protocol. Lack of detail in a study protocol may result in a refusal to review by CVM.

If data or other supportive information are used to justify study methodology and procedures, the data should be submitted before the protocol and identified as "data to support a protocol" to allow sufficient time for review of the supporting data. If a sponsor does not allow sufficient time for CVM to review this H submission before receiving a protocol, CVM may issue a protocol non-concurrence letter. Previous agreements from presubmission conferences should also be summarized and referenced by submission code. Any deviations from previous discussions regarding study design should be explained.

The submission should be addressed to the appropriate division director and state the INAD number, the drug name, the type of protocol, and the purpose of the submission.

C. Protocol Review and Amendments to the Protocol Submission

The sponsor should resolve any major study design issues raised during discussions with CVM before submitting the protocol to CVM for review. While the protocol is under review, CVM will address minor issues or request any needed clarification by telephone or e-mail with the sponsor. CVM may request minor amendments to facilitate review. By day 50 of the protocol review time, CVM will send the sponsor an email notifying them of concurrence or non-concurrence with the protocol, or the need for an End-Review Amendment (ERA) to complete the review of the protocol[3].

- Minor Amendments to the Protocol Submission

A minor amendment is an amendment requested by CVM within the 50-day review cycle that provides a relatively modest amount of specific information that corrects one or more deficiencies in the parent submission. The sponsor should submit the minor amendment in the

[3] See Animal Drug User Fee Act (ADUFA) Reauthorization Performance Goals and Procedures, (http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm044941.htm).

form of the full revised protocol by the Amendment Receipt Date (ARD), which is established by CVM and transmitted to the sponsor. Failure to submit the amendment by the ARD may result in a non-concurrence letter for the protocol. The sponsor should only change the requested items and corresponding sections affected by the requested items and highlight those items in the amended protocol. Additional changes to the amended protocol that were not discussed with CVM may result in protocol non-concurrence.

- End-Review Amendment (ERA) to the Protocol Submission

An ERA is an amendment to the protocol that is requested by CVM ***after*** it has completed its review of the submitted information and determined that the submission of additional non-substantial data or information would likely complete the submission and permit a concurrence/non-concurrence decision to be made[4].

The sponsor should submit a completed, revised protocol with all changes highlighted within the text of the protocol, including minor modifications necessary during the incorporation of the requested changes. The sponsor should certify that no other text changes beyond those highlighted have been made. Additional changes in the amended protocol that were not discussed with CVM may result in protocol non-concurrence.

If CVM receives the ERA within 10 days of the ERA email request date, CVM will issue a protocol concurrence or non-concurrence letter. Failure to submit the ERA within 10 days will result in protocol non-concurrence of the original protocol, and CVM will refuse to review the ERA. If the ERA protocol does not adequately address the ERA request, CVM will issue a protocol non-concurrence letter. If the ERA protocol is unacceptable for review, CVM will issue a non-concurrence letter for the original protocol and will issue a refuse to review letter for the ERA.

D. Protocol Concurrence or Non-concurrence

CVM concurrence means that CVM fundamentally agrees with the design, execution, and analyses proposed in the protocol and is a commitment that CVM will not later alter the perspectives on these issues unless public or animal health concerns appear that were not recognized at the time of the protocol assessment. However, concurrence with the protocol does not guarantee that the data obtained from a study that implements the protocol will support an approval. Because concurrence does not extend to any subsequent changes a sponsor makes to this protocol, a sponsor may want to seek CVM concurrence on the revised protocol if changes were made. When a sponsor submits a final study report, they should include a copy of the protocol under which the study was actually conducted and include any protocol deviations, amendments, and explanations. A sponsor may request a meeting or teleconference to discuss non-concurrence issues with CVM.

[4] See Animal Drug User Fee Act (ADUFA) Reauthorization Performance Goals and Procedures, (http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm044941.htm).