

Guidance for Industry

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

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

This draft guidance is intended to provide specific advice regarding the development of target animal safety and effectiveness data to support approval of veterinary NSAIDs, specifically cyclooxygenase inhibitors.

Comments and suggestions regarding this draft guidance should be sent to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.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.fda.gov/dockets/ecomments>. After bringing up this Internet site, select “[2004D-0468][Development of Target Animal Safety and Effectiveness Data to Support Approval of Non-steroidal Anti-inflammatory drugs (NSAIDS) for Use in Animals]” and follow the directions.

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Center for Veterinary Medicine (CVM)
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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**

I.	Introduction	3
II.	Dosage Characterization	4
III.	Target Animal Safety	5
IV.	Field Study	6
V.	Use of Pharmacokinetics In Drug Development	6
VI.	Labeling	7
	A. General Approach to the Indication Section of Labeling	7
	1. Inflammation	7
	2. Pain	8
	3. Pyrexia (Fever)	9
	B. Precaution Statement	9
	C. Comparison of COX-1 and COX-2	9

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This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on the development of target animal safety and effectiveness data to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 301-827-0135.

I. INTRODUCTION

This draft guidance document provides recommended approaches to the development of target animal safety and effectiveness data to support approval of veterinary non-steroidal anti-inflammatory drugs (NSAIDs) -- specifically, NSAIDs that reduce the production of prostaglandins by inhibiting the cyclooxygenase (COX) pathway. Recommendations in this document are based on the premise that NSAIDs are not tissue-specific and important clinical effects associated with toxicity of NSAIDs are frequently manifested in the gastrointestinal and/or renal systems.

CVM recommends that you discuss your product development plan and study protocols with CVM before you initiate any studies that may be used to support approval.

CVM may recommend alternative product development strategies for NSAIDs that inhibit lipooxygenase, or both lipooxygenase and cyclooxygenase, or act as cytokine antagonists. We recommend that you contact CVM to discuss which recommendations in this document may be applicable to the development of such drugs.

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 the Food and Drug Administration (FDA) can approve a new animal drug, a sponsor 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, the demonstration of effectiveness must generally include a demonstration 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). CVM recommends 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.

Prior to the enactment of the Animal Drug Availability Act of 1996 (ADAA), FDA was required under section 512(d)(1)(F) of the Federal Food, Drug, and Cosmetic Act to refuse to approve a new animal drug if, on the basis of any information before FDA, the tolerance limitation proposed, if any, exceeded that reasonably required to accomplish the physical or other technical effect for which the new animal drug is intended. In order to demonstrate by substantial evidence the minimal amount of a new animal drug reasonably required to accomplish the physical or technical effect, 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, dosage optimization is no longer required. It is recommended, however, that sponsors characterize the critical aspects of the dosage-response relationship in the new animal drug application. Dosage characterization, i.e., the characterization of the critical aspects of the dose-response relationship, need not be demonstrated by substantial evidence, but may factor into FDA decisions regarding the development of effectiveness data and its evaluation of the content of proposed labeling.

We recommend that sponsors characterize the dosage-response relationship for those dosage parameters relevant to the proposed intended use. In practice, characterization of some dosage parameters may be irrelevant (e.g., if proposed duration is limited to continuous feeding, dosing frequency is not relevant).

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. These parameters should also suggest the appropriate study endpoints for the one or more adequate and well-controlled studies necessary to provide substantial evidence of effectiveness. For some new animal drugs, this characterization information may be particularly useful for CVM to evaluate the adequacy of protocols for effectiveness

CONTAINS NON-BINDING RECOMMENDATIONS

studies. Sponsors should discuss with CVM the appropriate timing for submitting information to characterize the dosage-response relationship.

Neither dosage range selection nor dosage range characterization has to be supported by substantial evidence. However, the sponsor should present a well-reasoned, convincing, scientific basis for selecting the dosage or dosage range; the characterization of the dosage or dosage range should be similarly well-reasoned, scientific, and convincing in its description of the relative effectiveness of the drug over the labeled dosage range or of the selected dosage relative to alternative dosages. Methods for gathering such information may include dose titration studies, pilot studies, in vitro studies, and scientific literature. This information should be sufficient to allow qualified experts to make an informed risk-benefit assessment of the new animal drug and assure that the proposed labeling is not false or misleading.

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

The dosage characterization should be summarized in the Freedom of Information Summary.

III. TARGET ANIMAL SAFETY (TAS)

CVM recognizes that there are many valid ways available to evaluate the target animal safety (TAS) of NSAIDs. CVM recommends 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. The minimum toxic dose (the dose at which adverse reactions begin to manifest) should be identified, 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 #33), testing at multiples of the intended dose. For drugs intended for long term use, CVM recommends that safety studies be conducted for a minimum of six months.

CVM recommends that TAS studies for NSAIDs incorporate specific tests and examinations, including endoscopy, to identify signs of gastrointestinal or renal toxicity.

CVM recommends 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

CONTAINS NON-BINDING RECOMMENDATIONS

dosage forms. CVM encourages 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, data will be required to demonstrate substantial evidence of the drug's effectiveness in the presence of food (21 § CFR 514.4(a)).

IV. FIELD STUDY

CVM recommends 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

CVM encourages you to provide information to describe the mechanism of action and pharmacokinetics (PK) of the drug entity. Such information can be used to establish the dosing regimen used in the clinical safety and effectiveness studies. It can also provide labeling information to support dosage selection and conditions of use. The generation of PK data during safety and effectiveness trials may provide information to assist CVM in identifying any potential exposure–response relationship and in further elucidating the margin of safety associated with the product.

Appropriate pharmacokinetic information may include effects of prandial state and factors that may affect the 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. This information may be derived from *in vitro* or *in vivo* studies that have been published in peer-reviewed journals, or may be based upon contemporary studies you generate during drug development.

The kinds of studies recommended to support a new animal drug application will depend on the targeted conditions of use, the kind of release characteristics of the dosage form, the intended target animal species, and the drug's therapeutic considerations. Accordingly, recommendations associated with the generation of PK data will be highly product specific. For this reason, we encourage you to meet with CVM to discuss proposals for PK studies that may be used to support NAD approval.

VI. LABELING

A. General Approach to the Indication Section of Labeling

CVM recommends that the development plan for an NSAID be tailored to the proposed intended uses. In general, inflammation, pain, and pyrexia are three

CONTAINS NON-BINDING RECOMMENDATIONS

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.

Criteria used to measure effectiveness of the NSAID should be objective, repeatable, and clearly stated. Naturally occurring disease and/or established experimental (target animal) models may be used to demonstrate effectiveness.

CVM recommends 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. No representation regarding the safety and/or effectiveness of long-term use of the product should be made in labeling, unless long-term safety and/or effectiveness was evaluated during the approval process.

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

1. Inflammation

CVM recommends that the indication be based on the control of clinical signs of inflammation associated with a disease. The indication may be confirmed 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.

The effectiveness of NSAID® as an anti-inflammatory agent may be demonstrated in a laboratory carrageenan sponge model. A post-castration field study in horses may support the model by demonstrating control of clinical signs of inflammation (swelling).

2. Pain

CVM recommends that this indication be based on the control of clinical signs of pain associated with a disease. Two indications of frequent concern are control of osteoarthritis and postoperative pain.

Radiographs or other appropriate diagnostic modalities are recommended to

CONTAINS NON-BINDING RECOMMENDATIONS

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.^{1,2} Therefore, CVM recommends that effectiveness studies include evaluation of the response to treatment within the first 72 hours after surgery. It is generally recognized that 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. A single orthopedic procedure that is historically associated with a high degree of pain may be used in pursuit of 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, less pain would be expected following ovariohysterectomy than following radical mastectomy or thoracotomy. CVM recommends that a minimum of two types of procedures, representing the range of pain associated with soft tissue surgeries, be evaluated to establish a general indication for control of pain following soft tissue surgery. CVM suggests that a sufficient number of cases of each type of soft tissue surgery be evaluated to demonstrate the new animal drug's effectiveness in controlling pain for each procedure. Alternatively, an indication could be pursued 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.

The effectiveness of NSAID® may be demonstrated 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.

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

¹ Boothe, D., Tranquilli, W., and Radasch, R., "Overview of Pain Management Options," Proceedings of the North American Veterinary Conference, Small Animal Pharmacology, 1998, vol. 12, pp.571-573.

² 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.

CONTAINS NON-BINDING RECOMMENDATIONS

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

The effectiveness of NSAID® may be demonstrated in controlled field studies that evaluated post-operative pain after two representative soft tissue surgeries (e.g., ovariohysterectomy and ocular surgery).

3. Pyrexia

Pyrexia (fever) is defined as a sequela to an elevated set-point in the hypothalamic thermoregulatory system in response to circulating pyrogens. Validated target species model systems may be used to support this indication. A clinically significant decrease in core body temperature in field studies should be demonstrated. The magnitude of the decrease will depend on the animal species, the disease process, and the stage and severity of the disease process. CVM encourages you to discuss the definition of a clinically significant decrease in temperature 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.

The effectiveness of NSAID® may be supported by a validated laboratory target species model and confirmed in controlled field studies comprised of clinical cases of the specific disease.

B. Precaution Statement

Cyclooxygenase-inhibiting NSAIDs generally exhibit common toxicities that may not be found during laboratory Target Animal Safety studies, which are typically conducted in a limited number of healthy animals. CVM recommends that field studies be designed to ensure detection and documentation of adverse events. Further, adverse reactions that are relevant to NSAIDs as a class, but not necessarily identified in the field study should be addressed 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, CVM discourages such quantitative *in vitro* comparisons in labeling. CVM 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. CVM welcomes further research into the clinical relevance of *in vitro* comparison data.