
GENERAL REVIEW AND ENFORCEMENT POLICIES

REVIEW OF ANIMAL SAFETY AND EFFECTIVENESS DATA

1. Purpose:

This guide outlines the general procedures for determining if the animal safety and effectiveness data submitted by an applicant for an NADA is adequate to support approval of the application.

2. Initial Review:

a. Data Collection:

- (1) The initial step in the review of the animal safety and effectiveness data is to determine if the data has been collected in conformance with the Good Laboratory Practices Regulations for safety studies, and acceptable standards for the conduct of clinical investigations in animals, as provided in 21 CFR 511.1, New Animal Drugs for Investigational Use. This determination is made in part by submitting to HFV-234 the following information:
 - (a) The name of the applicant, application number, drug name and/or code number, and any related or pertinent INAD number(s).
 - (b) A list of clinical investigators involved.
 - (c) A list of the non-clinical laboratories performing target animal safety studies.
 - (d) A statement of compliance with the Good Laboratory Practices Regulations for each target animal safety study submitted.
- (2) If a check of the appropriate records indicates that there are no problems in this area, or that there is no inspectional history, appropriate statements should be put into the first review, as follows:

"Bioresearch Monitoring records in HFV-234 were reviewed and do not

provide an adequate basis for refusal to approve this application" or "No Bioresearch Monitoring records are currently available with respect to this NADA. Assignments to inspect pivotal safety and effectiveness studies should be planned."

- (3) If this check of records uncovers a problem, the reviewer should present the pertinent facts to the Team Leader for resolution before proceeding with the review of the data involved.
- (4) The reviewer should also submit to HFV-234 requests for routine inspections of pivotal target animal safety and effectiveness studies. During the review of the NADA, directed "for cause" inspections may also be requested.

b. Review of related INAD(s):

An additional step in the initial review process is an analysis of the related INAD(s). From this reviewer should determine the number of animals involved in the development of the NADA as well as the number and location of the trials and experiments involved. The purpose of this analysis is to verify that the applicant has supplied all of the data collected during the INAD stage. The reviewer should determine if any policy statements or other pertinent comments or commitments made would have an impact on the safety and effectiveness review.

3. Review of the Effectiveness Data:

- a. All of the pivotal effectiveness data submitted must either directly or indirectly relate to the specific claim made for the product. If more than one claim is made, conclusions regarding effectiveness should relate to each claim.
- b. Basically the applicant must demonstrate that the product produces the claimed effect. There are many facets dealing with a demonstration of efficacy. Efficacy data must have, as a minimum, the following four attributes:
 - (1) The data must be from adequate and well controlled studies as defined in 21 CFR 514.111(a)(5)(i) and (ii).
 - (2) The data must demonstrate that the dose response relationship has been determined.

- (3) The data must be from adequate and well-controlled studies run in more than one location so that any geographical (or environmental) effects can be evaluated.
 - (4) The pivotal data must come from studies in which the proposed dosage form was used.
- c. If data that will permit an evaluation of the above four points is not included in the application, it is conceivable that the application can be incomplete on the grounds that the product has not been shown to be effective. If the reviewer believes that the product is effective, and any exceptions to the above four criteria apply, the reviewer should discuss the rationale with the Team Leader and perhaps the Division Director.

There are many questions that must be raised relative to an effectiveness evaluation. Some of the questions to be asked are:

- (1) Are the experiments designed so that the appropriate modifying factors, such as weight, sex, breed, age, and condition of the animals can be evaluated?
 - (2) Were a sufficient number of the experiments run under field or use conditions? Did the applicant, in addition to evaluating the effectiveness, consider any untoward or unexpected effect from the use of the drug under field or use conditions?
 - (3) Were the diets utilized the trials nutritionally adequate and typical of the diets of animals in the specific geographic areas in which the tests were conducted? Were both non-medicated and medicated feeds assayed for drug content?
 - (4) Has the applicant addressed the issue of foreign non-clinical and clinical data as provided for in 21 CFR 514.1(b)(8) (iv)?
- d. The reviewer should send the dose determination and clinical effectiveness studies to the Biometrics Team for a consulting review if the applicant provided statistical analyses of the data.
- e. Based on the drug product, the species and proposed use, the reviewer should use the respective guidelines as an aid in the review process.

4. Review of Target Animal Safety

- (1) Reviews of target animal safety data for a drug product must relate all evaluations to the dosage level and route of administration of the drug as proposed in the labeling. The primary objective of this is to determine the margin of safety of the product relative to the rate (dosage level) and route of administration.
- (2) The primary reviewer should review the Target Animal Safety data, the prepare an overall summary specifically addressing the safety of the product.
 - (a) If the reviewer determines that the product has not been shown to be safe, a justification for such a conclusion is necessary, and it must include the specific reasons for the conclusion.
 - (b) If it has been determined that the product is safe, the conclusion should be justified. All restrictions or constraints applying to use of the product must be delineated as part of the review. All warning and caution statements to be placed on the labeling of the product must be presented as a part of this summary. If side effects are expected, they must be listed in this summary.
 - (c) If one or more studies do not meet the Target Animal Safety Guidelines, the summary should contain a brief statement of why the alternative procedure is acceptable.