

Guidance for Industry

DEVELOPMENT OF TARGET ANIMAL SAFETY AND EFFECTIVENESS DATA TO SUPPORT APPROVAL OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) FOR USE IN ANIMALS

This guidance is intended to provide specific recommendations regarding the development of target animal safety and effectiveness data to support approval of veterinary NSAIDs, specifically cyclo-oxygenase (cox) inhibitors.

Comments and suggestions regarding this guidance should be sent to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 2004D-0468. Comments may also be submitted electronically via the Internet at <http://www.regulations.gov>.

For questions regarding this document, contact Dr. Linda Wilmot, Center for Veterinary Medicine (HFV-120), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-276-8101, e-mail: linda.wilmot@fda.hhs.gov.

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 <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm>.

**U.S. Department of Health and Human Services
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**DEVELOPMENT OF TARGET ANIMAL SAFETY AND EFFECTIVENESS DATA TO
SUPPORT APPROVAL OF NON STEROIDAL ANTI-INFLAMMATORY DRUGS
(NSAIDS) FOR USE IN ANIMALS**

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DEVELOPMENT OF TARGET ANIMAL SAFETY AND EFFECTIVENESS DATA TO SUPPORT APPROVAL OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) FOR USE IN ANIMALS

This guidance represents the Food and Drug Administration's current thinking on the development of target animal safety and effectiveness data to support approval of non-steroidal anti-inflammatory drugs for use in animals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You may use an alternative approach if the approach satisfies the requirements of applicable statutes and regulations. If you want to discuss an alternative approach, contact Dr. Linda Wilmot at 240-276-8101.

I. INTRODUCTION

This guidance document provides our (the Food and Drug Administration's Center for Veterinary Medicine) recommendations on approaches for developing target animal safety and effectiveness data to support approval of veterinary non-steroidal anti-inflammatory drugs (NSAIDs) -- specifically, approval of NSAIDs that reduce the production of prostaglandins by inhibiting the cyclo-oxygenase (COX) pathway. These recommendations are based on the premise that NSAIDs are not tissue-specific, and important clinical effects associated with toxicity of NSAIDs frequently manifest themselves in the gastrointestinal and renal systems. In addition, alternative strategies for generating safety and effectiveness data for NSAIDs that inhibit lipo-oxygenase, or both lipo-oxygenase and cyclo-oxygenase, or act as cytokine antagonists may be appropriate.

We recommend that you discuss your product development plan and study protocols with us before you initiate any studies that you intend to use to support approval. 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. DOSAGE CHARACTERIZATION

Dosage includes the dose or dose range, the dosing frequency, and the dosing duration. Before we can approve a new animal drug, you must demonstrate by substantial evidence 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 proposed labeling. 21 U.S.C. § 360b(d)(1)(E). For a new animal drug intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease over a dosage range, you must demonstrate by substantial evidence that the new animal drug will be effective for the intended use at the lowest dose of the dosage range suggested in the proposed labeling for that intended use. 21 CFR § 514.4(b)(2)(i). We recommend basing the upper limit of the dosage range for a new animal drug on safety in the target animal (and human food safety in appropriate species) as well as on dosing practicality. Since the enactment of the Animal Drug Availability Act of 1996 (ADAA), we no longer require dosage optimization. However, we recommend that you characterize the critical aspects of the dosage-response relationship for those parameters relevant to the proposed indication in the new animal drug application. The parameters measured in the characterization of the dosage or

dosage range should specifically relate the proposed dosage or dosage range to the proposed indication. For some new animal drugs, this characterization information may be particularly useful to us in evaluating the adequacy of protocols for effectiveness studies. These parameters may suggest the appropriate study endpoints for the one or more adequate and well-controlled studies necessary to provide substantial evidence of effectiveness. Methods for gathering information to characterize the dose response relationship may include dose titration studies, pilot studies, *in vitro* studies, scientific literature, and assessments based upon the modeling of pharmacokinetic and pharmacodynamic data. Although you are required to demonstrate by substantial evidence that the new animal drug is effective at the dose or over the dose range selected (see 21 U.S.C. § 360b(d)(1)(E)), you need not demonstrate dosage characterization by substantial evidence. You should, however, submit sufficient information to characterize the critical aspects of the dose response relationship so that qualified experts can make an informed risk-benefit assessment of the new animal drug and ensure that the proposed labeling is not false or misleading. You should discuss the appropriate timing for submitting information to characterize the dosage-response relationship with us.

¹ Before the enactment of the ADAA, under 21 U.S.C. § 360b(d)(1)(F), FDA could not approve a new animal drug for use at a particular dose or over a dose range that exceeded the dose reasonably required to accomplish the physical or other technical effect for which the new animal drug was intended. In order to demonstrate by substantial evidence the minimal amount of a new animal drug reasonably required to accomplish the physical or other technical effect (i.e., the optimal dose), dose optimization, typically supported by adequate and well-controlled dose titration studies that characterize the critical aspects of the dose response relationship, was required. With the enactment of the ADAA, the requirement for dose optimization was eliminated.

You must submit all information, including published and unpublished studies, relating to safety and effectiveness, that led to your selection and characterization of the proposed dosage or dosage range (21 CFR § 514.1(b)(8)(iv)).

We encourage you to summarize the dosage characterization so that we can include it in the Freedom of Information Summary.

III. TARGET ANIMAL SAFETY (TAS)

We recognize that there are many valid ways to evaluate the target animal safety (TAS) of NSAIDs. We recommend that you meet with us to discuss TAS study design prior to initiating any studies.

TAS studies for novel chemical entities should identify the toxic syndrome associated with the formulation and identify a safe upper limit of the dose. You should identify the minimum toxic dose (the dose at which adverse reactions begin to manifest), unless multiples of the intended dose show no toxic effects. In general, we recommend that you follow CVM's Target Animal Safety Guidelines for New Animal Drugs (Guidance #85), testing at multiples of the intended dose. For drugs intended for long term use, we recommend that you conduct safety studies for a minimum of six months.

We also recommend that TAS studies for NSAIDs incorporate specific tests or examinations to

identify signs of either local gastrointestinal toxicity (e.g., endoscopy) or renal toxicity (e.g., specific gravity, BUN, and creatinine).

In addition, we recommend that you evaluate potential drug effects on platelet aggregation via appropriate methods, including Buccal Mucosal Bleeding Time or a similar test. Local gastrointestinal irritation caused by NSAIDs may be mitigated by administration with food. However, food may affect the bioavailability of oral dosage forms. Therefore, we encourage you to submit information concerning the safety and bioavailability of the drug in fed versus fasted conditions. If the drug is labeled for administration with food as a condition of use, we will require data to demonstrate substantial evidence of the drug's effectiveness in the presence of food (21 U.S.C. § 360b(d)(1)(E)).

IV. FIELD STUDY

We recommend that you conduct a field study to demonstrate that an NSAID is safe and effective for the target animal under the actual conditions of use for which it is labeled. Field studies should confirm results from any laboratory studies that were used to provide substantial evidence of effectiveness.

V. USE OF PHARMACOKINETICS IN NSAID DEVELOPMENT

We encourage you to provide information to describe the mechanism of action and pharmacokinetics (PK) of the drug entity. You may use such information to establish the dosing regimen to use in safety and effectiveness studies. This information can also provide support for dosage selection and conditions of use. The generation of PK data during safety and effectiveness trials may provide information to assist us in identifying any potential exposure–response relationship and in further elucidating the product's margin of safety.

Appropriate pharmacokinetic information may include effects of prandial state and factors that may affect the rate and extent of bioavailability, magnitude of accumulation of the active moiety(ies) with repeated administration, terminal elimination half-life, clearance mechanisms, protein binding, partitioning characteristics, and volume of distribution. Of interest are both the average kinetic properties and the variability in the PK characteristics that may be anticipated under clinical use conditions. You may derive this information from *in vitro* or *in vivo* studies that have been published in peer-reviewed journals or contemporary studies you conduct during drug development.

Because our recommendations about the generation of PK data may vary based on the type of product, we encourage you to meet with us to discuss proposals for conducting PK studies. In determining what type of studies may be appropriate, we recommend that you consider such factors as the proposed conditions of use, release characteristics of the dosage form, the intended target animal species, and the drug's therapeutic considerations. For example, for products intended for repeated administration, we recommend a multiple dose study to address questions regarding nonlinear kinetics with repeated administration. You may generate these data by obtaining blood samples during the target animal safety studies. In addition, if you develop multiple dosage forms in a single target species, we recommend that you evaluate the interchangeability and sequential use of the dosage forms.

VI. LABELING

A. General Approach to the Indication Section of Labeling

We recommend that you tailor the development plan for an NSAID to the proposed intended uses. In general, inflammation, pain, and pyrexia are three common pathophysiologic processes associated with tissue injury and animal illness that may be controlled by NSAIDs. Generally, NSAIDs ameliorate pathophysiologic responses, but do not cure the underlying disease. Therefore, we recommend that NSAIDs be labeled for control, not treatment, of the disease. An NSAID may be labeled for control of any single process or any combination of physiologic processes for which it is demonstrated to be safe and effective.

The criteria you use to measure effectiveness of the NSAID should be objective, repeatable, and clearly stated. You may use naturally occurring disease and/or established experimental (target animal) models to demonstrate effectiveness.

We recommend that labeling include the time to onset of drug effect, if appropriate, so that interim care can be initiated if onset of effect is delayed. You should not make any representation regarding the safety and/or effectiveness of long-term use of the product in labeling, unless you conducted long-term safety and/or effectiveness studies during the approval process.

The following hypothetical label indications and approaches are illustrative; you should not construe them as definitive indications or approaches. Following each example, a brief description of studies that you may use to support the indication appears in italics.

1. Inflammation

We recommend that you base the indication on the control of clinical signs of inflammation associated with a disease. You may confirm the indication through demonstration of control of one or more of the cardinal signs of inflammation clinically significant to the disease process. The cardinal signs of inflammation are pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (function laesa).

Example: Indication: NSAID® is indicated for the control of inflammation associated with soft tissue surgery in horses.

You may demonstrate the effectiveness of NSAID as an anti-inflammatory agent using a validated laboratory model such as carrageenan sponge or tissue cage. The field study variables should support the model; for example, a post-castration field study in horses may support the model by demonstrating control of clinical signs of inflammation (swelling).

2. Pain

We recommend that this indication be based on the control of clinical signs of pain associated with a disease. We encourage the use of validated methods of pain assessment in the target species. Two indications of frequent concern are control of pain associated with osteoarthritis and postoperative pain.

We recommend using radiographs or other appropriate diagnostic modalities to confirm the diagnosis of osteoarthritis. We suggest that clinical cases include an adequate number of representative osteoarthritic joints.

Postoperative pain is expected to be most intense in the immediate post-operative period, and to subside substantially within approximately 72 hours.^{2,3} Therefore,

² Boothe, D., Tranquilli, W., and Radasch, R., "Overview of Pain Management Options," Proceedings of

we recommend that effectiveness studies include evaluation of the response to treatment within the first 72 hours after surgery. The intensity of pain and the expression of pain vary greatly

depending on the type of surgical procedure, as well as from animal to animal. NSAIDs alone may not provide sufficient analgesia following procedures that are expected to induce intense pain; therefore, evaluation of drug combinations is also acceptable.

Orthopedic procedures frequently result in intense postoperative pain. You may use a single orthopedic procedure that is historically associated with a high degree of pain to support an indication for the control of pain following orthopedic surgery.

Soft tissue surgeries often involve lower levels of pain, but these levels may vary among types of soft tissue procedures. For example, we would expect less pain following ovariohysterectomy than following radical mastectomy or thoracotomy. We recommend that you evaluate a minimum of two types of procedures, representing the range of pain associated with soft tissue surgeries, to establish a general indication for control of pain following soft tissue surgery. We suggest that you evaluate a sufficient number of cases of each type of soft tissue surgery to demonstrate the new animal drug's effectiveness in controlling pain for each procedure. Alternatively, you could pursue an indication for a specific type of soft tissue surgery.

Example 1: Indication: NSAID® tablets are indicated for the control of pain associated with osteoarthritis in dogs.

You may demonstrate the effectiveness of NSAID® in adequate and well-controlled field studies for control of pain associated with osteoarthritis of the elbows, hips, and stifles in dogs.

Example 2: Indication: NSAID® is indicated for the control of postoperative pain associated with orthopedic surgery in dogs.

You may demonstrate the effectiveness of NSAID® in controlled field studies of a representative orthopedic procedure (e.g., pain associated with surgical repair of the cranial cruciate ligament).

Example 3: Indication: NSAID® is indicated for the control of pain associated with soft tissue surgery in cats.

You may demonstrate the effectiveness of NSAID® in controlled field studies that evaluate post-operative pain after two representative soft tissue surgeries (e.g., ovariohysterectomy and ocular surgery).

the North American Veterinary Conference, Small Animal Pharmacology, 1998, vol. 12, pp. 571-573. ³ Hellyer, P.W. and Gaynor, J.S., "Acute Postsurgical Pain in Dogs and Cats," *The Compendium on Continuing Education for the Practicing Veterinarian*, February 1998, vol. 20, no. 2, pp. 140-153.

3. Pyrexia

Pyrexia (fever) is defined as a sequela to an elevated set-point in the hypothalamic thermoregulatory system in response to circulating pyrogens. You may use validated target species model systems to support this indication. You should demonstrate a clinically significant decrease in core body temperature in field studies. The magnitude of the decrease will depend on the animal species, the disease process, and the stage and severity of the disease process. We encourage you to discuss the definition of a clinically significant decrease in temperature with us during the protocol review and build it into the protocol design.

Example 1: Indication: NSAID® is indicated for the control of pyrexia associated with bovine respiratory disease.

You may demonstrate the effectiveness of NSAID® by a validated laboratory target species model and confirm the effect in controlled field studies comprised of clinical cases of the specific disease.

B. Precaution Statement

Cyclo-oxygenase-inhibiting NSAIDs generally elicit toxicities that may not be found during laboratory Target Animal Safety studies, which are typically conducted in a limited number of healthy animals. We recommend that field studies be designed to ensure detection and documentation of adverse events. Further, you should address adverse reactions that are relevant to NSAIDs as a class, but not necessarily identified in the field study, in labeling .

C. Comparison of COX-1 and COX-2 Activity

The clinical relevance of quantitative *in vitro* comparisons of COX-1 and COX-2 activity of NSAIDs has not been shown. Therefore, we discourage such quantitative *in vitro* comparisons in labeling. We will continue to carefully review labeling submissions on a case-by-case basis, including any such *in vitro* comparisons and accompanying disclaimers indicating that the clinical relevance of this information is unknown. We welcome further research into the clinical relevance of *in vitro* comparison data.