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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.

Regarding oral formulations for group treatment such as medicated feed or water, a palatability claim is not relevant. However, for these formulations, consumption data may be necessary to confirm adequate uptake, and thus similar efficacy and safety, as compared to a reference product. Study design recommendations for such studies are given separately under section 9.

1. Introduction (background)

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

Although not always necessary, flavouring components are often added to VMPs 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 product is not considered palatable if it is consumed only when mixed with food or by forced intake.

The terms "palatability" and "voluntary acceptance" 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 VMPs intended for treatment of individual animals. 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.

For generic products intended for group treatment, guidance is given on how to demonstrate similar consumption as compared to the reference product, unless otherwise justified. This is considered important with regard to efficacy and safety since this aspect is not covered in the bioequivalence guideline (EMA/CVMP/016/00-Rev.2).

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.

Palatability of a VMP in one species may not be extrapolated to another species. Within a species there may be variation between subgroups of animals (e.g. breeds) which has to be accounted for when

evaluating palatability. Furthermore, voluntary acceptance of a VMP 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. Therefore, whenever possible, the palatability should be tested in animals which are representative of the target population for the VMP.

5. Applications where palatability studies are requested:

Palatability data should be provided if an applicant claims palatability for the following applications:

1. New VMPs,
2. Changes in formulation of existing VMPs to improve palatability,
3. Generic VMPs. Studies may be waived if the generic product is qualitatively and quantitatively comparable to the reference product, and the applicant can justify that any minor differences in the composition would not affect palatability.

6. Type of study

Palatability should preferably be evaluated in the target population under field conditions in order to ensure that the data are representative. This could be done as part of a clinical field study performed for the purpose of demonstrating efficacy. Such field trial should comply with the VICH GL 9 on Good Clinical Practice (GCP).

Palatability may 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 and assessment of voluntary acceptance

7.1. Study design

The palatability of a VMP should be demonstrated by comparing its voluntary acceptance rate to a pre-established threshold given by this guideline (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. For daily treatments lasting more than 14 days, seven daily consecutive administrations should generally be sufficient.

However, for products to be administered in longer intervals, such as once or twice monthly, the palatability should be tested at least for two administrations per animal. For laboratory studies, shorter intervals than recommended in the SPC could be accepted, if there is no safety concern.

7.2. Assessment of voluntary acceptance

The product should be administered according to the instructions given in the study protocol and with the same treatment interval 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.

The palatability of the tested product should be assessed without food to avoid any effect of palatability linked to the food composition.

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 (depending upon species behaviour) to assess voluntary acceptance during one minute. In case of failure, the product could be offered by hand for an additional minute, such that the maximum total offering time is two minutes. This basic presentation scheme should be adapted according to the species and to the pharmaceutical form of the product. The method of treatment administration should be clearly defined in the study protocol depending upon the pharmaceutical form (liquid, paste, powder, tablet).

Acceptance is defined as voluntary full consumption within the maximum offering time (e.g. two minutes).

Non-acceptance (failure) is defined by the occurrence of at least one of the following events:

1. Delayed uptake although complete consumption (time to be defined in the protocol),
2. Partial uptake,
3. Regurgitated or spitting out of the product,
4. Refusal

7.3. Primary and secondary endpoints

The **primary endpoint** is based on successful administration, which is defined as voluntary full consumption within the maximum offering time (e.g. two minutes) as described above. The statistical unit is the individual animal. The primary endpoint is the overall voluntary acceptance rate which is calculated for the entire period in the total number of animals as:

$$\frac{\text{Total number of successful administrations}}{\text{Total number of administrations}} * 100\%$$

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

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

$$\frac{\text{Number of successful administrations}}{\text{Total number of administrations}} * 100\%$$

- The average voluntary acceptance rate is 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.
- Scoring of ease of administration, with a scoring system appropriately chosen for the specific formulation.
- Rates of the different failures as defined in the study protocol.

7.4. 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% in all other species. The threshold should be reached in a group of at least 50 animals if the product is administered only once. The threshold should be reached in a group of at least 25 animals if the product is for at least two administrations.

In cases where palatability is evaluated as part of clinical studies with similar testing conditions, none of which have 25 or 50 animals treated with the investigational VMP, the results obtained could be pooled to accumulate the required number of animals in the studies.

8. Palatability claim in the SPC

Only 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).

Dosing methods may be adapted depending upon the pharmaceutical form, but should reflect the outcome of the study.

In the case of voluntary acceptance, the following sentence might be adapted "*The product is palatable i.e. it is usually taken voluntarily by [species] (voluntary consumption on > [70]/[80]% of occasions in animals studied)*".

Reference may also be made to the thresholds given in this guideline.

9. Generic 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 ensure that intake, and thus exposure, is appropriate among treated animals.

For generic products for which no clinical efficacy and safety data is required, data on medicated feed or water uptake are necessary to demonstrate adequate consumption.

However, such data are not required if the test product is qualitatively and quantitatively comparable to the reference product, and does not contain any other component recognized to affect consumption.

In order to confirm the adequate uptake of the generic product, the feed and water consumption of the group treated with the generic should be compared to either an untreated control group (negative control) or to a group treated with the reference product (positive control). The control group should be kept under the same conditions as the treated group. Baseline levels of feed/water consumption of all animals may be used to estimate the comparability of both groups. No deprivation of food or water before onset of trial is allowed.

The study may be conducted in healthy animals under field conditions, if feasible, or under experimental conditions. Parallel or cross-over design could be used. The study animals should represent the target population for treatment with regard to age, gender and weight. Water and feed consumption can be measured at the pen or room level, hence, the statistical unit would be the pen or the room. However, measurement of consumption in animals housed individually may also be accepted, provided that animal welfare is not affected. Then the statistical unit would be the animal. The posology and dosing instructions recommended in the SPC should be used. The measurement of consumption 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 study group should be calculated and presented in the protocol.

The primary endpoint is the mean daily water or feed consumption. The calculated actual daily dose per study group should be provided as additional information. The data should be presented for the whole treatment duration.

In case the individual animal is the statistical unit, the group means should be determined, and the 95% confidence interval of their difference should be calculated and compared to a predefined and justified non-inferiority margin. A non-inferiority margin of at most 15% of the control group (positive or negative control) mean should be applied.

In case the pen/room is the statistical unit, the following statistically pragmatic approach could be used: the lower 95% confidence limit for the mean consumption of the pens/rooms within the treatment group should be above a threshold of 95%, defined as a percentage of the mean consumption of the pens/rooms within the control group (positive or negative control).

10. Definitions

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

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:

The willingness of the target animal to consume voluntarily and spontaneously the veterinary medicinal product from bowl/trough/ground or from hand when offered as a treat by the animal owner.

11. References

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.

OECD Principles on Good Laboratory Practice.