Australian Government

Australian Pesticides and Veterinary Medicines Authority

Guideline for the evaluation of the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), with respect to anti-inflammatory, analgesic and anti-pyretic effects

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This publication is available from the APVMA website.

Contents

Guideline for the evaluation of the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), with respect to anti-inflammatory, analgesic and anti-pyretic effects

1. Scope

For the purposes of this guideline, an NSAID will be defined as that group of substances that can be classified by clinical-chemical tests *ex vivo* for their ability to inhibit isoforms of the enzyme cyclooxygenase (COX), which catalyses the conversion of arachidonic acid into prostaglandins and thromboxane *in vivo*. However, this guideline may be extended, where appropriate, to studies aimed at demonstrating the efficacy of other non-steroidal anti-inflammatory agents such as lipoxygenase inhibitors and cytokine antagonists.

This is a guideline about the types of information you can submit to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to address the efficacy criteria for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in animals. For further information on the efficacy criteria, refer to satisfying the statutory criteria. The objective of this guideline is to specify recommendations for the design, conduct, and evaluation of clinical studies for NSAIDs to be provided in support of an application to register a new NSAID, or to vary the indications of an already registered NSAID. It provides recommendations on how to appropriately demonstrate clinical efficacy through clinical trials where the selection of control and efficacy endpoints is regarded as a key issue for obtaining conclusive information. In conducting efficacy studies, safety aspects are also critical to include and consider e.g. documentation and analysis of adverse events. The guideline also includes safety aspects when studies are undertaken to assess efficacy.

Generally, the classification 'NSAID' is applied to drugs that inhibit one or more steps in the metabolism of arachidonic acid (AA). NSAIDs act primarily to reduce the biosynthesis or function of prostaglandins that are involved in inflammation, by inhibiting cyclooxygenase (COX-1 and/or COX-2). Other mechanisms of action may also be relevant to inflammation, pain and temperature regulation. Veterinary NSAIDs are commonly used to control fever, pain and other signs of inflammation in animals.

Note – This guideline may also be useful for veterinary medicines that are claimed to be useful in the management of inflammation but are not classically defined as NSAIDs.

Note – This guideline focusses on oral and injectable anti-inflammatory drugs but may also be useful for veterinary medicines used topically or by other routes, for example topical formulations. Other routes of administration may require further data, for example on bioavailability.

Note – This guideline should be read in conjunction with the APVMA's efficacy and target animal safety general guideline (Part 8).

The extent of clinical usage and the range of indications for NSAIDs have increased in recent years. However, it is not possible to provide detailed guidance for all proposed indications in various target animal species. This guideline will therefore focus on recognised pharmacological actions with potential therapeutic benefits of anti-pyretic, analgesic and anti-inflammatory effects.

2. Additional guidance material

This APVMA guideline references additional guidance material which may assist you in your submission (Table 1). However, the requirements outlined in this APVMA guideline should still be followed. Any deviations from this APVMA guideline must be fully justified in applicant submissions.

Table 1: Reference documents

Reference document	Section in reference document
Guideline for the conduct of efficacy studies for nonsteroidal anti-inflammatory drugs Adopted by CVMP July 2021 EMA/CVMP/EWP/1061/2001-Rev.1	5. Pre-clinical documentation 5.1. Pharmacodynamics 5.2. Pharmacokinetics 5.3. Pk/PD 6. Clinical documentation 6.1. Selection of primary and secondary endpoints 6.2. Type of Control 7. Clinical trials 7.1. Efficacy
Guidance for Industry for development of target animal safety and effectiveness data to support approval of non-steroidal anti-inflammatory drugs (NSAIDs) for use in animals. FDA published January 2006 Guidance for Industry #123	IV) Field study V) Labelling General approach to the indication section of labelling 1. Inflammation 2. Pain 3. Pyrexia (fever)
APVMA Efficacy and Target Animal Safety General Guideline (Part 8)	All Sections

3. General requirements

Claims for efficacy should be based on a documented NSAID effect, demonstrated by pre-clinical studies and supported by clinical trials carried out in each proposed target animal species.

The following should be addressed:

- Describe and justify (using appropriate data), the proposed route of administration, dosage (or dose range), frequency and duration of administration of the Investigational Veterinary Medicinal Product (IVMP)
- For treatments of short duration (for example, up to 10 days), use a duration for the clinical trial that encompasses the entire recommended treatment period.

- In case of long-term administration, use a duration of clinical trial that you consider sufficient (based on evidence and/or scientific argument), paying particular attention to the potential adverse effects resulting from such use.
- Combined efficacy and target animal safety studies should be performed for at least the longest recommended duration of use. For veterinary medicines intended for long term use this would be at least 6 months.
- Target animal safety studies for NSAIDs should incorporate specific tests or examinations to identify signs associated with toxicity, such as local gastrointestinal toxicity (example: endoscopy) or renal toxicity (example: specific gravity, blood urea nitrogen, and creatinine). In addition, you should evaluate potential drug effects on platelet aggregation via appropriate methods, including Buccal Mucosal Bleeding Time or a similar test.
- Use appropriate statistical methods.
- Randomise the allocation of test animals to treatment groups, stating the method of randomisation and justify the method selected.
- Use blinding/masking methods and allocation concealment. If not, justify not using these methods. The methods should be described in detail (example: for treatment, for clinical observation).
- Examination and observation methods should be appropriate to generate adequate sensitivity (see later discussion on subjective variables).
- Apply the principles of Good Laboratory Practice (GLP) or Good Clinical Practice (GCP), where appropriate.

4. Pre-clinical studies

This guideline is focused on establishing clinical efficacy of NSAIDs. However, pre-clinical studies are also a critical part of a submission to the APVMA to support consideration of efficacy. For further guidance on pre-clinical studies please refer to the references listed above in Table 1.

A well-designed study in the target species may perform multiple functions and generate multiple data sets. For example, a well-designed dose-response study may also generate overdose safety (margin of safety) and pharmacokinetic data. This can be helpful in reducing the number of test animals, in particular target species animals used.

4.1. Pharmacodynamics

The mode of action of the active substance underlying the desired effect(s) should be described. The way the active substance affects body organs and organ systems should be described in relation to dose and desired therapeutic effect, as well as secondary and adverse effects. Pharmacodynamic (PD) studies may include *in vitro*, *in vivo* and *ex vivo* designs as appropriate. Regardless of the experimental design employed, and the method(s) of measurement, the NSAID effect should be fully described and justified by the applicant.

The specific activity against COX-1 and/or COX-2 should be stated, including the model used to determine activity, for example, whole blood, synovial cells. This activity will normally be defined as an inhibitory concentration (IC) in a population and should attain at least an IC_{80} in a model consistent with the approach used for the currently registered formulation (if comparing against an existing formulation)[1] or an IC that is correlated with a clinically significant effect when not comparing to a registered formulation.

If enantiomers exist (Example, S(+) and R(-) carprofen), it must be stated if the formulation contains a single enantiomer or is a mixture and, if the latter, the proportion of the enantiomers (as detailed in the Chemistry and Manufacturing section of the application) must be referenced here (since any differences in efficacy may relate to differences in enantiomer composition).

Any comparisons between a proposed veterinary medicine and an existing (currently registered) veterinary medicine must use the same mixture of enantiomers (if applicable) and consider at least an IC_{80} for comparing efficacy.

Experimental models should be fully valid for their intended purpose. For example, in an *in vivo* model the suitability of parameters such as the choice of response variables, assessment time points and observation intervals should be established in relation to the expected and clinically relevant level and duration of effects. If the IVMP produces a long-acting effect, it is important to choose an experimental model with a sufficiently long duration to obtain a reliable result.

In *in vivo* studies NSAID effects may be measured directly, for example, reduction of pyrexia, or via validated surrogate markers. When surrogate markers are used, their correlation to the clinical effect of the product should be clearly explained and justified in terms of clinical relevance. Pain scales, including Visual Analog Scales (VAS) are considered useful during clinical trials.

4.2. Pharmacokinetics

In the context of dose-response relationships, pharmacokinetic (PK) data on NSAIDs are considered useful for interpretation of plasma level profiles and related observed effect(s) including potential toxicity linked to dose level and/or treatment duration. PK studies also support the determination and confirmation of the treatment dose as well as dosing frequency and interval. It is noted that PK data alone are insufficient for establishing dosing regimens or claims of efficacy for NSAID products: for example, the elimination half-life for a NSAID may differ significantly between plasma and the inflammatory exudate. Furthermore, the correlation between exposure pattern and enzyme inhibition is often weak.

As animal species may differ in their response to NSAID treatment, dosages based on results from laboratory animal experiments may not result in similar effects in a target animal species, and care should be taken when interpreting PK data extrapolated from other species. Therefore, while such studies might provide useful supportive data, pivotal PK studies must be carried out in the target animal species and using the route of administration expected for the proposed registered product.

[1] Refer Lees et al 2004

PK data must also explore potential influence of feeding (if doses are recommended to be given with food) and could also be useful to explore other external factors on exposure, if such a relationship is expected.

If a formulation other than the final one proposed for registration has been used in the PK studies, the results could still be valid, provided bioequivalence to the final formulation is demonstrated or justified.

4.3. Dose determination

Dose-determination studies should be conducted in the target species using a range of doses selected based on preliminary studies, parameters that are relevant for the anticipated effect and a dose range that is considered appropriate for further use. Preferably, a minimum of 3 different doses should be included, the central dose being the expected recommended dose. Selection of the higher doses in such studies should consider the safety margin of the product under investigation. The reason for the choice of doses selected should be explained. Dose-determination studies should aim to incorporate not only the dose itself, but also the intended dosing frequency if relevant for a given indication. Alternatively, a PK/PD study may be applied to propose a dose to be further confirmed (dose confirmation studies). *In vivo* PK/PD studies in the target species, if conclusive and conducted over a sufficient exposure range, may serve as an aid in the establishment of a dosing strategy and may potentially reduce the need for comprehensive dose-finding data, and if adequately designed, be used in replacement of the latter. Fewer than 3 doses may be used in such a study providing that a sufficient exposure range is covered.

Where the active constituent is well-characterised, published data, generated in the target species (or similar species with appropriate scientific justification), may be presented as an alternative to dose determination trial data.

4.4. Dose confirmation

Dose-confirmation studies should be performed in the target animal species under experimental conditions, using the proposed dose regimen and be conducted with the final formulation. Any deviation should be justified. Dose-confirmation studies may also be performed in the field, if justified. If a dose range has been selected as a result of dose-dependent differences in clinical effects as claimed, each dose should be studied with respect to its corresponding effect.

If a formulation other than the final one proposed for registration has been used in the dose confirmation study, the results could still be valid, provided bioequivalence to the final formulation is demonstrated.

5. Clinical studies

Field studies should be conducted to demonstrate that an NSAID is safe and effective for the target animal under the actual conditions of use for which it is labelled. Field studies should confirm results from any laboratory studies that were used to provide substantial evidence of effectiveness. At least one clinical trial should be performed for each claim. 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.

Approval by an institutional animal ethics committee for each study is essential and must be stated, including approval number.

5.1. Selection of primary and secondary outcome measures

Efficacy assessment should be based on objective primary outcome measures and result in quantitative data. Selection of appropriate primary and secondary outcome measures concerns both pre-clinical studies and clinical trials. Clearly state and define in advance primary and secondary outcome measures for inflammation, pain and pyrexia.

Select the outcome measures most relevant to the proposed label claims. Use direct, objective measures (For example: blinded veterinary assessment, force plate, accelerometer, video tracking) instead of more subjective measures (For example: owner/investigator grading pain level) where possible. These can be further analysed in terms of pre-determined definitions of response to treatment so that the % of animals that are considered responders to treatment could be evaluated.

The selected primary measures should objectively quantify the changes induced by treatment so that changes in magnitude can be interpreted for their **clinical relevance** and be relevant for the proposed label claims. If objective measures cannot be used, subjective measures, for example, owner assessment of improvements in lameness, may be acceptable. However, validated methods to quantify the data should be applied where possible, for example, VAS, and the trial design should include adequate blinding/masking (For example: each observer is blinded/masked to treatment versus placebo). To reduce variability, observations should preferably be made by the same adequately trained personnel throughout the trial, and information on this and any other measures undertaken to reduce observer variation should be provided.

5.2. Ensuring clinical studies are relevant to proposed label claims and uses

The development plan for a NSAID should be tailored to the proposed intended uses. The following hypothetical approach and proposed label claims are examples only and should not be perceived as definitive indications or approaches. Following each example, a brief description of studies that you may use to support the indication appears in *italics*.

5.2.1. 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, heat, redness, swelling, and loss of function.

Example 1: Proposed label claim: For the control of inflammation associated with soft tissue surgery in horses.

You may demonstrate effectiveness of NSAID as an anti-inflammatory agent using a validated laboratory model such as carrageenan sponge or tissue cage. The field study outcome measures 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).

Example 2: Proposed label claim: For the control of inflammation associated with soft tissue surgery or injury in horses.

Using the above example and adding a field study in horses demonstrating control of clinical signs following non-surgical soft tissue trauma / injury.

5.2.2. Pain

This indication should be based on the control of clinical signs of pain associated with a disease. Pain in limbs may manifest as lameness. You should use 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, as an inclusion criterion for entry into the trial. Clinical cases should include an adequate number of representative osteoarthritic joints. Radiographic or similar evidence will be necessary if claims are being made regarding reduction of lesion severity.

Postoperative pain is expected to be most intense in the immediate post-operative period and subside substantially within 72 hours. Therefore, the effectiveness studies should 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. It is also important to design studies to eliminate or reduce the differing residual analgesic effects of different anaesthetic agents (For example: equal representation of anaesthetic agents in groups.

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

Soft tissue surgeries often involve lower pain intensity but may vary among types of soft tissue procedures. For example, we would expect less pain following ovariohysterectomy than following radical mastectomy or thoracotomy. You should evaluate a minimum of 2 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

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: Proposed label claim: For the control of pain associated with osteoarthritis in dogs.

You may demonstrate the effectiveness of an NSAID as an analgesic agent using a validated laboratory model and adequate, well-controlled field studies for control of pain associated with osteoarthritis of the elbows, hips, and stifles in dogs.

Example 2: Proposed label claim: For the control of postoperative pain associated with orthopaedic surgery in dogs.

You may demonstrate the effectiveness of NSAID as an analgesic agent using a validated laboratory model and in controlled field studies of a representative orthopaedic procedure, for example, pain associated with surgical repair of fractures.

Note here that descriptions of the surgeries undertaken would need to be detailed. For example, if surgery associated with improving cruciate instability was selected you would need to specify the types of repair undertaken.

Example 3: Proposed label claim: For the control of pain associated with soft tissue surgery in cats.

You may demonstrate the effectiveness of NSAID as an analgesic agent using a validated laboratory model and in controlled field studies that evaluate postoperative pain after two representative soft tissue surgeries, for example, ovariohysterectomy and ocular surgery, in cats.

5.2.3. Pyrexia

You may use validated target species model systems to support this indication. Noting that rating scales are not useful or relevant where quantitative measurements such as (rectal) temperature are available. You should demonstrate a statistically and clinically significant decrease in core body temperature in field studies. The definition of a clinically significant decrease in core body temperature must be included in the study design before the study commences. The magnitude of the decrease will depend on the animal species, the disease process, and the stage and severity of the disease process.

Example 1: Proposed label claim: For the control of pyrexia associated with [disease such as bovine respiratory disease].

You may demonstrate the effectiveness of NSAID as an anti-pyretic agent using a validated laboratory model and in controlled field studies comprised of clinical cases of the specific disease.

5.3. Rating scales

Quantitative measures should be used where possible, for example, force plate analysis, limb circumference. Rating scales can be used for assessing (usually subjective) changes in clinical signs associated with inflammation and pain. Rating scales often apply ordinal data and need appropriate statistical consideration. They can take the form of visual analogue scales, numerical rating scales, and simple descriptive scales. Numerical

ratings from zero (normal) to 4 or 5 or 10 are commonly used and the criteria for each category must be defined in the study design and protocol.

If the proposed label claim relates to inflammation, then clinical signs associated with inflammation must be included for rating. Validation of the rating method used would consider the types of clinical signs to be included (see below).

If the proposed label claim relates to pain, then clinical signs associated with pain must be included for rating. Validation of the rating method used would consider the types of clinical signs to be included (see below).

In clinical studies, assessment may be performed by suitably trained assessors, including veterinarians and owners (for owner-relevant assessments). Assessors should be blinded/masked to the IVMP, positive control or placebo being given. A veterinarian must perform at least some of the assessments pre- and post-IVMP administration and should be assessing the primary outcome measure/s.

5.4. Validation of rating scales

Rating scales must be validated either through peer-reviewed literature or validation data provided to justify the use of a particular rating scale.

Any rating scale used must be:

- reliable (demonstrating minimal inter-observer and intra-observer variation)
- sensitive (able to detect small enough variations in clinical responses to identify clinically relevant differences in treatment effect)
- measuring parameters which are clearly and directly related to treatment effect and therefore the proposed label claims
- validated using veterinary assessments where they are based on subjective outcome measures assessed by the client in a home environment.

To be considered validated, these aspects should usually have been established for different breeds (where relevant to proposed label claims), different active substances (with similar indications), different observers and in a sufficient overall number of animals.

The APVMA recommends the use of veterinary-scored rating scales and parameters as primary outcome measures. Client-scored rating scales and parameters can be used as secondary measures. Client-specified outcome measures in which the measures are determined by the client on a case-by-case basis would not be suitable for use in clinical trials due to their inherent variability and difficulty in considering aggregated data. Outcome measures should be pre-determined and standardised prior to commencing the study and applied to all participating clients/owners.

For pain scales to assess surgical interventions, reliable results using different surgical procedures must be included if a broad label claim is proposed.

If baseline measures (parameter values for clinical signs before intervention/start of treatment) are used to identify parameter changes as a result of treatment, the statistical analysis should consider the limitations of results based on such values. Use of unadjusted 'change from baseline' values may bias the results and have less statistical power than using regression to correct for baseline imbalance between groups[2].

Both for treatment of existing clinical signs and for pre-emptive use, and in addition to the primary outcome measures, the following parameters should be reported for each animal:

- The lag time from IVMP administration to the start of the claimed effect:
  - The precise time of administration of the IVMP and reference product(s) and the frequency of observations (after intervention) should be sufficient to enable the detection of the anticipated treatment effects and hence cover the period over which a treatment effect is expected to be perceptible
- The duration of the claimed effect:
  - The length of the observation period and the choice of time points for measurements should be justified
- Other subjective observations (such as demeanour and mobility), if not already part of the chosen rating scale

In addition, the investigator should record and report any observed adverse reaction or other adverse events occurring during the trial. The methods by which any adverse events were investigated, and the results of those investigations, should be documented by the applicant.

5.5. Control groups

Negative controls – To confirm the efficacy and potency and hence support effectiveness of an NSAID, a negative control group should be used (untreated or placebo treated group of animals) in at least one trial, unless there are serious animal welfare implications in using such a group. Use of an untreated or placebo control group is the only way to identify the proportion of animals that are poor or non-responders to treatment, or to detect the level of spontaneous recovery. Untreated or placebo control groups often show substantial improvements over time depending on the nature of inflammatory processes. Potential animal welfare concerns should be carefully considered through the implementation of appropriate exit rules and rescue protocols.

Positive controls – A positive control group should include a substance from the same or a closely related NSAID-class, authorised for the same indication as the proposed veterinary medicine. Design and implementation of studies using a positive control group should be such that its internal validity is assured. A positive control group is not necessary where a negative control group is included in the trial.

When using a positive control group, justify the choice of the comparator, considering the class and target receptor selectivity of the comparator, its approved indications and conditions for use, route of administration and recommended timing and duration of treatment. Time to onset of efficacy, duration of action and safety may also need to be considered, depending upon the study objectives. The use of a positive control in the design and implementation of clinical trials should be such that the internal validity of the study is assured. Assay sensitivity should be able to detect clinically relevant treatment effects and should be such that a study has internal validity

[2] Reference is made to the current 'CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)' (EMA/CVMP/EWP/81976/2010).

and is able to distinguish a clinically relevant treatment effect from a less effective or ineffective treatment (assay sensitivity). The positive comparator must be a fully registered product in either Australia, Canada, Europe, New Zealand, UK, or US.

Choose a statistical analysis that is relevant for either positive or negative controls.

When applying a non-inferiority trial design, the non-inferiority margin[3] must be based on statistical reasoning and clinical judgement. It should be tailored specifically to the particular clinical context. An appropriate non-inferiority margin must provide assurance that the test drug has a clinically relevant effect greater than that if a placebo was used, and that any difference in efficacy between the 2 products will not be a clinically relevant difference.

Relative risks and odds ratios can also be used.

5.6. Experiment/study design

- Clinical trials should be conducted in accordance with the principles of GCP
- The product formulation used in the clinical trials should be identical to that proposed for registration. Evidence demonstrating that product formulation used in the clinical trials is identical to that proposed for registration should be provided (For example: a Certificate of Analysis or batch release protocol for the batch/es used in the study). If a formulation other than the one applied for is used, the relative bioavailability should be demonstrated.
- Indications related to clinical effects should be based on actual trial results in the target species. When designing new studies to support an indication for peri- or post-operative use, the procedure under investigation should be one that is practised and ethically acceptable in Australia
- For a given indication, the study population should be representative of the target population, including breed and age
- The studied primary outcome measures must be representative of the proposed label claims. For example, if the proposed label claim is for anti-inflammatory effects in musculoskeletal disorders in dogs, then a variety of musculoskeletal disorders must be studied in the clinical study
- Justify and fully describe the study design employed and the method(s) of measuring the anti-inflammatory, analgesic, and/or antipyretic effect(s). Primary outcome measures should involve direct measurements of the clinical effect. When measurements of surrogate markers are made (Example: swelling or redness as surrogate markers of inflammation; improved gait as a surrogate marker of analgesia or reduction of inflammation), the correlation between parameters measured and the proposed label claims for the product should be clearly explained in terms of clinical relevance
- Provide a definition for ‘responders’ (that has been defined and verified pre-study) in the study protocol to ensure the clinical relevance of the treatment results. Where the percentage of responders/non-responders is not the primary outcome measure analysis, this should be presented in addition to the primary outcome measure analysis

[3] Reference is made to CPMP Guideline (on the choice of the non-inferiority margin EMEA/CPMP/EWP/2158/99)

- Disease diagnosis – Use and describe sufficiently sensitive examination and evaluation methods to reliably identify the disease condition of the animal if the NSAID is used for treatment of existing clinical signs
- Disease staging – Fully describe a rating system if used for diagnosis and describe the involvement of veterinarians in diagnosis and initial rating severity. The inclusion criteria should be clear and ensure that a well-defined study population is formed for which disease severity is sufficient to allow the determination of a treatment effect
- Other medications – For proposed indications that necessitate the use of a NSAID in conjunction with other medications, design the study to demonstrate the level of therapeutic benefit of the co-medication when used alone compared with administration together with the IVMP. For example, to assess the efficacy of a NSAID used in conjunction with an antimicrobial for the treatment of pneumonia, clinical trials should be performed according to the following design where animal welfare considerations permit: reference group [antimicrobial plus placebo] versus test group [antimicrobial plus IVMP]
- Exclude animals that have had recent medication that may interfere with study results (Example: other NSAIDs, corticosteroids). In addition, exclude animals suffering from medical conditions for which the use of a given NSAID would be contraindicated (for example, renal or hepatic impairment)
- 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. Design clinical studies to ensure the detection and documentation of adverse events
- For peri-operative use, follow renal parameters for at least 21 days after the procedure
- Ensure the statistical analysis is adequately sensitive to detect relevant differences, including subclinical differences

6. Label claims

Wording of the claims must clearly communicate to the end user the expected level of efficacy of the product based on the scientific evidence provided.

In general, inflammation, pain, and pyrexia are 3 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 labelled for the reduction of inflammation, pain and/or pyrexia in disease, and not treatment of the disease (see Table 2 for demonstrated efficacy requirement). Claims for alleviation or reduction (partial control/prevention) should include a percentage reduction in the incidence of the disease, the reduction in pain, inflammation and/or pyrexia of the specific disease or condition.

Table 2: Appropriate label claims with corresponding demonstrated efficacy requirement

Claim	Demonstrated efficacy: lessening of pain, improvements in inflammation clinical signs (redness, swelling), reduction in fever
Controls	≥ 80% of animals in a treatment group demonstrate a clinically relevant reduction (from pre-treatment) in clinical signs associated with pain, inflammation, and/or fever and show no or very mild clinical signs after treatment. A clinically relevant reduction (from pre-treatment) in clinical signs associated with pain and inflammation would be at least a pre-defined 1-point reduction in a 5-point rating scale or a 2-point reduction in a 10-point rating scale. This is in addition to demonstrating statistically and clinically significant comparisons with negative and/or positive controls. Non-inferiority with positive controls should be demonstrated.
Reduces	≥ 80% of animals in a treatment group demonstrate a clinically relevant reduction (from pre-treatment) in clinical signs associated with pain, inflammation, and/or fever. A clinically relevant reduction (from pre-treatment) in clinical signs associated with pain and inflammation would be at least a pre-defined 1-point reduction in a 5-point rating scale or a 2-point reduction in a 10-point rating scale. This is in addition to demonstrating statistically and clinically significant comparisons with negative and/or positive controls. Non-inferiority with positive controls should be demonstrated.
Prevents (for pre-operative and peri-operative analgesia)	≥ 80% of animals in a clinical trial show no, or only mild, clinical signs that would normally be associated with pain and inflammation expected from surgery. This is in addition to demonstrating statistically and clinically significant comparisons with negative and/or positive controls. Non-inferiority with positive controls should be demonstrated.
Alleviates	Between 60 and 80% of animals in a clinical trial demonstrate a clinically relevant reduction (from pre-treatment) in clinical signs associated with pain, inflammation and/or fever. This is in addition to demonstrating statistically and clinically significant comparisons with negative and/or positive controls. Non-inferiority with positive controls should be demonstrated.
May aid in the control/prevention/reduction	Where specific clinical trials may not be performed but adequate evidence[4] is provided of a likely reduction in pain, inflammation or fever.

[4] Adequate evidence would include use of an APVMA-approved active constituent that is not Schedule 4 and may include documented traditional use for the purpose claimed supported by reputable published scientific data. Testimonials are not considered reputable, published scientific data.

Where adequately supported by data, a ‘combination’ claim would be supported (Example: Control of mild pain, reduction of severe pain and reduction of inflammation).

Most studies incorporate pyrexia into a ‘clinical score’ for inflammation. Allowing a claim for treatment of inflammation based on reduction of pyrexia alone is not appropriate.

We recommend that labelling 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 labelling unless you have conducted long-term safety and/or effectiveness studies during the registration process. Given the long-term nature of many inflammatory conditions, you should indicate the length of assessment of clinical signs and adverse events in clinical studies in your labelling descriptions.

Acronyms and abbreviations

Shortened term	Full term
COX	Cyclooxygenase
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IC	Inhibitory Concentration
IVMP	Investigational Veterinary Medicinal Product
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
PD	Pharmacodynamic
PK	Pharmacokinetic
VAS	Visual Analog Scales

References

Lees P, Giraudel J, Landoni MF and Toutain PL (2004) 'PK–PD integration and PK–PD modelling of nonsteroidal anti-inflammatory drugs: principles and applications in veterinary pharmacology' *Journal of Veterinary Pharmacology and Therapeutics* 27(6):491-502.