10 July 2014
EMA/CVMP/EWP/391535/2013
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on Guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011-CONSULTATION)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	IFAH-Europe
2	EGGVP – European Group for Generic Veterinary products

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	IFAH-Europe welcomes this draft guideline and the opportunity to comment, as companies require the possibility to claim palatability of veterinary medicinal products. The draft guideline is generally well written, but we do have one major issue. We feel that the inclusion of herd or group treatments within this guideline leads to unnecessary complication and confusion. In line with our comments on the original concept paper for this guideline we strongly recommend that the scope of the guideline be limited to "palatability" of products for oral treatment of individual animals only. Compliance with uptake of medicated food/water for group treatment should be dealt with in the relevant guidance for such products. The rationale for applying for a "palatability claim" (e.g. anthelmintics for companion animals) is very different from the necessity of compliance with uptake of medicated food/water in livestock therapy. The two topics (i.e. easy application of tablets to single dogs and the acceptance of swine to drink medicated water) are too different to be considered in one single guideline.	Partly accepted. It is accepted that palatability is not considered an appropriate claim for group treatment. However, to address some issues that are not covered by the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), a separate section dealing with generic products intended for group treatment has been included in the guideline.
1	It should be clearly specified that testing the palatability of new products could also be performed on healthy animals in some instances. We agree that the study population should be representative of the target population, especially when the health condition of the animals significantly influences feed intake. However, in some cases a palatability study in healthy animals could also be acceptable. One example would be systemic endo- or	Accepted. The text of section 6 (type of study) has been amended according to the comments made on line 87. This states that palatability may also be conducted in some occasions in healthy animals.

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	ectoparasiticidal treatments.	
1	One of the main objectives of this new guideline should be to define what “palatability” is in the context of oral pharmaceutical dosage forms. Please use the words “palatability” and “voluntary acceptance (rate)” consistently throughout the guideline text as defined in the definitions section. Please avoid the introduction of other expressions, where possible, for instance: “voluntary uptake” (l. 34) “correct uptake” (l. 41) “adequate uptake” (Lines 42/43) “similar consumption” (l. 157) “free choice acceptance” (l. 194)	Partly accepted. The words “uptake” and “consumption” are not considered synonymous to palatability or acceptance. The expression “free choice acceptance” has been deleted and only “voluntary acceptance” has been kept.
1	Chapter 2 (scope) and chapter 5: This is an example of the lack of clarity caused by the inclusion of group treatment and why group treatments should be removed from the scope of this guideline. The draft guideline does not make it clear that for group treatments palatability studies are required in the following two different circumstances: 1.) optionally in case palatability shall be claimed for individual treatments and 2.) mandatory in any case of generic oral products (uptake in water or feed) intended for herd or group treatment	Partly accepted. It is accepted that palatability is not considered an appropriate claim for group treatment. However, to address some issues that are not covered by the CVMP Bioequivalence guideline, a separate section dealing with generic products intended for group treatment has been included in the guideline.
1	Chapter 7.2: This is another example of the lack of clarity caused by the inclusion of group treatment. This chapter is only relevant for generic	Partly accepted. It is accepted that palatability is not considered an

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	applications for oral products (uptake in water or feed) intended for herd or group treatment mainly clarifying the needs for these applications, independent from palatability claims (which are not accepted for herd and group treatment). We recommend this section is deleted as per our earlier comments regarding the removal of group treatment to other relevant guidance.	appropriate claim for group treatment. However, to address some issues that are not covered by the CVMP Bioequivalence guideline, a separate section dealing with generic products intended for group treatment has been included in the guideline.
2	EGGVP welcomes and fully supports the proposal of the CVMP and the Efficacy Working Group herewith providing guideline for the demonstration of palatability. EGGVP supports the development of transparent and pragmatic guidance to allow a level playing for veterinary medicines which claim having palatability properties. The principal comment from EGGVP on this paper refers to the requirement to routinely conduct studies for generic veterinary medicines with palatability claims intended for herd treatment. In our opinion, these studies may be omitted, pending on appropriate justification (and not the contrary approach). EGGVP is also concerned by the fact that the guideline generally accepts comparison between the reference product and its generic; in our view this approach is not appropriate and comparison should only be needed in case of significant palatability problems of the generic product. Rationale on both issues is provided in the specific comments section.	Partly accepted. Palatability is not considered an appropriate claim for group treatment. However, to address some issues that are not covered by the CVMP Bioequivalence guideline, a separate section dealing with generic products intended for group treatment has been included in the guideline.

2. Specific comments on text

Line No.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
29-30	1	Comments: "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 as necessary as part of the efficacy evaluation." This sentence requires amendment. Proposed change: Group or herd treatments should be removed from the guideline and the sentence should be amended as follows: "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 as necessary as part of the efficacy evaluation~~." If herd or group treatment remains within the scope of the guideline then this clear objective would be complicated because the first decision step with regard to palatability testing would then have to be to define whether such a testing is necessary for a certain oral product (*e.g.* not necessary for originator products if safety and efficacy are proven). For example the objective would become: "The objective of this guideline is to specify **the necessity as well as the** 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**~~."	Partly accepted. The executive summary was amended. To address some issues that are not covered by the CVMP Bioequivalence guideline, a separate section dealing with the evaluation of consumption of generic products intended for group treatment was added.
36-37	1	Comments: "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." It is possible to obtain the palatability claim without	Accepted.

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		the addition of flavouring components in the formula. (*I.e.* product with high acceptance without necessary specific additional ingredient which could be coated tabs for example. Proposed change (if any): "**Although not always necessary,** 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."	
45-47 and 85-86	2	Comments: The wording in lines 85-86 differs from the wording in lines 45-47. The wording in the 85-86 states that *"comparative palatability studies have to be required*" (=absolute), unless otherwise justified (further explained in line 158), whilst in line 45-47 "*palatability may have to be taken into account*". It is also unclear why palatability of a generic oral product for group treatment – e.g. a water soluble powder – should per se be related to the palatability of the originator. This is only valid if there are problems with the palatability of the medicated drinking water containing the generic product when compared to normal water intake. Assuming medicated water intake with a generic product is very poor, then comparison with the originator may be valid. But it should also be realised that a small decrease in water intake (e.g. <10%), can also be circumvented by a slight increase in concentration of the medication. This is similar to an increase of the concentration in drinking water when diseased animals consume less (unrelated to palatability). This is commonly accepted in veterinary practice. Therefore palatability of a generic oral product for group treatment – e.g. a water soluble powder – should only be related to the palatability of the originator when the water consumption with medication decreases more than 10-15% in comparison to normal water consumption. Proposed change (if any): For generic VMPs intended for group treatment palatability data may have to be provided to support similar exposure as	Partly accepted. It is accepted that palatability is not considered an appropriate claim for group treatment. Section 5 (Applications where palatability studies are requested) was amended in order to improve the clarity and the consistency of the text. The last sentence (line 85-86) of section 5 was deleted. To address some issues that are not covered by the bioequivalence guideline, a separate section dealing with the evaluation of consumption of generic products intended for group treatment was added.

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		compared to the reference product, ~~unless otherwise~~ if not justified otherwise.	
49	1	Comments: "The terms "palatability", "voluntary acceptance", and "compliance" are defined in the section "Definitions". The term "compliance" is not mentioned in the introduction. Compliance is only applicable in the case of group treatments and should be removed. Proposed change (if any): Change wording to: "The terms "palatability" **and** "voluntary acceptance", ~~and "compliance"~~ are defined in the section "Definitions"."	Accepted. The term "compliance" was deleted.
51-53	1	Comments: The current text of the scope section refers to "studies for the demonstration of palatability of veterinary medicinal products intended for individual or group animal treatment." However, a claim of palatability is only relevant for oral dosage forms intended for individual treatment. For group treatment it is only necessary to determine similar consumption to the originator product. The use of the term palatability for both instances in the same document leads to a lack of clarity. Proposed change (if any): For clarity all references to group treatment should be removed from this guideline. "studies for the demonstration of palatability of veterinary medicinal products intended for individual ~~or group animal~~ treatment."	Partly accepted. The word "group" was removed from line 53 in the section 2 (scope) and the last paragraph was replaced by a new text presenting the aim of the section dealing with consumption of herd/group treatment. To address some issues that are not covered by the CVMP Bioequivalence guideline, a separate section dealing with generic products intended for group treatment was presented at the end of the guideline. The term "palatability" was replaced by "feed and water consumption" for group/herd treatment.
56 – 58	1	Comments: It seems highly improbable that the safety of the VMP could be impacted by palatability. Higher potential doses associated with palatability and therefore better observance is assessed by TAS studies performed with	Accepted. The sentence was deleted and replaced

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		the VMP. For the purpose of an EIA, the initial PEC_{soil} is a theoretical calculation which already assumes 100% of the expected therapeutic dose is excreted. Safety for the user may be impacted by a flavouring agent; however appropriate measures (*e.g.* labelling and storage) are available to answer this issue. Regarding efficacy, this is assessed by clinical trials performed with the VMP. Proposed change (if any): This sentence should be deleted as it adds no useful information to the guideline.	by a new text presenting the aim of the section dealing with consumption of herd/group treatment.
74	1	Comments: A lot of factors may influence palatability: age, physiological status, type of food routinely given, feeding habits, *etc*… IFAH-Europe is not aware of any evidence to demonstrate clinically relevant differences in palatability between breeds of cats and dogs. Proposed change (if any): delete "may differ between breeds".	Not accepted. The breed effect is well-known (Thombre A. G, 2004: oral delivery of medications to companion animals: palatability considerations, Advanced Drug Delivery Reviews 56, 1399 – 1413).
74-75	2	Comments: Palatability may differ between breeds and also between different animal categories (ages). Any studies requested to support palatability claims should be performed in the most sensitive breed / category only (e.g. Piglets for porcine) and not for all breeds / categories.	Partly accepted. The text was amended clarifying that the palatability should be, whenever possible, tested preferably in animals that are representative of the target population for the VMP.
79	1	Comments: It should be highlighted that claiming palatability is optional. Proposed change (if any): add only:" Palatability data should **only** be provided…"	Partly accepted. The sentence has been modified: "*Palatability data should be provided if an applicant claims palatability for the following applications…*"

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79-86	1	Comments: The inclusion of group treatment again causes unnecessary confusion, particularly as the two circumstances are not clearly identified (e.g. line 79 should start with “1.)” and line 85 with “2.)”. Proposed change (if any): To improve clarity we suggest the deletion of lines 85 and 86 in line with our earlier comments.	Accepted. Lines 85 and 86 have been deleted.
82-84	1	Comments: Generic VMP applications (regarding formulations intended for individual treatment) should follow the same requirements with regard to palatability as new VMPs (intended for individual treatment). Whether the reference VMP does or does not have a palatability claim, the applicant of a generic application has to provide appropriate data to have a palatability claim. Since there are no differences in terms of data requirements for palatability between a full and a generic application, it is proposed to delete the last sentence. Generic applications should only gain the palatability claim if formulations are qualitatively and quantitatively identical (see also the comment lines 156-158). Proposed change (if any): **“**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.~~”	Partly accepted. The word “comparable” was not replaced by “identical”, but a clarification was added (i.e.…”*and the applicant can justify that any minor differences in the composition would not affect palatability”).*
82-84	2	Comments: Some generic applications are concerned with different formulations of authorised products, which are not related to differences in composition but to other differences, such as intended use (e.g. oral powder for use in individual animals vs. premix for medicated feed). In such cases exposure to the product would remain the same and no palatability study would be necessary. Proposed change (if any): text may be modified to read as follows: “Generic VMP applications regarding formulations intended for individual treatment.	Partly accepted. The sentence in lines 82-84 was amended (see previous comment). A separate section deals with the generic products intended for group treatment.

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		Studies may be waived if the generic product is qualitatively and quantitatively comparable to the reference product or to the authorised product intended for herd or group treatment."	
87	1	Comments: What is the justification for differentiating requirements for new VMPs, new claims to existing products or generic products? Target animals under controlled conditions studies are important during the development program and could be useful for demonstrating palatability even for new VMPs. Proposed change (if any): We would suggest to rewrite the section as follows: For all products, for which a palatability claim may be desired, palatability should preferably be evaluated in the target population under field conditions for the sake of representativeness. This could be as part of the pivotal clinical field study performed for the purposes of demonstrating efficacy. Such field trials should comply with the VICH GL 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). However, it should be ensured that the study outcome is valid for the target population (see section 7).	Accepted. Section 6 has been amended. It clarifies that palatability should preferably be evaluated in the target population under field conditions but that it may also be evaluated in healthy target animals, if justified.
93-97	2	Comments: For some generic applications, clinical studies may be required ("hybrid" applications). Such studies are performed in target animal species. Hence, palatability could be evaluated within clinical (e.g. dose-confirmation, tolerance) studies of appropriate design. Proposed change (if any): "For a new claim to existing products, and for	Accepted. Section 6 has been amended (please refer also to previous comment).

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		generic products claiming palatability and which are intended for individual treatment, palatability may however also be evaluated in healthy target animals under controlled conditions, or in efficacy or safety studies of appropriate design, 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)."	
93-94	2	Comments: sometimes and depending on the molecule, healthy animals can accept the product but, refuse it when they are sick, due to palatability sensitivity. It should remain up to the applicant to evaluate the need to perform the palatability study.	Accepted.
101	1	Comments: Requires clarification. Proposed change (if any): Please add: "to **a pre-established** threshold **given by this guideline**"	Accepted.
106-107	1	Comments: The concepts of short-term and long-term are not clearly defined and should take treatment-interval into consideration. Would once monthly treatments be considered short-term or long-term? We would suggest that infrequently administered products (*e.g.* anthelmintics) should be tested on a single administration because taste preference/aversions are unlikely to develop with infrequent administrations. Proposed change (if any): Define short term and long term or add dosage regimen (*e.g.*: daily)	Accepted. The concepts of short-term and long-term were deleted. A sentence was added defining the time points of assessment for products administered in longer intervals.
106-107	1	Comments: Experience shows that 7 days are sufficient for the assessment of the palatability of products intended for long term treatment. Proposed change (if any): "Therefore, the palatability should be assessed during the entire course of short-term treatments and/or for approximately	Accepted. The text was amended taking into account the proposed 7 days for the

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		~~14~~ 7 days in case of long-term treatments."	assessment.
112-117	1	Comments: The current times given in the basic presentation are too short and restrictive, although we do acknowledge the statement that this should be adapted according to species and pharmaceutical form. According to the article "Oral delivery of medications to companion animals: palatability considerations" (A.G. Thombre, Advanced drug delivery review 56 (2004) 1399 -14132), placebo tablets containing different palatents have been presented to dogs and the results display that the lapsed time from offering the tablet to the time of consumption is between 22 and 62 seconds. For horses, it seems highly improbable that the oral VMPs are presented on the ground (or in a bowl) in field conditions, particularly with sick animals. Likewise for pets, because of the relationship between the owners and the pets, considered together with species behaviour (cats). We consider that the administration method (for acceptance purpose) should be specified in the protocol based on pharmaceutical form, intended method of administration and behaviour of the target animals (individual treatments). Again 30 seconds might be too short as cats often smell the goods for a longer time duration before intake. Proposed change (if any): replace the whole paragraph with: "Acceptance of the product should be assessed considering the VMP (pharmaceutical form), together with target species behaviour, and in-field common practices. Acceptance criteria should be clearly defined in the study protocol."	Accepted. The text was amended clarifying that the study protocol may be adapted according to species and pharmaceutical form. The maximum offering time which was given as an example was increased to two minutes.
115	2	Comments: If offering by hand also fails, wouldn't it be a good option to test the acceptance of the medication, by placing the product on top of the food? Proposed change (if any): Add this option here or insert at line 125.	Not accepted. The palatability of the tested product is only assessed without food avoiding any bias linked to the food composition. As a

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			product is not considered palatable if it is administered with food or placed directly into the mouth of the animal, a sentence was added in the introduction. The failure cases numbered 4 (consumption with food/water) and 5 (forced intake) were deleted (please see section 7.2).
119-127	1	Comments: The criteria seem to be written for dry single unit forms and they do not consider other oral forms (liquid, paste, powder *etc*.). For instance some VMPs are administered in food or directly to the mouth of the animal as an individual treatment which would invalidate some of the options as a failure. Therefore we suggest that the list of failure criteria given is treated as an example and the criteria to be used should be specified in the study protocol Proposed change (if any): "Failure **criteria should be defined in the study protocol based on the pharmaceutical form and intended method of administration. Examples of** ~~might be of~~ different types **of failure are** as follows:"	Partly accepted. It is not considered possible to test the voluntary acceptance of the product by placing it in food or directly into the mouth of the animal. These methods are alternatives for administering products which are not palatable. The failure cases numbered 4 (consumption with food/water) and 5 (forced intake) were deleted.
125	2	Comments: Tablets, oral pastes and similar forms are common for individual treatment via oral route. Nevertheless, some forms are intended to be used in drinking water (or feed), even in individually treated companion animals (e.g. powder for oral solution). Hence, it might be appropriate to insert additional wording "unless this is the recommended mode of administration". Proposed change (if any): it might be appropriate to insert additional wording "unless this is the recommended mode of administration".	Partly accepted. It is only accepted to dissolve the product into water, if required. The text was amended to leave more flexibility for the method of treatment administration. However, a product is not considered palatable if it is administered with food or placed directly into the mouth of the animal (see

Line No.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
			introduction).
131	1	Comments: Requires clarification on what is a successful dosing. Proposed change (if any): Please define successful dosing as 'complete consumption of the dosage form'.	Accepted. The term successful dosing has been replaced by "*successful administration, which is defined as voluntary full consumption within the maximum offering time (e.g. two minutes*)".
133	1	Comments: What is the aim and purpose of the secondary end points? How will these criteria be used and translated in the SPC? Are they intended to be used in comparative trials with another product having a palatability claim? Proposed change (if any): As they appear not to be considered in Section 7.1.3 we suggest replacing line 133 with the following: **"Additional analyses may be calculated as follows:"**	Partly accepted. One of the secondary endpoints has been deleted. The other endpoints are considered important to qualify the palatability of the product.
143	1	Comments: See comment for line 122. Proposed change (if any): **"**Rates of the different failure types ~~1 to 6~~ as defined ~~above~~ **in the study protocol**."	Accepted.
145-146	1	Comments: We can envisage circumstances where the given thresholds are not attainable, *i.e.* in diseased animals where the disease is known to adversely impact feeding. Proposed change (if any): **"**overall voluntary acceptance rates should at least reach the threshold of 80 % in dogs, and 70 % for all other species, **unless otherwise justified**."	Not accepted. The thresholds for dogs and other animals as defined in this guideline should always apply irrespective of the health status of the animals and irrespective of the kind of product.
145-148	1	Comments: We would be interested to know the background to the selection of the numbers of animals required. Statistically it may not always be	Not accepted. The proposed sentence was not added.

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		necessary to use the number of animals given. Proposed change (if any): **"**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. **Fewer animals may be acceptable if suitable justification is provided.**"	Justification: For VMP administered once, and for an acceptance rate of 80% observed in 50 animals, the lower confidence limit 66.28% would be above 65% for a non-inferiority margin of 15% to the threshold. For multiple administrations, it is assumed that it would lead to the same confidence limits as one-time administration to 50 animals.
146-148	1	Comments: The concept of "multiple administrations" is not clearly defined. Why are single administrations and multiple administrations differentiated without reference to a treatment interval? Proposed change (if any): Please clarify by addition of dosage regimen (*e.g.:* daily or quarterly).	Accepted. The text has been clarified.
146	2	Comments: 80% (dogs) and 70% (other species) are very arbitrary and especially for cats hardly realistic. In cats a 50% voluntary uptake is considered very good and indicates a good palatability in this species. Most treats developed specially for cats will not even reach 70%. Cat owners will already be very happy with a 50% voluntary uptake of a lifelong medication, so for cats the percentage should be lowered. Furthermore if an API is very bitter, it is really an improvement if for example 50% of the dogs eat this tablet voluntary, though this may subsequently not be claimed as being palatable. Therefore in such cases it should be possible to claim in the SPC that the product is flavoured and that 50% had voluntary uptake. Proposed change (if any): Lower limit for palatability claim in dogs to 70%	Not accepted. The threshold of overall voluntary acceptance have not been changed since 80% in dogs and 70% in other animals should be achievable to classify a product as palatable. A voluntary acceptance of only one half of all administrations is not at all deemed sufficient to claim palatability. Now that criteria for palatability have been defined in the guideline, statements that a product contains a

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		and in cats to 50% and require percentage of voluntary uptake to be mentioned in SPC. Make it possible for products with lower levels to include a claim that a product is flavoured and again require percentage of voluntary uptake to be mentioned in SPC.	flavouring will no longer be accepted in section 4.9 of the SPC. (Factual information on the identity of the excipients will still be found in section 6.1).
146 - 148	2	Comments: For some products, palatability may be evaluated within clinical (e.g. dose confirmation) studies under controlled conditions. If there are several studies none of which have 25/50 animals treated with the investigational VMP (e.g. 10 animals treated in the study), the results obtained might be pooled to accumulate the required number of the animals (25 or 50). Proposed change (if any): "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. In cases where palatability is evaluated as part of clinical (e.g. dose-confirmation or tolerance) studies and there are several studies, 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."	Accepted. The following sentence was added: *"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."*
149-178	1	Comments: As stated in the general comments we strongly recommend the removal of herd or group treatments from the scope of this guideline for simplification and to improve clarity. Proposed change (if any): delete Section 7.2	Partly accepted. The text was amended and a separate section dealing with consumption data of products intended for group treatment was added at the end of the palatability guideline to bridge a gap with regard to the CVMP Bioequivalence guideline.
	2	Comments: Products intended for herd or group treatment are commonly administered via medicated food or water. This is in contrast to (some)	Partly accepted.

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		pharmaceutical forms for individual treatment, where consumption of the product hidden in food/water is considered as one of the failures of the palatability. Medicated portion may represent the sole source of water or feed during treatment or it may represent only a part of the daily intake (requirement). In some cases, consumption within a time-limit is desired (e.g. within 4 hours). Consumption may be facilitated by favourable palatability of the product and/or the feed (for products administered via medicated feed) as well as by other means, such as restriction of food or water before administration in order to stimulate thirst or appetite. Thus, various measures are applicable to provide sufficient exposure of treated animals to the VMP. Such recommendations might apply for the reference as well as for the generic product and would depend of the composition of the product. Therefore, consumption of the generic product (and exposure to) might be determined as not-worse, equal or superior when compared to the reference. It is unclear why palatability of a generic oral product for group treatment should per se be related to the palatability of the originator. This is only valid if there are problems with the palatability of the medicated drinking water/feed containing the generic product when compared to normal water/feed intake. Only when medicated water/feed intake with a generic product is very poor, then comparison with the originator – for which water/feed intake may also be poor - is valid. Palatability of a generic oral product for group treatment should only be related to the palatability of the originator when the water/feed consumption with medication decreases more than 10-15%? in comparison to normal water/feed consumption. In conclusion: comparison with a reference product should only be needed in case of significant palatability problems of the generic product.	To address some issues that are not covered by the CVMP Bioequivalence guideline, the section dealing with generic products intended for group treatment was presented at the end of the guideline. The first sentence of this section explains that data are necessary to demonstrate similar consumption of the generic and the reference product, unless otherwise justified (qualitatively and quantitatively comparable formulations). The text of section 9 has been revised partly according to this comment. The control group may be the reference product but may also be an untreated control group.
154-155	1	Comments: **"**Thus, specific palatability studies are not required if efficacy	Accepted.

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		has been demonstrated and a palatability claim is not relevant." In other statements within the guideline a palatability claim is never relevant for a herd or group treatment; yet in this statement the implication is that in some circumstances it is relevant. This lack of clarity again demonstrates why IFAH-Europe strongly suggests that herd or group treatment is removed from the scope of this guideline. Proposed change (if any): Suggest the deletion of Section 7.2. Alternatively amend the sentence as follows: **"**Thus, specific palatability studies are not required if efficacy has been demonstrated ~~and a palatability claim is not relevant~~."	The sentence has been deleted. The term "palatability" was replaced by "feed and water consumption" for generic VMP intended for herd/group treatment.
156-158	1	Comments: Small changes in formulations influence palatability; therefore unless the generic product is nearly identical to the reference product similar consumption should be demonstrated. See also comment to lines 82-84. Proposed change (if any): Change to "unless otherwise justified (qualitatively and quantitatively ~~comparable~~ **identical** formulations)".	Not accepted. The word "comparable" was not replaced by "identical" since minor changes in formulation may not have any impact on the VMP uptake.
156-158	2	Comments: For generic products the studies may be omitted, pending on appropriate justification (qualitatively and quantitatively comparable formulations). It might be appropriate to add to these exceptions minor differences in formulations, for which available data suggest minor or negligible influence on feed or water consumption. If for a generic product, one can argue that physico-chemical parameters are equivalent to a reference product (in drinking water or in the feed), then it should not be required to perform a study regarding palatability even if formulations differ qualitatively and quantitatively. For oral generic products such as pharmaceutical forms for in-feed use or for in drinking water it is not always the case that the amount of active substance is the same as for the reference product. As it is the final	Partly accepted. The text of section 9 has partly been revised. The sentence has been replaced by "*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.*"

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		concentration of the active substance once a medicinal product is presented in a feed or solution prior to administration, that is important. A justification for a qualitatively comparable formulation is therefore not always possible which implicates that for these type of products data must always be gathered. Proposed change (if any): In case of generic products for which no clinical efficacy and safety data is required, data ~~are necessary~~ may be required to demonstrate similar consumption as compared to the reference product, ~~unless otherwise justified~~ if not justified otherwise (comparable physic-chemical parameters or ingredients known not to affect water consumption). (~~qualitatively and quantitatively comparable formulations~~)	
158	2	Comments: It is not clear what the definition of “comparable formulation” is, as this is not such a strict requirement as “identical formulation”.	This means that the applicant can justify that any minor differences in the composition would not affect palatability (see also section 5).
159-179	2	Comments: It should be realised that demonstrating non-inferiority with a reference product statistically, using the pen/room as statistical unit with animals housed common to field-practice will result in very large numbers of test-animals being used. And this is totally in contradiction with industries and authorities wishes to reduce these numbers. Furthermore in lines 173-175 it is stated that mean daily water and feed consumption “should comply with normal physiological levels” , so then why is it needed to compare this with a reference product anyway?	Accepted. The text of section 9 has been revised according this comment. The control group may be the reference product but may be also an untreated control group. A statistically pragmatic approach may also be possible in case the pen/room is the statistical unit.
176-178	2	Comments: A short indication is given on how the difference between the 2 formulations should be compared. This indication is however not concrete and very general. A more precise guidance is therefore requested to use (for instance range of the margin).	Please refer to the CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)

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			(EMA/CVMP/EWP/81976/2010). A more threshold value has been added.
180-182	1	Comments: There is currently no guidance how a palatability claim in the SPC should be phrased. For example should the percentage of "voluntary acceptance" be stated; but would this be a mean percentage or broken down by species, weight band, age *etc*.), or should it only state that the formulation is palatable (meaning that an acceptable threshold level was attained)? Proposed change (if any): Standard sentences should be proposed but deviation from the standard sentences should be possible, where justified.	Accepted. An example of standard sentence which might be adapted has been added. It is also proposed to make a reference to the thresholds given in the guideline.
180-182	1	Comments: The current wording "if palatability has been demonstrated" could be taken to mean that even for herd or group treatments palatability can be mentioned in the SPC, even if not a palatability claim *per se*.: Proposed change (if any): As previously stated, for ease of understanding and clarity we suggest that herd and group treatment are removed from the scope of this guideline. In addition the following amendment should be made: "If palatability has been demonstrated **for individual treatment with oral dosage forms** 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~~."	Partly accepted. The last sentence has been deleted. To address some issues that are not covered by the CVMP bioequivalence guideline, a separate section dealing with the evaluation of consumption of generic products intended for group treatment was added.
180-182	2	Comments: see comment at line 146 Proposed change (if any): see proposal at line 146	See comment at line 146.

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194	1	Comments: "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." The word "free choice acceptance" is not mentioned anywhere in the guideline and therefore its use here is an unnecessary complication. Please delete it from the definitions section. The last part of the sentence as the exact definition how to assess voluntary acceptance (i.e. bowl etc. or hand) is described in section 7.1.1). Only referring to bowl/trough/ground in the definitions section but not to direct feeding is misleading. Proposed change (if any): "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~~."	Partly accepted. The words "free choice acceptance" is deleted. The voluntary acceptance is defined as "t*he 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."*
205-206	1	Comments: The reference to the bioequivalence guideline is unnecessary if herd or group treatment is removed from the scope of this guideline. The Bioequivalence guideline would be a good location to contain the herd or group treatment guidance. Proposed change (if any): Delete the reference to the bioequivalence guideline.	Partly accepted. To address some issues that are not covered by the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), the section dealing with generic products intended for group treatment was presented at the end of the guideline.
208-212	1	Comments: No benefit can be seen in referencing the VICH anthelmintic efficacy guidelines in this guideline.	Accepted. The references were deleted.

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		Proposed change (if any): Delete the references.	