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4 Guideline on the demonstration of palatability of 5 veterinary medicinal products

6 Draft

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Guideline on the demonstration of palatability of veterinary medicinal products

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Executive summary

The objective of this guideline is to specify requirements for the design, conduct, and evaluation of palatability studies for all oral dosage forms of pharmaceutical veterinary medicinal products (VMP) where palatability is claimed or regarded necessary as part of the efficacy evaluation.

1. Introduction (background)

In order to facilitate successful administration of veterinary medicinal products for oral use in individually treated animals, voluntary uptake is beneficial. Applications for a specific claim for palatability can be made for new or existing oral dosage forms of veterinary medicinal products (VMP).

Flavouring components are often added to veterinary medicinal products to improve the palatability and to enhance the voluntary uptake of the VMP by the animal. In case improved palatability is claimed for such products this needs to be supported by appropriate studies whereas reference only to composition will not be sufficient to grant a palatability claim.

A palatability claim is only relevant for oral dosage forms intended for individual treatment.

For oral formulations intended for group treatment, correct uptake of the medicated food or water is a prerequisite for sufficient exposure and thus effective treatment. For an original product, adequate uptake is confirmed indirectly through clinical efficacy and safety studies or directly through the measuring of feed and water intake. Since sufficient palatability is a prerequisite for efficacy, a specific palatability claim will not be relevant. However, for a generic oral formulation intended for group treatment palatability may have to be taken into account in the assessment of similarity to a previously authorised product. Notably, a palatability claim would not be relevant neither for the original products nor for the generics.

The terms “palatability”, “voluntary acceptance”, and “compliance” are defined in section “Definitions”.

2. Scope

The aim of this guideline is to provide recommendations regarding the design, conduct, and evaluation of studies for the demonstration of palatability of veterinary medicinal products intended for individual or group animal treatment. This guidance document is intended to address the requirements for the approval of palatability claims for new oral formulations and also for existing products reformulated to improve palatability.

The guideline does not cover situations where the safety and/or efficacy profiles are impacted by changes in the palatability. In those cases additional data may be required and the applicant is recommended to seek scientific advice and when necessary refer to Regulation (EC) No 1234/2008.

3. Legal basis

This document should be read in conjunction with Directive 2001/82/EC. Applicants should also refer to other relevant European and VICH guidelines, including those listed among the references at the end of this document.

4. General considerations

Palatability is influenced by the smell and taste of the product, and also by its more immediate physical characteristics (e.g. shape, size, texture, hardness, colour). Since the palatability of a product cannot

be claimed based solely on its composition (flavourings, sweeteners and/or masking agent) and its formulation, palatability will have to be demonstrated in appropriate *in vivo* studies.

Voluntary acceptance of a veterinary medicinal product may differ between animals kept under controlled and field conditions. Voluntary acceptance may also differ between healthy and sick animals which may suffer a reduced appetite or altered perception of taste. If the voluntary acceptance of a formulation is good, most of the animals will voluntarily ingest the complete dose throughout the entire course of therapy. This will improve treatment administration and treatment compliance.

Palatability of veterinary medicinal product in one species may not be extrapolated to another species. In addition palatability may differ between breeds and vary depending on individual factors such as health status. Nutritional peculiarities and anatomical differences might play a major role in the difference between species or breeds. Therefore, it is important to test the palatability in animals which are representative of the target population for the VMP.

5. Applications where palatability studies are requested

Palatability data should be provided in following applications for which an applicant claims palatability:

- New VMPs intended for individual treatment,
- Changes in formulation of existing VMPs to improve palatability,
- Generic VMP applications regarding formulations intended for individual treatment. Studies may be waived if the generic product is qualitatively and quantitatively comparable to the reference product.

For generic VMPs intended for group treatment palatability data have to be provided to support similar exposure as compared to the reference product, unless otherwise justified.

6. Type of study

For new and existing products, palatability should preferably be evaluated in the target population under field conditions for the sake of the representativeness.

For new products, palatability could be demonstrated as part of the pivotal clinical field study performed for the purpose of demonstrating efficacy. Such field trial should comply with the VICH GL on Good Clinical Practice (GCP).

For a new claim to existing products, and for generic products claiming palatability and which are intended for individual treatment, palatability may however also be evaluated in healthy target animals under controlled conditions following the principles of GCP or Good Laboratory Practice (GLP), if justified. However, it should be ensured that the study outcome is valid for the target population (see section 7).

7. Study design

7.1. Study design for products intended for individual treatment

The palatability of an investigational veterinary medicinal product (VMP) should be demonstrated by comparing its voluntary acceptance rate to a threshold (one-group test).

Generally, measures should be taken to ensure that the study outcome is relevant for the target population. Several factors might affect the voluntary acceptance of the product by an animal such as conditioning, breed, number of administered tablets/quantities of paste/solution, evolution of the disease, feeding behaviour, and memory of a product's taste. The impact of some of these factors may

change over time. Therefore, the palatability should be assessed during the entire course of short-term treatments and/or for approximately 14 days in case of long-term treatments.

7.1.1. Assessment of voluntary acceptance

The product should be administered following the instructions according to the study protocol and at the posology as specified in the SPC. The voluntary acceptance of each animal should be assessed at each dose administration, or at predefined time points, if justified.

For assessing the acceptance of the test product, it could be offered in the following pre-determined order: First, it may be offered in an empty bowl or trough, or on the ground to assess voluntary acceptance during 30 seconds. In case of failure, the product could be offered by hand for an additional 30 seconds, such that the maximum total offering time is one minute. This basic presentation scheme should be adapted according to the species and to the pharmaceutical form of the product.

7.1.2. Primary and secondary endpoints

The **primary endpoint** is based on success which is defined as voluntary full consumption within the maximum offering time (e.g. one minute).

Failure might be of different types as follows:

1. Delayed uptake although complete consumption (time to be defined in the protocol),
2. Partial intake,
3. Regurgitated or spitting out of the product,
4. Consumption only when hidden in food/water,
5. Forced intake by placing the product into the mouth and making sure the animal swallows,
6. Refusal

In individual treatment, the statistical unit is the individual animal.

The **primary endpoint** is the overall voluntary acceptance rate which is calculated for the entire period as:

$$\frac{\text{Number of all successful dosings}}{\text{Number of all dosings}} * 100\%$$

As **secondary endpoint**, the following parameters could be considered:

- Individual voluntary acceptance rate calculated for the entire period for each animal as:

$$\frac{\text{Number of all successful dosings of the animal}}{\text{Number of all dosings of the animal}} * 100\%$$

  - Average voluntary acceptance rate calculated for each time point throughout treatment period. Changes in the acceptance over time provide information about the overall compliance with the dose regimen, which is of particular interest in case of long term treatment.
  - Time to consumption,
  - Scoring of ease of administration, with a scoring system appropriately chosen for the specific formulation,

– Rates of the different failure types 1 to 6 as defined above.

7.1.3. Criteria to grant a palatability claim

To be granted a palatability claim, the overall voluntary acceptance rates should at least reach the threshold of 80 % in dogs, and 70 % for all other species. The threshold should be reached in a group of at least 50 animals in case the product is administered only once, and in a group of at least 25 animals in case of multiple administrations.

7.2. Products intended for herd or group treatment

The uptake of water or feed is a prerequisite to ensure adequate therapeutic exposure to formulations intended for group treatment. Sufficient consumption of an originator product is already ensured by clinical efficacy and safety studies in diseased animals. Sufficient effect and acceptable treatment failure ratios ensures that intake, and thus exposure, is appropriate among treated animals. Thus, specific palatability studies are not required if efficacy has been demonstrated and a palatability claim is not relevant.

In case of generic products for which no clinical efficacy and safety data is required, data are necessary to demonstrate similar consumption as compared to the reference product, unless otherwise justified (qualitatively and quantitatively comparable formulations).

The trial may be performed under experimental conditions using healthy animals where the measurement of water and feed consumption can be made at the pen/room level. The statistical unit would be the pen/room. The groups (test and reference) may be compared in a parallel or in a cross-over design. Due to high variability linked to different factors when it comes to feed and water consumption, special attention should be paid to the randomisation and to the comparability of groups before treatment. The animals included in the study should represent the target group for treatment with regard to factors that may influence intake, such as age, gender and weight. Furthermore, they should be housed according to common practice in the field. Baseline value of body weights and water/feed consumption should be established before randomisation to evaluate the comparability of treatment groups.

The palatability should be tested at the posology as specified in the SPC. The palatability test should be repeated for an appropriate number of times within each test group to obtain a good estimate of the consumption and its variability. The sample size of each test group and the number of repetitions has to be calculated and presented in the protocol.

The primary endpoint is the mean daily water or feed consumption per kg of bodyweight (for water soluble or feed treatment) for the whole treatment duration. Those means should comply with normal physiological levels.

The group means and the 95 % confidence interval of their difference should be calculated and compared to a pre-defined and justified non-inferiority margin. The statistical method should be planned ahead before start of the trial.

8. Palatability claim in the SPC

If palatability has been demonstrated as defined in this guideline, it can be mentioned in the SPC. This information should be included in the section 4.9 (amounts to be administered and administration route).

No palatability claim is acceptable for products intended for herd or group treatment.

Definitions

For the purpose of this guideline, the following terms were used:

Compliance: describes the degree to which an animal owner correctly follows veterinary advice for the VMP administration and especially the dosing regimen which is referred to as dosing compliance or treatment compliance.

Investigational VMP: Investigational veterinary medicinal product: veterinary medicinal product to be tested.

Palatability: the property of being acceptable to the mouth, “pleasant to the taste” or “acceptable to the taste”. When applied to a VMP, this term suggests that the product is palatable enough to ensure voluntary uptake.

Voluntary acceptance or free choice acceptance: The willingness of the target animal to consume voluntarily and spontaneously the veterinary medicinal product from bowl/trough/ground as offered by the animal owner.

VMP: veterinary medicinal product.

References

- Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.
- Classification guideline: Information from European Union institutions and bodies commission.
- CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010).
- CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).
- VICH GL 9: Guideline on Good Clinical Practices.
- VICH GL 15: Efficacy of anthelmintics: Specific recommendations for equines.
- VICH GL 16: Efficacy of anthelmintics: Specific recommendations for porcines.
- VICH GL 19: Efficacy of anthelmintics: Specific recommendations for canines.
- VICH GL 20: Efficacy of anthelmintics: Specific recommendations for felines.
- VICH GL 21: Efficacy of anthelmintics: Specific recommendations for poultry.
- OECD Principles on Good Laboratory Practice.