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GUIDELINE FOR THE CONDUCT OF EFFICACY STUDIES FOR NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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GUIDELINES FOR THE CONDUCT OF EFFICACY STUDIES FOR NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

1. INTRODUCTION

1.1 The general aim of this document is to provide information and guidance on trial and reporting standards for efficacy studies submitted in support of an application to register a non-steroidal anti-inflammatory drug (NSAID), or to vary the indications of a registered NSAID.

1.2 It is recognised that there are acceptable methods, other than those described in these guidelines, that are capable of achieving the principles of this document. If in a particular circumstance, it is deemed necessary to deviate from the guidelines outlined in this document, a reasoned argument for the deviation should be submitted with the application.

1.3 For the purposes of this guideline, NSAID will be defined as that group of acidic anti-inflammatory agents which inhibit the enzyme which catalyses the conversion of arachidonic acid into prostaglandins and thromboxane. 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.

1.4 The extent of clinical usage and the range of indications for NSAIDs have increased in recent years such that it is not possible to provide detailed guidance on efficacy studies to account for all proposed indications. This document will focus on recognised pharmacological actions with potential therapeutic benefit such as anti-inflammatory, analgesic, anti-pyretic, anti-endotoxic or anti-thrombotic effects, but may be extended, where appropriate, to studies aimed at demonstrating the efficacy of a NSAID product involving other modes of pharmacological action.

1.5 When conducting efficacy studies for NSAIDs, due consideration must be given to the potential adverse effects resulting from their use, in particular, when such products have a proposed indication for long-term therapy.

1.6 This note should be read together with the note for guidance on good clinical practice for the conduct of clinical trials and the note for guidance on biostatistical methodology in clinical trials and, where appropriate, the note for guidance on investigation of chiral active substances.

2. OBJECTIVES

The objectives of this guideline are:

- To assist investigators in designing pre-clinical and clinical trials to demonstrate the efficacy of a non-steroidal anti-inflammatory drug and in targeting precise indications for product use.

- To optimise the number of trials performed, thereby avoiding the unnecessary use of experimental animals.

3. GENERAL REQUIREMENTS

3.1 The efficacy of the product should be investigated in the target species. Pre-clinical data gathered from investigations in species other than the target species may be submitted as supportive data, if appropriate. Traditional pharmacokinetic 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.

3.2 Claims for efficacy should be based on a documented NSAID effect, demonstrated by both *in vitro* studies and controlled experimental (*in vivo*) studies, and should be supported by field studies in the target species.

3.3 The proposed route of administration, dosage and frequency of administration of the test product should be described and justified using appropriate data. In addition, any claims for prolonged duration therapy should be supported by appropriate safety and efficacy data. For products with a proposed indication for peri-operative use, the time of administration of the test product (that is, either pre-, during or post-surgery) may influence efficacy or safety. Therefore, claims for use peri-operatively should specify the appropriate time of administration of the test product which in turn should be supported by appropriate data.

3.4 Where a dose range for a given indication is stated on the label, it should be justified by appropriate efficacy data (for example, pre-clinical, dose confirmation studies or field trial data).

3.5 Appropriate statistical methods should be used (see note for guidance on biostatistical methodology in clinical trials).

3.6 For all studies, allocation of test subjects to treatment groups should be randomised. The method of randomisation should be stated and justified. Allocation of treatments (either no treatment, placebo, reference product or test product) should be blinded. Full blinding methods are encouraged, and justification is required if such methods are not employed.

3.7 All analytical methods (for chemical parameters) used during the course of pre-clinical studies should be appropriate and validated. For field studies, such methods should be appropriate and validated or, at least, accompanied by appropriate quality controls.

4. SPECIFIC REQUIREMENTS

4.1 Pre-clinical studies

4.1.1 The principles of good laboratory practice [GLP] (or good clinical practice [GCP], where appropriate) should apply to pre-clinical studies, in particular pivotal pre-clinical studies, and sponsors should work within the principles of GLP (or, GCP) recommendations.

4.1.2 If a developmental product/formulation is used in pre-clinical studies, the relevance of the difference between the test product and the final formulation should be documented. Dose confirmation and target animal tolerance studies should be conducted with the final formulation or any deviation should be justified. If bioequivalence has been shown, studies which use a formulation other than the final formulation can be used to support efficacy.

4.1.3 For dose determination studies, the range of doses used should be selected on the basis of preliminary studies. A minimum of three different doses should be included, the central dose being the expected recommended dose. Selection of the higher doses in such studies should take into account the safety margin of the product under investigation. The reason for the doses

selected should be explained. Where possible, dose determination studies should incorporate not only the dose itself, but for a given indication, the intended dosing frequency.

Dose confirmation studies should be performed for each claim. The absence of such studies for a specific claim should be adequately justified.

4.1.4 The experimental design employed and the method(s) of measuring the NSAID effect should be fully described and justified by the applicant. The effect may be measured directly or indirectly. When indirect measures are made, the correlation between parameters measured and the NSAID effect of the product should be clearly explained in terms of clinical relevance.

4.1.5 A form of negative control should be used. Preferably this should be an untreated group of animals, unless such is not acceptable on animal welfare grounds. In certain situations, a crossover design is suitable with each animal acting as its own control. For crossover studies, it should be demonstrated that the treatments and/or the manipulations administered to the test animals in the first period do not influence the outcome of the second period of the study. The washout period between treatments in a crossover study should take into account the known pharmacokinetics of the NSAID used. In addition to systemic data, it may be appropriate to take into account the pharmacokinetics in tissues/exudate.

4.1.6 The method of evaluating the disease condition of the study animals should be appropriate and fully described (*see examples 1*). If a grading system is used for evaluating the disease condition, the grading criteria should be described (*see examples 2*).

4.1.7 Study animals should be free of the effects of medication that may interfere with study results (e.g. other NSAIDs, corticosteroids).

4.1.8 The following parameters should be reported for each animal

- the lag time from drug administration to the start of the NSAID effect.
- the duration of the NSAID effect
- the extent to which the NSAID was effective
- subjective observations (such as demeanour, pain, mobility) by the investigator. In addition, the investigator should record and report any observed suspected adverse drug reactions (e.g. blood in faeces) 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.

If a grading system is used to determine efficacy, the grading criteria should be explained in terms of clinical recovery (*see example 3*). In order to reduce variability, observations should be made by the same person.

4.2 Field studies

4.2.1 Field studies must be conducted in accordance with the principles of good clinical practice (GCP).

4.2.2 The product formulation used in the field studies should be identical to that proposed for registration. If bioequivalence has been shown, studies which use a formulation other than the final formulation can be used to support efficacy.

4.2.3 At least one field study should be performed for each claim. The experimental design employed and the method(s) of measuring the NSAID effect should be justified and fully described by the applicant. The effect may be measured directly or indirectly. When indirect measures are made, the correlation between parameters measured and the NSAID effect of the product should be clearly explained in terms of clinical relevance.

4.2.4 A control group must be included. If a positive control group is used, the choice of reference product should be justified taking into account the indications for use, the chemical similarity to the test product, route of administration and recommended timing and duration of treatment.

4.2.5 For proposed indications that necessitate the use of a NSAID in conjunction with other medications, it is necessary that the study is appropriately designed to demonstrate the therapeutic benefit of the NSAID alone. For example, in order to assess the efficacy of a NSAID used in conjunction with an antimicrobial for the treatment of pneumonia, field studies should be performed according to the following design: Reference Group [antimicrobial plus placebo] versus Test Group [antimicrobial plus test product].

4.2.6 For a given indication, the study population should be representative of the target population.

4.2.7 Study animals should be free of the effects of medication that may interfere with study results (e.g. other NSAIDs, corticosteroids). In addition, animals suffering from medical conditions for which the use of a given NSAID would be contraindicated (for example, renal, hepatic impairment) should be excluded from study. Due to increased risk of toxicity in hypovolaemic animals, suitable precautions should be taken (for example, intensive monitoring, appropriate fluid replacement therapy) when such animals are included in these studies.

4.2.8 The method of diagnosing the disease condition of the study animals should be appropriate and fully described (*see examples 1*). This should include steps taken to rule out other causes of the disease. If a grading system is used for diagnosis, the grading criteria should be fully described (*see examples 2*).

4.2.9 The following parameters should be reported for each animal

- the extent to which the NSAID was effective
- subjective observations (such as demeanour, pain, mobility) by the investigator.
- any observed suspected adverse drug reactions (e.g. blood in faeces) or other adverse events occurring during the trial.

If a grading system is used to determine the extent of efficacy, the grades used should be explained in terms of clinical recovery (*see examples 3*). Where it is practical, observations should be made by the same person. Data gathered by an animal owner is important, in particular, for monitoring low grade chronic pain, but can only be used as secondary efficacy data.

A record should be kept of all concurrent medication and interactions with other medicinal products prescribed concurrently should be looked for during clinical trials. Where there is reason to suspect that interactions may occur with commonly used medicinal products, specific studies to investigate the mechanism/effects of the interaction should be undertaken.

4.2.10 The time points for measurement of the beneficial effects of treatment in field cases should be explained and justified. Depending on the claim, consideration should be given to performing post-treatment measurements after the effects of medication would be expected to have ceased, to assess final outcome (for example, in cases of field studies on bovine respiratory disease). The choice of time point for measurements post therapy should be explained and justified.

Examples 1: Method of evaluating the Disease Condition

The method of evaluating the disease condition of the study animals should be appropriate and fully described.

Parameters to be measured depend on the proposed indication(s) for use of the product. While it is accepted that it is not possible to provide detailed guidance on efficacy studies to account for all proposed indications, what follows are examples of what may be considered as appropriate parameters when attempting to evaluate efficacy of a NSAID for a number of specific indications. It must be emphasised that inclusion of a particular end-point under 'assessment of acute pain', for example, does not mean that it will always be appropriate to use it when assessing the analgesic effect of a NSAID. Furthermore, inclusion of particular end-points in the following examples is not meant to imply that these end-points are likely to be more appropriate than possible alternatives.

Example 1(a). Assessment of acute pain (for example, post-surgery)

1. Unidimensional pain rating scales (attempt to assign a score to intensity of pain based on behavioural signs displayed by the animal under observation)

Simple descriptive scale	e.g. no pain/mild/moderate/severe pain
Numerical rating scale	ordinal scale, 0 to 10

2. Multidimensional pain rating scale

Semi quantitative pain rating scale.
Chose a variety of categories, e.g. demeanor, posture, mobility, attention to painful area and response to touch.
Define expressions within each category and allocate a score to each expression, e.g.

demeanor	excitable (0), alert (1), subdued (2), very subdued (3)
posture	normal (0), hunched/ tense (1), rigid (2)

It may be appropriate to 'weight' expressions. Composite score will then serve as a semi quantitative measure of pain intensity.

3. Other physiological signs — e.g. heart rate, respiratory rate.

Example 1(b). Assessment of Lameness

1.	Unidimensional pain rating scales (attempt to assign a score to intensity of lameness based on behavioural signs displayed by the animal under observation)	
	Simple descriptive scale	e.g. no lameness, mild, moderate, severe lameness
	Numerical rating scale	
2.	Multidimentional lameness rating scale	Semi quantitative pain rating scale as described above, suitable categories in this instance may include demeanor, activity, lameness, pain on palpation, pain on manipulation, mobility of joint, swelling.
3.	Chemical parameters	may include concentrations of active substance/relevant inflammatory mediators in synovial fluid /inflammatory exudate.
4.	Cytological parameters	may include differential white cell counts in synovial fluid/inflammatory exudate.
5.	Quantitative measures of lameness	may include force plate analysis of gait, kinematic analysis of gait (e.g. digital analysis of gait or goniometry).

Example 1(c). Assessment of Anti-Pyretic Effect

Pre-clinical study
E.-coli endotoxin-induced fever model

1.	Clinical parameters	rectal temperature

Example 1(d). Assessment of Acute Inflammatory Process

Example (a) - Pre-clinical study
Implantation of carrageenan sponges into subcutaneous pouches

1.	Clinical parameters	Lesion swelling
2.	Chemical parameters	may include concentrations of active substance/relevant inflammatory mediators in inflammatory exudate.
3.	Cytological parameters	may include differential white cell counts in inflammatory exudate.

Example (b) - Field study
Spontaneously occurring bovine respiratory disease

1.	Clinical parameters	rectal temperature demeanor character of respiration daily feed intake weight gain mortality
2.	Histopathological parameters	lung pathology

Examples 2: Evaluating the Disease Condition using Grading Systems

If a grading system is used for evaluating the disease condition, the grading criteria should be described (see examples 2).

Lameness Score for Dogs

Score	Description	
0	normal	no lameness
1	slight	limp visible, but dog unconcerned and will exercise normally
2	moderate	obvious limp present all of the time, dog having some difficulty with exercise.
3	severe	dog barely weight bearing/not weight bearing

Pain on palpation

Score	Description	
0	normal	no response to firm pressure
1	slight	digital pressure at site of lesion induces slight avoidance movement
2	moderate	digital pressure at site of lesion induces definite limb withdrawal
3	severe	attempted digital pressure induces marked withdrawal

Example 3: Evaluating the Extent of Efficacy using Grading Systems

If a grading system is used to determine the extent of efficacy, the grading criteria should be explained in terms of clinical recovery (see example 3).

Clinical evaluation (response to treatment)	Description
Excellent	no detectable lameness, animal returned to normal activity
Good	marked reduction in lameness, but not completely resolved
Fair	only slight reduction in lameness
Poor	no improvement, condition worsened