EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2021
EMA/CVMP/EWP/1061/2001-Rev.1*
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs

Adoption of guideline by Committee for Medicinal Products for Veterinary Use (CVMP)	15 January 2014
Revised guideline (revision 1) agreed by Efficacy Working Party (EWP-V)	June 2021
Adoption by CVMP	15 July 2021
Date for coming into effect	28 January 2022

This guideline replaces the guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001).

Keywords	***Veterinary medicinal products, non-steroidal anti-inflammatory drugs, efficacy***

*The current revision consists of administrative changes made in order to align the guideline to the new definitions and terminology provided by Article 4 of Regulation (EU) 2019/6. The references to the legislation applicable and other scientific guidelines have also been updated. As no changes were made to the scientific content, no concept paper and no public consultation were deemed necessary.

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Executive summary

The objective of this guideline is to specify recommendations for the design, conduct, and evaluation of studies for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) to be provided in support of an application to register a new NSAID, or to vary the indications of an already authorised NSAID. The guideline provides recommendations on how to demonstrate the pharmacological characteristics for the NSAID under study through pre-clinical studies as well as how to appropriately demonstrate clinical efficacy and safety through clinical trials where the selection of control and efficacy endpoints is regarded as key issues for obtaining conclusive information.

1. Introduction (background)

NSAIDs have become an important class of veterinary medicines for most mammalian animal species. 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 only focus on recognised pharmacological actions with potential therapeutic benefits of anti-pyretic, analgesic, anti-inflammatory or anti-thrombotic effects in the first place. Studies aimed at demonstrating other effects, involving other modes of pharmacological action and resulting in other therapeutic benefits (e.g. antitumour effects in tumours which express COX enzymes) should also consider other appropriate guidelines (e.g. CVMP Guideline on dossier requirements for anticancer medicinal products for dogs and cats (EMA/CVMP/28510/2008)).

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 cyclo-oxygenase (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.

2. Scope

The general aim of this guideline is to provide information and guidance on trial design and conduct, as well as on reporting standards for efficacy studies submitted in support of an application to authorise a new NSAID, or to vary the indications of an already authorised NSAID.

The 3R principles (replacement, refinement and reduction) should be applied, in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on the protection of animals used for scientific purposes.

It is recognised that there may be acceptable methods, other than those described in this guideline, that are capable of achieving the principles set out in this document.

If in a particular circumstance it is deemed necessary to deviate from recommendations outlined in this document, a reasoned argument for the deviation should be submitted with the application.

3. Legal basis

This guideline should be read together with Regulation (EU) 2019/6. Applicants should also refer to other relevant European and VICH guidelines, including those listed in the reference list of this document.

4. 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 target species. The proposed route of administration, dosage (or dose range), frequency and duration of administration of the investigational veterinary medicinal product (IVMP) should be described and justified using appropriate data.

The duration of clinical trials should encompass the entire recommended treatment period for treatments of short duration. In case of long-term administration, the duration of clinical trials should be sufficient and particular attention must be given to the potential adverse effects resulting from such use.

Appropriate statistical methods should be used.

For all studies, the allocation of test animals to treatment groups should be randomised. The method of randomisation should be stated and justified. Blinding methods and allocation concealment are encouraged and justification is required if such methods are not employed.

All analytical methods (for clinical pathology tests) used during the course of pre-clinical studies should be appropriate and validated. For clinical trials, examination and observation methods should be appropriate to warrant adequate assay sensitivity.

The principles of good laboratory practice (GLP) or good clinical practice (GCP), where appropriate, should be applied.

5. Pre-clinical documentation

5.1. 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 e.g. *in vitro, in vivo* and *ex vivo* designs. Regardless of the experimental design employed and the method(s) of measurement, the NSAID effect should be fully described and justified by the applicant.

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 (e.g. reduction of pyrexia) or via surrogate markers (e.g. cortisol). When surrogate markers are used their correlation to the clinical effect of the product should be clearly explained in terms of clinical relevance.

5.2. Pharmacokinetics

In the context of dose-response relationships, pharmacokinetic 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. Pharmacokinetic studies also support the determination and confirmation of the treatment dose as well as dosing frequency and interval (see section 5.3, PK/PD). It is noted that 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. 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 species, and care should be taken when interpreting pharmacokinetic data extrapolated from other species. Therefore, while such studies might provide useful supportive data, pivotal pharmacokinetic studies should be carried out in the target animal species. Pharmacokinetic data could also be useful to explore potential influence of external factors (e.g. feeding) on exposure, if such a relationship is expected.

5.3. PK/PD

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.

The validity of any PK/PD model study used has to be ensured in every essential aspect. The appropriateness of the pharmacodynamic parameter(s) included would have to be justified in relation to the claimed effect, as well as the sampling frequency and sampling duration.

The cut-off limits used to reflect sufficient effect (e.g. EC_{50} or IC_{50}, EC_{80} or IC_{80}) should be justified. Furthermore, the accuracy of any simulations of anticipated effects for various dosage regimens should be ensured e.g. by demonstrating that dose linearity and exposure seen in experimental animals corresponds with that seen in the target animals, for any particular dose.

5.4. Dose determination

Dose-determination studies should be conducted in the target species using a range of doses selected on the basis of 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 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 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 (see section 5.3). Fewer than three doses may be used in such a study providing that a sufficient exposure range is covered.

5.5. 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 has been used in the dose confirmation study, the results could still be valid, provided bioequivalence to the final formulation is demonstrated.

6. Clinical documentation

6.1. Selection of primary and secondary endpoints

Selection of appropriate primary and secondary endpoints concerns both pre-clinical studies and clinical trials. Primary and secondary endpoints should be clearly stated and defined in advance.

When selecting appropriate endpoints, consideration must be given to the aim of the treatment. For example, relevant endpoints for treatment of existing clinical signs may differ from relevant endpoints for pre-emptive use (e.g. for peri-operative analgesia).

Whenever possible, efficacy assessment should be based on objective endpoints. The selected primary parameters should quantify the changes induced by treatment in a meaningful way, meaning that changes in magnitude can be interpreted for their clinical relevance. If objective endpoints cannot be used, subjective assessment methods may be acceptable, provided their validity can be justified and sufficient blinding is applied. In order 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.

If rating scales are used, it is recommended to use methods that have been used on a wider scale, and which are preferably based on a validated method and supported by peer reviewed literature.

Rating scales can take the form of visual analogue scales, numerical rating scales, and simple descriptive scales. Any rating scale used must be reliable (minimal inter-observer variation), sensitive (able to detect small enough variations in clinical responses to identify clinically relevant differences in treatment effect) and must measure parameters which are clearly and directly related to treatment effect. To be considered validated, these aspects should usually have been established for different breeds, different active substances (with similar indications), different observers and in a sufficient overall number of animals. For scales such as pain scales, it is also important that reliable results have been obtained with different surgical procedures, if applicable.

If baseline values (parameter-values for clinical signs before intervention/start of treatment) are used to identify parameter changes as a result of treatment, limitations in statistical evaluation of results based on such values should be taken into account. Use of unadjusted "change from baseline" in the analysis might bias the result and will have less statistical power than using regression to adjust for baseline imbalance between groups (inclusion of baseline value as a covariate in the analysis). Reference is made to the current "CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)" (EMA/CVMP/EWP/81976/2010).

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

- the lag time from IVMP administration to the start of the NSAID effect,
- the duration of the NSAID effect,
- 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.

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 length of the observation period and the choice of time points for measurements should be justified.

6.2. Type of Control

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. 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. Potential animal welfare concerns should be carefully taken into account through the implementation of appropriate exit rules and rescue protocols. The positive control should be included, using a substance from the same or a closely related NSAID-class, authorised for the same indication as the IVMP. Design and implementation of studies using a positive control group should be such that its internal validity is assured. Clinical trials could include a negative control or a positive control group as a reference (see section 7.1).

7. Clinical trials

7.1. Efficacy

Clinical trials should be conducted in accordance with the principles of good clinical practice (GCP).

The product formulation used in the clinical trials should be identical to that proposed for marketing authorisation. 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 practised and ethically acceptable in the EU.

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

At least one clinical trial should be performed for each claim. The study design employed and the method(s) of measuring the NSAID effect(s) should be justified and fully described by the applicant. The effects may be measured directly or using surrogate markers. Primary endpoints should, however, usually involve direct measurements of the clinical NSAID effect. When measurements of surrogate markers are made, the correlation between parameters measured and the NSAID effect of the product should be clearly explained in terms of clinical relevance.

A pre-defined definition for "responders" should be provided in the study protocol to ensure the clinical relevance of the treatment results. Where the percentage of responders/non-responders is not the primary endpoint analysis this should be presented in addition to the primary endpoint analysis. If the NSAID is used for treatment of existing clinical signs (vs. pre-emptive treatment), examination and evaluation methods used in the study should be sufficiently sensitive to reliably identify the disease condition of the animals, and should therefore fully be described.

If a grading system is used for diagnosis, the grading criteria should be fully described. 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 and the changes induced by treatment (see also section 5.1).

A control group should be included. When using a positive control group, the choice of the comparator should be justified, taking into account the class and target receptor selectivity of the comparator, its 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. Design and implementation of clinical trials using a positive control group should be such that its internal validity is assured. Assay sensitivity should be able to detect clinically relevant treatment effects and should be such that a study has internal validity and is able to distinguish a clinically relevant treatment effect from a less effective or ineffective treatment (assay sensitivity).

When a non-inferiority trial design is applied, the non-inferiority margin should be based on statistical reasoning and on clinical judgment, and should be tailored specifically to the particular clinical context (see CVMP/EWP/81976/2010). An appropriate non-inferiority margin must provide assurance that the test drug has a clinically relevant effect greater than zero (placebo), and that any difference in efficacy between the two products will not be a clinically relevant difference. Reference is made to CPMP Guideline (on the choice of the non-inferiority margin EMEA/CPMP/EWP/2158/99).

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 level of therapeutic benefit of the co-medication when used alone compared with administration together with the IVMP. For example, in order 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].

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 or hepatic impairment) should be excluded from the study.

7.2. Clinical safety

When conducting clinical trials for NSAIDs, detailed safety monitoring should be implemented as the margin of safety can be relatively small.

If a dose range is used, a description of the relationship between the actual dose and observed adverse effects should be provided, if relevant.

Definitions

Assay sensitivity
The ability to distinguish an effective treatment from a less effective or ineffective one, on the basis of specific examination and observation methods within a given study design.
In non-inferiority or equivalence trials with two active arms only, assay sensitivity implies that if a placebo could have been included then both active treatments would have been superior to placebo. Generally, assay sensitivity is inferred from previous studies.

Baseline value
A value attributed to an observation that represents the normal or beginning level of a quality or condition and that is used for comparison with values representing the response to an intervention/treatment, implying that baseline and response values refer to the same individual or disorder (type, seriousness and diagnostic method).

Clinical pathology:
Haematology, clinical chemistry and urinalysis.

EC_{50}, EC_{80}
Effective concentration: the concentration of a drug which gives rise to a specified percentage (50%, 80%) of the maximum effect/response, commonly used as a measure of potency.

IC_{50}, IC_{80}
Inhibitory concentration: the concentration of a drug which gives rise to a specified percentage (50%, 80%) of the maximum inhibitory effect.

***Ex vivo / in vitro* study**
Experimentations or measurements carried out on viable tissue or blood samples outside an animal, under artificial conditions but with minimum alteration to the sample (e.g. determination of IC_{50} thromboxane/IC_{50} prostaglandin ratio's in blood).

IVMP
Investigational veterinary medicinal product.

Pre-emptive use
Any use of a medicinal product before an intervention/exposure to induce an effect that should prevent or mitigate the consequences of such intervention/exposure (e.g. pre-operative administration of an NSAID to induce post-operative analgesia).

Non-responder
Animal in which administration of an IVMP (e.g. NSAID) does not cause an effect of a magnitude that would qualify the animal to be regarded a responder, according to the pre-determined definition of responder.

Rescue treatment
Treatment measures taken on the basis of appearance and/or deterioration of clinical signs to an extent which is unacceptable for animal welfare reasons in animals (e.g. untreated or placebo treated). Rescue treatment is generally incorporated into studies in which the beneficial effect of treatment with a medicinal product is evaluated.

Responder
Animal in which administration of an IVMP (e.g. NSAID) produces a certain pre-specified magnitude of effect in any appropriate endpoint or combination of endpoints. The endpoint(s) should be well suited to reflect the aspired effect of treatment and the pre-determined cut off level should reflect a clinically relevant level of effect. This aspect needs to be justified beforehand.

References

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes

CVMP Guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/1999)

CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000)

VICH GL9: Guideline on Good Clinical Practices (CVMP/VICH/595/1998)

OECD Principles on Good Laboratory Practice

CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)

CPMP Guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99)

CVMP Guideline on dossier requirements for anticancer medicinal products for dogs and cats (EMA/CVMP/28510/2008)