#265

Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs

Guidance for Industry

Draft Guidance

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For further information regarding this document, contact Susan Storey, Center for Veterinary Medicine (HFV-131), Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, 240-402-0578, email: susan.storey@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at either https://www.fda.gov/animal-veterinary or https://www.regulations.gov.

U.S. Department of Health and Human Services
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Center for Veterinary Medicine (CVM)
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

FDA is issuing this draft Guidance for Industry (GFI), as required under section 305 of the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (Pub. L. 115-234), to assist sponsors in incorporating data from foreign countries into proposed clinical investigation protocols and applications for new animal drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Section 305 of Pub. L. 115-234, among other things, directed FDA to hold a public meeting for interested parties to discuss innovative animal drug investigation designs and to issue guidance addressing the incorporation of the use of such elements of investigations as complex adaptive and other novel investigation designs, data from foreign countries, real-world evidence (including ongoing surveillance activities, observational studies, and registry data), biomarkers, and surrogate endpoints into clinical investigation protocols and applications to support the effectiveness of new animal drugs.

In general, FDA's guidance documents 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. Background

In the *Federal Register* of July 9, 2019 (84 FR 32749), FDA's Center for Veterinary Medicine published a notice of a public meeting entitled "Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs" giving interested persons until August 17, 2019, to comment on the topics discussed at the public meeting and the questions published in the meeting notice (84 FR at 32750-32751).[1] On August 13, 2019, we published a notice announcing the extension of the comment period to September 16, 2019 (84 FR 40071). CVM received numerous comments on the topics discussed at the public meeting and the questions

[1] https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/public-meeting-incorporating-alternative-approaches-clinical-investigations-new-animal-drugs

published in the meeting notice and those comments were considered as the draft guidances were developed.

This document describes principles for designing, conducting, and reporting the results for investigations or studies including data from foreign countries to demonstrate substantial evidence of effectiveness or a reasonable expectation of effectiveness of drugs intended for use in animals and to support the approval of a new animal drug application (NADA) or an application for conditional approval of a new animal drug (CNADA). This guidance also provides information about obtaining feedback from FDA with respect to incorporating data from foreign countries in investigations and study protocols for new animal drugs. Other centers within FDA, including the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), have released draft and final guidance documents on the topic of data from foreign countries.

CVM will consider all foreign data in submissions to investigational new animal drug (INAD) files, NADAs, and CNADAs to demonstrate substantial evidence of effectiveness or a reasonable expectation of effectiveness. This guidance document provides CVM's recommendations specific to investigations for animal drugs.

Some concepts and language in the recommendations for animal drugs are intended to be similar to or the same as those in other guidance documents issued by FDA on the same or similar topics. Because these recommendations are specific to investigations for animal drugs, they have been tailored to the unique aspects of and considerations for animal drug development.

III. Scope

The purpose of this guidance is to provide guidance to animal drug sponsors on specific areas of the approval process where the use of data from foreign investigational studies may be considered acceptable to support the effectiveness requirement of a new animal drug application. In this context, a new animal drug application may be an NADA or an CNADA.[2] In addition, this guidance describes how sponsors may obtain feedback from CVM on the use of data from foreign investigational studies before the submission of an application.

The use of data from foreign investigational studies intended to support effectiveness of the drug may be acceptable to support NADAs submitted to CVM if certain conditions are met. This guidance outlines what CVM would expect to see in the documentation provided in support of any application that uses foreign investigational studies to demonstrate effectiveness. This guidance does not address the use of data from foreign investigational studies to support technical sections other than Effectiveness or Reasonable Expectation of Effectiveness. For the purpose of this guidance, CVM considers foreign data to be data generated outside of the United States both by entities based within or outside of the United States.

[2] See CVM Draft GFI #261, "Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs," dated September 2019. When final, this guidance will represent FDA's current thinking on this topic.

FDA is committed to supporting data that may be recognized globally in order to enhance animal drug development, facilitate the use of foreign data and minimize the need to conduct duplicative studies. The Food and Drug Administration Safety and Innovation Act (FDASIA) reaffirms FDA's longstanding practice of accepting data from foreign investigational studies provided that the data are adequate under applicable standards to support approval (see section 1123 Optimizing Global Clinical Trials).[3]

FDA also supports international harmonization activities that help leverage work and expertise from other expert authorities. Pathways exist for international collaboration on the use of data from foreign investigational studies to support regulatory decisions. For example, Health Canada's Veterinary Drugs Directorate (VDD) and CVM coordinate their respective submission and review processes to enable simultaneous reviews of veterinary drug applications though the US-Canada Regulatory Cooperation Council (RCC). The International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medical Products (VICH) is a joint effort between the U.S., the European Union, and Japan whose aim is harmonizing technical requirements for veterinary product registration.

IV. Acceptance of Foreign Investigational Studies

A. Substantial Evidence of Effectiveness

To establish substantial evidence of effectiveness, one or more adequate and well-controlled studies must be conducted in accordance with an appropriate standard of conduct (21 CFR 514.117) and include all the information required by 21 CFR 514.1(b)(8). The standard of conduct generally used for effectiveness field studies is Good Clinical Practice (GCP),[4] although some laboratory effectiveness studies are conducted according to Good Laboratory Practice (GLP, 21 CFR part 58). GCP is intended to be an international scientific quality standard for designing, conducting, monitoring, recording, auditing, analyzing, and reporting effectiveness studies evaluating veterinary products. GCP provides public assurance about the integrity of the study data, and that due regard has been given to animal welfare and protection of the personnel involved in the study, the environment, and the human and animal food chains. Although GCP is a guidance rather than a regulation, studies conducted to this standard are more likely to meet the requirements for substantial evidence of effectiveness; therefore, CVM recommends that sponsors adhere to GCP.

B. Adequacy of Foreign Data for Regulatory Use

To demonstrate that a study supporting an effectiveness claim is adequate and well-controlled, sponsors typically submit extensive documentation of study planning, protocol, conduct, and data handling to FDA, and study documentation is made available at the study sites. CVM's ability to review the copies of raw data for information critical to a study, whether submitted to CVM or at the study site, has proven to be important in regulatory decisions; however, FDA recognizes that the extent of documentation

[3] https://www.govinfo.gov/content/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf

[4] See CVM GFI #85 (VICH GL9), "Good Clinical Practice," (May 2001)

necessary depends on the specific study, the types of data involved, and the other evidence available to support the claim. Therefore, CVM may accept different levels of documentation to support data quality and integrity, as long as the adequacy of the scientific evidence can be assured.[5] Sponsors are encouraged to consult with CVM prior to submitting the specific study.

C. Field Effectiveness Studies

The field effectiveness study should use a design that permits a valid comparison with a control to provide an appropriate evaluation of the drug's effect. Within the broad range of studies conducted to support a determination of the effectiveness of a new animal drug, certain controls would be appropriate depending on the study conducted (e.g., placebo concurrent control, untreated concurrent control, active treatment concurrent control, or historical control). The choice of an active treatment concurrent control may have implications on the interpretability of the results.

1. Use of an active control

An "active treatment concurrent control" (active control) is defined as a known effective therapy (see 21 CFR 514.117(b)(4)(iii)). Typically, effectiveness of the investigational new animal drug may be demonstrated through non-inferiority to an active control if the active control is a U.S. approved new animal drug in the target species for the same indication as the investigational new animal drug.[6] Under certain conditions (see next section), a non-inferiority study using an active control that is not approved in the U.S. may be used to support substantial evidence of effectiveness. The sponsor should contact CVM to discuss specific details regarding the design of a study that uses an active control.

2. Use of an active control not approved in the United States

For CVM to accept the use of a non-inferiority study utilizing an active control that is not approved for use in the U.S. (unapproved active control), the sponsor should provide sufficient data or information commensurate with substantial evidence of effectiveness. Specifically, the information should support a clinically relevant effect size to allow the determination of an acceptable noninferiority margin. Additionally, the information provided for effectiveness should be inferred to the intended target animal population in the U.S.

If the unapproved active control drug is approved outside of the U.S., then ideally the unapproved active control drug indication(s) should be the same as the indication(s) proposed for the investigational new animal drug. If the proposed investigational new animal drug indication(s) deviate from the indication(s) for the unapproved active control drug, then more robust information may be needed to support the use of

[5] See CVM GFI #106, "The Use of Published Literature in Support of New Animal Drug Approval," (August 2000)

[6] See CVM GFI #204, "Active Controls in Studies to Demonstrate Effectiveness of a New Animal Drug for Use in Companion Animals," (December 2015)

the unapproved drug as an active control to demonstrate substantial evidence of effectiveness (NADA). If the unapproved active control is recognized as standard of care, the use should be similar to the proposed indication for the investigational new animal drug.

The information the investigational drug sponsor submits to support the effectiveness of the unapproved active control that is contained within their INAD or NADA belongs to the sponsor of the investigational drug[7] and is considered proprietary information. For example, all information related to the unapproved active control would be submitted to the INAD file including Notice of Claimed Investigational Exemptions (NCIEs) and Investigational Food Use Authorizations.

D. Laboratory Effectiveness Studies

Many laboratory dose confirmation effectiveness studies are conducted in other countries to support approval of various investigational new animal drugs, such as anthelmintics. Data generated from studies that comply with the existing VICH anthelmintic GFIs are acceptable for submission to CVM. Generally, the principles of GCP should be followed. The standard used to conduct the study (e.g., Organisation for Economic Co-operation and Development [OECD], GLP or GCP) should be stated in the Final Study Report (FSR).[8] Any departures from these standards should be documented and the impact on the study conduct and results should be discussed in the FSR.

E. Foreign Data Applicable to the U.S. Population

Because of differences in animal breeds, nutrition, husbandry practices, and disease, sponsors of foreign studies should show that the study conditions are representative of the U.S. For CVM to accept data from a study conducted outside of the U.S., the sponsor should include a justification for using the foreign sites and discuss similarities and differences in the following areas between the U.S. and the country where the study was conducted:

- Conditions of use of the investigational drug product;
- The standard of practice of veterinary medicine with respect to any differences that may impact the study;
- Management and husbandry practices;
- Species, breeds, or classes used in the study;
- Bacterial strains, including target pathogen virulence, and target pathogen susceptibility to the investigational antimicrobial;

[7] See 21 CFR 514.11 and 514.12 for the general proposition that information contained in INADs/NADAs is confidential. 21 CFR 514.1(a) states, "Any reference to information furnished by a person other than the applicant may not be considered unless its use is authorized in a written statement signed by the person who submitted it."

[8] http://www.oecd.org/

- Parasitic strains, including source, age, and susceptibility (if applicable); and
- Any other practices or conditions (if applicable) that could impact the study conduct or results.

If there are differences, the sponsor should document them and state the impact of those differences on the study conduct or on an animal's response to the drug. For anthelmintics, see CVM GFI #90 (VICH GL7), "Effectiveness of Anthelmintics: General Recommendations" (October 2001).[9]

Management, husbandry, and other practices, as well as bacterial pathogen virulence and sensitivity, may be similar across the U.S., Canada, and Mexico. Therefore, the information needed to accept use of data from Canada and Mexico may be minimal. FDA encourages sponsors to talk with us early in development when these issues can be discussed.

F. Foreign BioResearch Monitoring (BIMO)

FDA may conduct inspections of clinical investigations in support of a U.S. drug approval. For more information on the compliance program, refer to Compliance Program Guidance Manual (CPGM) 7348.811, Chapter 48-Bioresearch Monitoring Clinical Investigators and Sponsor-Investigators (December 2008).[10]

V. The Use of Data to Support Effectiveness of New Animal Drugs

For CVM to consider the use of foreign investigational studies to support the effectiveness of a new animal drug, the studies should have the same data qualities and study integrity standards as expected from domestic studies. As with any study submitted to FDA, data is generally assessed by evaluating several factors including, but not limited to, those outlined below:

- Adherence to applicable FDA regulations;
- Adherence to protocols, standard operating procedures, and previous agreements with CVM;
- Maintenance of data and study integrity; and
- Construct of the FSR and access to the copies of raw data for information critical to a study.

VI. International Cooperation

A. Parallel Scientific Advice

Parallel Scientific Advice (PSA) is an opportunity to receive feedback on a set of questions from CVM and the European Medicines Agency (EMA) in parallel. To

[9] https://www.fda.gov/media/70349/download

[10] https://www.fda.gov/media/75927/download

participate, a PSA request should be simultaneously submitted to CVM and EMA with a set of scientific and regulatory questions. A request could also include a protocol with specific questions, but PSA is not intended for granting protocol concurrence. After CVM receives the request, CVM and EMA will meet to discuss the questions and the respective responses with the goal of harmonizing responses where possible. The sponsor would then receive separate responses from CVM and EMA.

CVM recommends using PSA at the point when a sponsor would be seeking a presubmission conference with CVM. Before making a Parallel Scientific Advice request to CVM, the sponsor should contact CVM and EMA so that each Agency can prepare for receipt of the request.

B. Simultaneous Review with Health Canada's Veterinary Drug Directorate (VDD)

CVM and Health Canada's VDD simultaneously review new animal drug applications on a case-by-case basis though the US-Canada RCC. If a sponsor is interested in including a new animal drug in simultaneous review, they should contact both CVM and VDD. If both Agencies agree that the project is acceptable for simultaneous review, they will send the sponsor a letter requesting a commitment to provide both agencies with identical submissions simultaneously and authorization to discuss the full content of the submissions between Agencies. CVM and VDD reviewers will meet to discuss the submissions under review and both Agencies will be invited to participate in meetings with the sponsor. Simultaneous review does not guarantee the same conclusions from both Agencies, as CVM and VDD have different regulations and requirements. A benefit of simultaneous review is that the process can lead to simultaneous approval of the animal drug product in two countries.

VII. Special Considerations

A. Translations

Requirements for Data, Reports, and Published Literature – As required by 21 CFR 514.1(a), "if any part of the application is in a foreign language, an accurate and complete English translation of each part that is not in English shall be appended[.]" 21 CFR 514.1(a) also requires the sponsor to submit translations of literature printed in a foreign language in addition to copies of the original publication.

- For data, study reports, and published literature that are in a foreign language, a certified translation is not required. The sponsor should verify the information and that it is accurately translated into English. By signing the eSubmitter Administrative Cover Form, the sponsor is attesting to that accuracy.[11]

[11] See CVM Program Policy and Procedures (P&P) Manual 1243.2180 Certifications for New Animal Drug Submissions and Applications (July 2019)

- For paper submissions, the sponsor attests that the translations are accurate using FORM FDA 356v.[12] In accordance with the reauthorization of the Animal Drug User Fee Act (ADUFA), effective October 1, 2018, all applications and submissions should be submitted electronically using the eSubmitter tool.[13] Therefore, paper submissions are not typically accepted by CVM; however, there are rare exceptions to this requirement, and these should be discussed with CVM prior to submission.

B. Units of Measurements

- All units of measurements should be consistent with the Imperial system of measurement (e.g., inches, pounds, and ounces/gallon), with the International System of units (SI Units) or acceptable SI derivatives (e.g., centimeters, kilograms, and milligrams per milliliter), or a combination of both as appropriate (e.g., milligrams per pound.).

- Raw data should be submitted as recorded (e.g., in kilograms, grams, pounds, etc.); however, all data for a specific variable should be converted to the same unit of measure for evaluation and documentation in the FSR.

- Unit conversion details should be provided in the FSR.

C. Regulatory Requirements

Sponsors should be aware that the requirements for the conduct of studies may differ between regulatory authorities. CVM will evaluate submitted information and determine whether the information is sufficient to satisfy the regulatory requirements for the approval of a new animal drug. CVM recommends that sponsors consider potential differences to FDA regulatory requirements prior to completing FSRs containing data from foreign investigational studies and discuss the impact of those differences with CVM prior to the submission.

CVM recognizes that foreign privacy laws may pose challenges in the submission of data to CVM; therefore, we recommend sponsors consult with experts of their locality to determine how to navigate their local laws while still meeting the requirements for approval of new animal drugs in the U.S.

VIII. Obtaining CVM Feedback on Use of Data from Foreign Investigational Studies

There are various approaches that sponsors may take to open a discussion with CVM on the use of data from foreign investigational studies as part of their development program to demonstrate effectiveness or a reasonable expectation of effectiveness. The sponsor's decision regarding which approach to select may be affected by where the project is in the development process.

[12] See additional information regarding the FDA eSubmitter tool at https://www.fda.gov/industry/fda-esubmitter.

[13] See section 301 of the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (Pub. L. No. 113-14)

Communication about data from foreign investigational studies may occur at any point in the development process.

The Office of New Animal Drug Evaluation (ONADE) project managers (PMs) serve as a central point of contact for drug sponsors and can provide information about the new animal drug review process and ONADE's regulatory procedures. If you have questions about the approval process and do not have an ONADE PM assigned to your company, you can contact the PMs through the CVM mailbox AskCVM@fda.hhs.gov.

A. When to submit information regarding the use of data from foreign investigational studies

There are a variety of points in the development process and a variety of submission types that can be used to obtain feedback. CVM encourages sponsors interested in using data from foreign investigational studies as part of their development program for a new animal drug to inform CVM as early in the product development process as possible.

Sponsors planning to incorporate data from foreign investigational studies to demonstrate effectiveness or reasonable expectation of effectiveness are encouraged to inform CVM of their intent either as part of their initial request to open a General Correspondence (GC) file or an INAD file (A-0000), or as part of their initial presubmission conference with CVM to discuss the drug product development plan (Z-submission product development meeting). If one or more studies incorporating data from foreign investigational studies is already complete, sponsors should provide CVM with a summary of the design and conduct of the study during the drug product development meeting or contact their assigned PM for assistance in determining the most appropriate method for obtaining feedback from CVM.

B. How to submit information regarding the use of data from foreign investigational studies

There are several ways that sponsors may submit detailed information about plans for incorporating data from foreign investigational studies as part of their development program to demonstrate effectiveness or reasonable expectation of effectiveness. The regulatory pathway selected (CNADA versus NADA), the stage of development, the information available, and the feedback being sought from CVM, among other factors, may influence the submission type selected.

Sponsors may submit information to support the use of data from foreign investigational studies to a GC file prior to opening an INAD file; as part of their initial request to open an INAD file; as part of a meeting request for a presubmission conference (Z-submission)[14] to discuss the Effectiveness technical section requirements; or as part of an

[14] See CVM P&P Manual 1243.2200 Submission and Review of Early Information (EI) Prior to Presubmission Conferences and Protocol Review (June 2020) and CVM P&P Manual 1243.3050 Determining Technical Section Requirements for New Animal Drug Product Approval (May 2019)

information submission (H-submission) or meeting request (Z-submission) to discuss study protocol design.

The submission of a study protocol utilizing data from foreign investigational studies should only be considered after the proposed study design has been discussed with CVM. Obtaining CVM input regarding study design will make reaching protocol concurrence more efficient. Sponsors considering incorporating data from foreign investigational studies into future studies to demonstrate effectiveness or reasonable expectation of effectiveness should, prior to conducting a study, submit a study protocol for review (E-submission).

Sponsors may also open a Veterinary Master File (VMF) to hold detailed information regarding a specific study design if the information will be used in the development of multiple applications.[15] The VMF is confidential and is typically used when a holder wishes the material in the VMF to remain proprietary, although the material may be referenced by multiple third-party products or files (INAD, NADA, or CNADA). Alternatively, if multiple sponsors are cooperating on product development, sponsors may establish a Public Master File (PMF) to allow all cooperators to reference the information. As suggested by the name, the information in a PMF is publicly available.

Regardless of how information is submitted to CVM, sponsors should submit an organized and focused information package. This will allow CVM the best opportunity to provide appropriate recommendations in response. Although full information may not be available in the early stages of the development program, the amount of information provided and the level of detail of the information provided should be commensurate with the submission type. The information should address some or all of the following elements, as appropriate for the submission type:

1. Indicate how the study will fit within the overall development plan for the investigational new animal drug (i.e., support substantial evidence of effectiveness, reasonable expectation of effectiveness or dosage characterization, or some other aspect of the effectiveness evaluation);

2. Indicate the regulatory standard to be followed;

3. Indicate how the data are applicable to the U.S. target animal population, U.S. veterinary medical practice, and U.S. production/husbandry practice;

4. Information regarding the use of an active control that is not approved in the U.S.; and

5. Information regarding differences in study conduct as discussed in section IV. Acceptance of Foreign Investigational Studies.

[15] See CVM P&P Manual 1243.2400 Veterinary Master Files with Manufacturing Information (August 2019)

IX. Glossary

The following definitions are supplied to provide the reader with an understanding of the specific terms used in this guidance as applicable to new animal drugs. These definitions should not be construed to be new interpretations or clarification of the use of similar words or phrases in the FD&C Act, related code or regulation, other Federal, State, or local laws, or other guidance documents.

Active Control: The new animal drug is compared with known effective therapy. The use of this control is appropriate when the use of a placebo control or of an untreated concurrent control would unreasonably compromise the welfare of the animals. Similarity of the new animal drug and the active control drug can mean either that both drugs were effective or that neither was effective. The study report should assess the ability of the study to have detected a difference between treatments. The evaluation of the study should explain why the new animal drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control. (21 CFR 514.117(b)(4)(iii)).

Data from Foreign Investigational Studies: Data generated outside of the United States both by entities based within or outside of the United States.

eSubmitter: A computer-based tool that allows animal drug sponsors to create regulatory submissions that can then be submitted electronically and securely to CVM.

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).

Non-inferiority Margin: The non-inferiority margin, also called the margin of difference or delta (Δ), defines the extent to which the investigational new animal drug can be less effective than the active control and still allow the applicant and CVM to conclude that is the new animal drug is "non-inferior." The margin of difference is specified before conducting the study because it will determine whether a study supports the effectiveness of the investigational new animal drug. In the active control comparison, the results provide a point estimate of the difference between treatments and a confidence interval around that difference. In general, the study seeks to show that the upper bound of that confidence interval is less than the acceptable Δ.[16]

Raw Data (for clinical studies): Any original worksheets, calibration data, records, memoranda, and notes of first-hand 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, magnetic, electronic or optical media, information recorded from automated instruments, and hand-recorded datasheets. Facsimile transmissions and transcribed data are not considered raw data.

[16] See footnote 5.

Substantial Evidence of Effectiveness: Evidence consisting of one or more adequate and well-controlled studies, such as a study in a target species, study in laboratory animals, field study, bioequivalence study, or an in vitro study, on the basis of which it could fairly and reasonably be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved that the new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect (21 CFR 514.4(a)).