European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE TESTING AND EVALUATION OF THE EFFICACY OF ANTIPARASITIC SUBSTANCES FOR THE TREATMENT AND PREVENTION OF TICK AND FLEA INFESTATIONS IN DOGS AND CATS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	ClinVet International	South Africa
2	IFAH Europe	Belgium
3	Association of Veterinary Consultants (AVC)	Belgium

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
IFAH Europe: The revised guideline clarifies a number of points and gives a better guidance. We are glad to see that for the level for the evaluation of efficacy of a product against ticks is now set >90%. We wonder why this level was not kept in line for fleas, that this guideline for consultation set now at >95%. However only a very few number of the proposals provided from IFAH-Europe in March 2006 were considered. For instance, the difficulty to perform tick studies in cats (section 4), the use of tick field strains recently collected as infestation material for laboratory studies (section 4.1.1), the use of geometric means instead of arithmetic means (4.1.7), and the proposal to a longer intervals than 48 hours (if appropriate) for short- and long-term persistent efficacy were not taken into account. We would like the CVMP to reconsider the original proposals since they have a high relevance and ask for a subsequent answer to our proposals.

SPECIFIC COMMENTS ON TEXT

1 SCOPE

Paragraph No.	**Comment and Rationale**	**Outcome**
	AVC: Add “and cats” “to systemic use for the treatment and prevention of flea infestations in dogs”: these products could be valid for cats as well	Accepted

3. DATA REQUIREMENTS		
Paragraph No.	**Comment and Rationale**	**Outcome**
3.1 Ectoparasite species	AVC: Fleas *Ctenocephalides canis* Add (dog only) as it is misleading to suggest that studies are needed to address this parasite in cats	*Ct. felis* is the predominant species on cats and dogs in Europe. *Ct. canis* is predominantly found on wild canides but can be occasionally found on dogs and in rare cases on cats as well. Therefore, the proposed change can be accepted. Literature: Wall R, Shaw, SE, Penaliggon, J (1997): The prevalence of flea species on cats and dogs in Ireland. Medical Vet. Entomol., 11, 404-406 Visser M; Rehbein S; Wiedemann C (2001): Species of flea (Siphonaptera) infesting pets and hedgehogs in Germany. J. Vet. Med. B Infect. Dis. Vet. Pub. Health; 48, 197-202 Bond R; Riddle A; Mottram L; Beugnet F; Stevenson R (2007): Survey of flea infestation in dogs and cats in the United Kingdom during 2005. Vet. Rec., 160, 503-506.
	ClinVet International: The list of most relevant tick species in dogs and cats in Europe should be amended to read as follows: *Dermacentor reticulatus* *Ixodes hexagonus* *Ixodes ricinus* *Rhipicephalus sanguineus group (including Rhipicephalus sanguineus sensu stricto and R. turanicus)* **Motivation:** *Rhipicephalus sanguineus* s. str., also known as the kennel tick or pan-tropical dog tick, has often been confused with other ticks in what is now known as the *sanguineus*-group (Walker *et al.*, 2003). According to Walker *et al*. (2000) *R. sanguineus* s.str. is a nearly host specific parasite of domestic dogs in all its stages of development. It is only found on other hosts if these are in close association with dogs, and very rarely on other animals. They record 547 collections from dogs, one from cats, 16 from other domestic animals and 15 from wild animals.	Accepted with minor modifications It is acknowledged that the dog is the preferred domestic host of *R. sanguineus* sensu strictu and they may never or rarely occur on cats. On the other hand the sheep-associated tick species, *R. turanicus* is predominantly found on sheep, goats and cattle but may be found on dogs, cats, and man as well (Professor Dr. Schein, FU Berlin, personal communication). Moreover, WAAVP (2007) does also not list *R. turanicus* as typical tick species in dogs and cats. Generally, it appears that the biosystematics of the *R. sanguineus* group ticks incl. their host preferences is not finally clarified. It should be noted that the guideline lists the most common tick species in Europe but is not exhaustive, e.g. *Hyalomma bursa* or *Rhipicephalus bursa* [WAAVP, 2007] are not listed.

	In the many years of tick identification shared by Walker, Heyne and Horak, in which animals of many, many different species have been examined we have very rarely identified *R. sanguineus* s.str. from any other host but domestic dogs. In a tick survey currently being conducted by Horak on domestic cats in South Africa no *R. sanguineus* s.str. have been seen in any of the 103 collections taken from cats to date. In surveys in which a total of 180 wild carnivores belonging to 25 different species were examined at various localities in South Africa, no *R. sanguineus* s.str. were collected from any of these animals (Horak *et al*. 1987, 2000b). Efforts to experimentally infest cats with *R sanguineus* s.str. under laboratory conditions in Germany (Turberg, pers comm) and South Africa, in order to test the efficacy of acaricides were unsuccessful. A survey conducted in 1995-96 of ticks on dogs and cats in Savona, north-western Italy, however, indicated that 26.3% of the ticks collected from cats were *Rhipicephalus sanguineus* (Manfredi *et al.*, 1999). This was most likely a misidentification. Our experience would therefore indicate that the findings of Walker *et al*. (2000), that, with few exceptions, dogs are the only hosts of *R. sanguineus* s.str., are correct. Outside Africa cats and dogs are amongst the preferred hosts of *Rhipicephalus turanicus* (Walker *et al.*, 2000). The tick occurs in several Mediterranean countries and their immediate neighbors as well as Afghanistan, China, India, Iran, Iraq, Nepal, Pakistan, Russia, Saudi Arabia, Sri Lanka, and Syria (Walker *et al.*, 2000). Several records from countries of the former Yugoslavia and Albania are believed to refer to this species (Estrada – Peña *et al.*, 2004). Recently this tick species was also collected from cats and dogs in the Netherlands (Jongejan, pers comm). The difficulties of experimental infestation studies on cats are acknowledged in the guidelines. The guidelines, however, recommend that dose confirmation studies on cats should be conducted. Since both adult and immature *R. turanicus* ticks infest cats (Walker *et al.*, 2000), and the breeding of the tick is not problematic we would suggest that adult *R. turanicus* is a suitable tick for acaricide efficacy tests on cats and in view of its distribution and host preferences is a relevant tick	The following change is made: *Ticks:* ***Dermacentor reticulatus*** ***Ixodes hexagonus*** ***Ixodes ricinus*** *Rhipicephalus sanguineus (dogs)*

	species which should be acknowledged in the guidelines. In conclusion, it would be logical to suggest using *R. sanguineus* s.str. exclusively for efficacy tests on dogs and to add *R. turanicus* for test on cats (it should also be realized that *R. turanicus* does feed on dogs creating the possibility of using this tick also for testing anti tick compounds on dogs). **References:** Estrada-Peña, A., Bouattour, A., Camicas, J.-L. & Walker, A.R. 2004. Ticks of domestic animals in Africa: a guide to identification of species. University of Zaragoza, Spain. Horak, I.G., Jacot Guillarmod, Amy, Moolman, L.C. & De Vos, V. 1987. Parasites of domestic and wild animals in South Africa. XXII. Ixodid ticks on domestic dogs and on wild carnivores. *Onderstepoort Journal of Veterinary Research*, 54:573-580. Horak, I.G., Braack, L.E.O., Fourie, L.J. & Walker, Jane B. 2000b. Parasites of domestic and wild animals in South Africa. XXXVIII. Ixodid ticks collected from 23 wild carnivore species. *Onderstepoort Journal of Veterinary Research*, 67:239-250. Manfredi, M.T., Dini, V., Piacenza, S. & Genchi, C. 1999. Tick species parasitising people in an area endemic for tick borne diseases in north western Italy. *Parasitologia* 41:555-560 Walker, A.R., Bouattour, A., Camicas, J.-L., Estrada-Peña, A., Horak, I.G., Latif, A.A., Pegram, R.G. & Preston, P. 2003. Ticks of domestic animals in Africa: a guide to identification of species. Bioscience reports: Edinburgh. Walker, Jane B., Keirans, J.E. & Horak I.G. 2000. The genus *Rhipicephalus* (Acari, Ixodidae): a guide to the brown ticks of the World. Cambridge Academic Press: Cambridge.	

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
2nd paragraph, 2nd and 3rd sentences and 4th line	IFAH Europe: In cats, dose confirmation studies and field studies are demanded. However, for well-known reasons tick studies in cats are difficult to perform and pharmacokinetic studies are not always possible (e.g. in case of topical treatment without absorption through the skin). Therefore, we propose to apply more flexible criteria to demonstrate efficacy in cats, i.e. a dose confirmation study and/or a field study, supported by pharmacokinetic data, wherever feasible. Amend to read: *"However, a ~~dose confirmation~~ clinical study in cats should always be performed, using experimental or natural infestation. ~~In view of the difficulties of experimental infection study in cats,~~ Wherever feasible, this study may be supported by pharmacokinetics parameters ~~may be used instead~~."*	The proposed wording (clinical studies in cats using either experimental or natural infestations) is not supported. Indeed, the wording in the 2nd paragraph of section 4 provides flexibility, i.e. it is acknowledged that experimental dose confirmation studies in cats are difficult to perform and, therefore, the studies can be replaced by pharmacokinetic studies, aiming to evaluate the distribution and concentration profile of the product across the animal's skin or fur following topical administration. It is well known that the often low extent of systemic absorption has no significant effect on the level of acaricidal activity of a product since ticks are killed rather by contact than by systemic exposure. In a second step, the concentrations of the active in the fur or skin, in relation to the minimum effective level of efficacy (e.g. LC_{50}) could then be used to conclude on the effective dose in cats or to support the dose established in experimental studies in dogs. In any case, efficacy must be confirmed in a field trial under practical use conditions, i.e. in cats with natural tick infestations. For clarification, the text has been amended as follows: *..In view of the difficulties of experimental infection studies in cats, studies on the distribution and concentration profile of the proposed products in the cat's skin and fur may be performed instead and used to conclude on the efficacy .*
	Amend to read: *"… experimental ~~infection~~ infestation …"*	Accepted.
4.1.1 **2nd paragraph, 1st sentence**	IFAH Europe: The scientific value of testing 2 tick strains for a given tick species is not justified. Amend to read: *" … at least 2 established tick ~~strains per indication~~ species …"*	Accepted. Indeed, the corresponding WAAVP guideline does not recommend the testing of two strains per tick species in the laboratory. Therefore, the text is changed as follows: *Normally, one established tick strain per tick species claimed will be sufficient for laboratory testing.*

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
4.1.1 2nd paragraph	IFAH Europe: Some tick species (e.g. *Ixodes ricinus*) are difficult to breed and therefore, the collection from the field and direct use in controlled studies was proposed. Amend to read: *"~~The use of laboratory t~~Tick strains obtained from recent field may also be used ~~collections and multiplied in the laboratory for at least 2 generations is encouraged~~."*	Not accepted. To our knowledge all major tick species common in Europe, including *I. ricinus* can be reared in the laboratory with acceptable quality. The use of field species collected from nature, with unknown "quality" is not supported, since this might lead to very variable results due to variable attachment rates. Moreover, it should be considered that ticks in the field can be infected with e.g. *Ehrlichia, Borrelia* or in some regions with *Babesia* spp. Therefore, it is strongly recommended, to multiply ticks from recent field collections in the laboratory for at least 2 generations. These ticks would still be representative of the current field situation but without any risk of disease transmission.
4.1.4 Tick infestation, 1st paragraph	IFAH Europe: Tick studies in cats are difficult to perform. Cats do not seem to be good hosts for ticks and attachment of ticks may be hampered by grooming, even when Elisabethan collars [animal welfare relevance!] are used. Please add the following sentence: *"Lower tick infestation rates are acceptable in dose confirmation studies in cat due to grooming behaviour and other technical constraints."*	Not accepted. As outlined in section 4, second paragraph of the guideline and commented above, laboratory studies on cats are dispensable. In case such a study would be performed, treatment results based on an infestation rate < 25% (i.e. 1 to 11 ticks/animal) would be difficult to assess, especially if differences between test and untreated control were small. It should be noted that a similar approach is recommended by WAAVP (2007, Vet. Parasitol, 145, 332-344).
4.1.4 -Whole body infestation	IFAH Europe: The description of infestation procedures is good practice and will help to judge how closely the procedures resemble the real world situation, and to identify area of possible bias. Please add the following sentence: *"The applicant should describe and justify the infestation method."*	Accepted.
4.1.5.1	AVC: "In general no ticks should be detectable on the animal 24 hours following administration of the product". Is this saying 100% repellency is expected for a repellent claim? This is high if so.	Owners can expect that ticks will be repelled as soon as possible after treatment and normally no tick will be detectable 24 hours after treatment. In principle, the repellent efficacy of a proposed product should be more than 90% (ref. section 4.1.7) 24 h after each experimental infestation in case of persistent efficacy (4.1.6.2.).

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
4.1.5.2	AVC: Most concern about ticks is in terms of their ability to transmit disease – far more than in the case of fleas. Currently this guideline addresses the role of fleas in the transmission of disease far more effectively (5.2.3) than it does ticks – which is the wrong way round!	Point noted. It is recognized that the risk of transmission of infectious diseases is more relevant in ticks than in fleas. Since no scientifically justified recognized methods are available to demonstrate the effectiveness in the prevention of disease transmission, a separate claim is at present not acceptable (see comment on section 4.1.5.2) and, therefore, not dealt with in the guideline. The sentence concerning the role of fleas in disease transmission is deleted (see also section 5.2.3, IFAH comment)
4.1.5.2 1st paragraph	IFAH Europe: We believe that acaricidal activity (death of ticks) and disease transmission should be two separate and distinct claims. In the current draft of the guideline, a differentiation between criteria to get acaricidal and disease transmission claims is not made. Therefore, efficacy calculation should be mainly based on the ratio dead/live ticks, whereas for the prevention of disease transmission the evaluation of engorgement should be made. Amend to read: *"~~In evaluating~~ For the evaluation of the acaricidal efficacy of a product, killing of ticks should be the only efficacy criterion. Furthermore, the feeding or engorgement of ticks should be taken into considerations as an additional criterion specified as the "disease transmission prevention criterion"."*	Not accepted. The proposal is considered unrealistic in view of the current state of knowledge. In addition to the risk of disease transmission, any other negative/unwanted effects of ticks such as toxic/allergic reactions, skin irritation, wounds etc are also tightly related to feeding. In addition to killing, the presence/ absence of engorgement is, therefore, an essential element in interpreting the efficacy of an acaricidal for pet animals. The categorisation of ticks for counting has been adopted in the recently published WAAVP recommendations. The validity of a separate disease transmission claim will become dependant on the ability to demonstrate the presence of infection in the tick and its absence in the host. It would be up to the applicant to demonstrate that ticks carrying a confirmed infection do not transmit the infection to the host, despite attachment. Not the presence of blood in the parasite, but the absence of transmission, and hence infection in the host, as a consequence of tick feeding will then be the major criterion. In principle, all possible infective agents should be included in such an approach; this is considered impossible. Moreover, the number of methods currently available for the detection of relevant infective agents in ticks is low. It should be pointed out that such an approach will also depend on the reliability of a negative test result, which is known to be low.

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
4.1.5.2	IFAH Europe:	Not accepted (ref. comment under 4.1.5.2)
4.1.5.2 **Page 6, 1st sentence**	IFAH Europe: Ticks do not have an intestine. Amend to read: *"… blood in the ~~intestine~~ digestive tract"*.	Accepted.
4.1.5.2 **Page 6, 3rd paragraph**	IFAH Europe: We continue to believe "prevention" claims are warranted for an acaricidal product. Even if not 100%. The only precautionary measures that Industry should accept are the proposed statement in the SPC and packaging. *"~~Indications such as „to prevent..." or „for prophylactic use" should be omitted if the effect is purely acaricidal, because as a rule, an attachment of the ticks is not prevented by the acaricidal substance.Thus, a preventive effect is not warranted. As a consequence, a note corresponding in meaning to that proposed below should be included in the SPC and package insert if an acaricidal effect has been claimed~~* or:*"*	Not accepted. By definition, acaricidal products without any repellent activity can not prevent the attachment of ticks on the skin. The objection of IFAH is considered not scientifically justified.
4.1.6 **2nd and 3rd sentence**	IFAH Europe: Although accurate with respect to the products currently registered, this sentence seems too limitative and is of no added value within the guideline scope. Please delete this part: *"~~Products with short-term effects typically include shampoos, sprays and spot ons/pour ons. Products with long-term effects include typically collars.~~"*	Accepted. Most of the modern acaricidal products have a persistent efficacy against ticks of about 4 to 6 weeks.

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
4.1.6 **6th sentence**	IFAH Europe: In the US, comb counts are the gold standard for post-treatment tick counts. Palpation and visual assessment are analogous to thumb counts for assessing flea efficacy and it has been shown that this method is not as sensitive as a comb count. Amend to read: *"It is recommended that tick counts are made by comb counts, or alternatively palpating the dog and by visual assessment."*	It is accepted that comb counting is also useful, but, looking at retreats of ticks such as the interdigital space or the auricular canal, comb counting may be impracticable. The phrase is amended as follows: *It is recommended that tick counts are made by comb counting or by palpating the dog and by visual assessment, as appropriate.*
4.1.6.1. **Table**	IFAH Europe: Day -7: from the pre-treatment tick counts, the number of ticks recovered from each dog should be rank ordered from highest to lowest tick counts and animals randomly allocated by blocks so that each treatment group has equal numbers of animals that are able to maintain high to low numbers of ticks.	Accepted.
	IFAH Europe: Short- and long-term persistent efficacy: for products with a slow onset of action it should be possible to assess efficacy after longer intervals than 48 hours as long as the applicant offers a plausible justification. In line with FDA and APVMA criteria evaluation of tick efficacy should be possible for *"up to 48 hours or longer if appropriate"*. Time needed for killing should be added on the label. Amend to read: Short-term persistent efficacy: *"Weekly infestation of ticks, efficacy testing up to 48 h or longer if justified (e.g. up to 48 h acting by contact or up to 72 h for systematically acting products) following each challenge as described above."* Long-term persistent efficacy: *"Tick infestation every 4 weeks over the period of effectiveness claimed, efficacy testing up to 48 h or longer if justified (e.g. up to 48 h acting by contact or up to 72 h for systematically acting products) after each challenge as described above."*	Not accepted. The slower the onset of acaricidal activity, the higher the risk of disease transmission and the longer undesired clinical effects persist. Recently, Heile and Schein (2007) could experimentally demonstrate that unfed *Dermacentor reticulatus* ticks need to be attached at least 48 h before transmission of *Babesia*. Moreover, persistence of ticks up to 72 h, i.e. three days after treatment appears not acceptable to owners for cosmetic reasons. Heile and Schein (2007): Shortest transmission times of *Babesia canis canis* by *Dermacentor reticulatus*. Meeting of the DVG section "Parasitology and Parasitic Diseases", 4.-6. June 2007, Celle, Germany.

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
4.1.7 Formula	IFAH Europe: As mentioned before (section 4.1.5.2), only killed ticks should be used for calculation of efficacy. Amend to read: *"**Treatment group (m_t):** Mean number of live (categories 1-3) ~~or killed, engorged~~ ticks ~~(category 6)~~ on the host animals."*	Not accepted (ref. to comment under 4.1.5.2)
4.1.7 Last paragraph	IFAH Europe: Geometric means for the tick or flea counts provide a better estimate of the center of the data and should be used as a reference, as it is recommended in guidelines for other parasites (e.g. helmintics). They are the method of choice for measuring parasiticidal efficacy and are recommended by both WAAVP and VICH. Log-transformed flea or tick counts (geometric mean) provide a better estimate of the centre of the data than do untransformed counts (arithmetic mean). Amend to read: *"Arithmetic means are usually acceptable for this calculation. However ~~If~~ geometric means are recommended by both WAAVP and VICH, but ~~used, the transformation must be justified and~~ the arithmetic means should also be recorded.* *The efficacy of the proposed product should be >90% based on geometric means."*	Not accepted. Logarithmic transformation of the counts is deemed inappropriate for to the following reasons: - In contrast to endoparasites all animals will be infested artificially with the same number of ectoparasites. Thus, remarkable "skew" distribution within a group, which is considered the strongest argument for log-transformation are normally avoided. - Moreover, all animals are allocated after initial block ranking (ref. IFAH comment to section 4.1.6.1. Table) ensuring homogeneous infestation status within the groups. - Transformation has in general only minor influence on the mean number of ectoparasites in both the control group and the treatment group before starting the experiment. - To the contrary, transformation of the results may possibly mask individual therapy failures after treatment, as already shown for nematodes (McKenna et al, 1998). Literature: McKenna, PB (1998): What do anthelmintic efficacy really signify, New Zeal. Vet. Journal, 46, 82-83)
4.1.9 Warning line	IFAH Europe: The common sense should be that: "the absence of evidence is not evidence of absence". It is therefore preferable to state what has been demonstrated and what has not been tested, rather than state suppositions in the absence of evidence. Amend to read: *"Avoid frequent swimming or shampooing the animal or remove collar beforehand because the maintenance of effectiveness of the product in these cases has not been tested ~~there may be a reduction of the effectiveness~~."*	Accepted.

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
4.2 Field study	AVC: Suggest investigators in a field study should demonstrate in some way that there is on-going tick challenge	Point noted. This could only be realised by including an untreated control group in the field study which is, however, not recommended for animal welfare reasons. It is the responsibility and also in the interest of the Applicant to select appropriate geographic regions where the relevant tick species under investigation are abundant and to perform the field study during periods of peak seasonal activity of the tick species. Indeed, investigators are requested to confirm tick infestation of the study animal prior to treatment and identify the tick species. No change deemed necessary.
4.2 Field study	IFAH Europe: Suggest that speciation and staging of ticks could be valuable information within a field study	In clinical field trials, often lasting for several weeks, counting of ticks will be done by trained personnel, normally the owners. Staging of tick is not foreseen as this could be hardly realised under these conditions. Moreover, larval/nymphal stages are believed to be more sensitive to treatment than adults. Thus, the value of stage differentiation under field conditions is limited. However, since field trials aim to largely confirm the results obtained in the controlled laboratory studies including more detailed parameters, identification of the species is deemed necessary. Advice on counting (section 4.2.3) is amended as follows: *Counts should be undertaken at weekly intervals and the tick species should be identified.*
Section 4.2.3	IFAH Europe: The need for weekly counts by the owner is questionable and too prescriptive. The frequency of the counts should be variable according to the residual effect of the product as shown in laboratory studies. Amend to read: *"~~Counts should be undertaken at weekly intervals.~~ Appropriate intervals for counts will be proposed by the applicant dependent on the specific product characteristics, particularly its recommended duration of efficacy."*	Not accepted. Weekly intervals for follow up clinical observations are generally recommended taking into account the variable and possibly low infestation pressure depending on regional and seasonal conditions and the temporary persistence of ticks on the host (7 to 10 days for adults). In particular, for products with a persistent efficacy claim, the frequency of follow up measures should be increased particularly towards the end of the proposed treatment period. It should be noted that the guideline is a guideline and the given recommendations are not binding. Should Applicants follow a different approach this would be accepted based on appropriate justification.

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
4.2.5.	AVC: A field study conducted to GCP will have to cover all of these items and therefore the ANNEX may not be needed at all. The terminology in this guideline that Annex I represents a field study protocol is misleading, as a study protocol is not simply some questions but has a large amount of additional detail as it will be conducted to GCP standards and thus follow the recommendations of GCP guidelines.	Accepted. Indeed the terminology is wrong and the given example in Annex I is an individual animal record rather than a study protocol (see also **5.2.5 and 5.3.2)**
5. STUDY DESIGN – FLEAS		
Paragraph No.	**Comment and Rationale**	**Outcome**
5.1.3. 1st paragraph, 3rd sentence	IFAH Europe: For a treatment claim on Day 0, it is important that the fleas are distributed over the entire host animal at the time of (prior to) treatment (=knockdown of pre-existing infestations when an animal is first started on the experimental pulicide). By adding "at the time of treatment" this ensures that dogs are not treated (on Day 0) and then fleas are placed on the animal onto areas of skin/hair where higher concentrations of the chemical are located. In contrast, to assess post-treatment residual efficacy, new cohorts of fleas are placed on treated animals at different time points post-treatment to evaluate the persistence of the compound that was applied on Day 0. This may be a minor point but does provide more clarity. Amend to read: *"Fleas should be distributed over the entire host animal at the time of treatment."*	Accepted.
5.1.3. 1st paragraph	IFAH Europe: The description of infestation procedures is good practice and will help to judge how closely the procedures resemble the real world situation, and to identify area of possible bias. Please add the following sentence: "*The applicant should describe and justify the infestation method*."	Accepted.

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
5.1.4 **2nd and 3rd sentence**	IFAH Europe: As stated for section 4.1.6, although accurate with respect to the products currently registered, this sentence seems too limitative and is of no added value within the guideline scope. Please delete this part: *"~~Products with short-term effects usually include dusts, sprays, spot ons/pour-ons, tablets and oral suspensions. Products with long-term effects typically include collars, suspension for injection.~~"*	Accepted. The given examples do not add any relevant information about efficacy testing.
5.1.4 **Table**	IFAH Europe: Prior to day -2, the animals should be infested to assess ability of animals to maintain a flea population and the comb counts should be used to rank order the animals from highest to lowest flea counts and randomly allocated by blocks so that (like the comment for ticks above), each treatment group has equal numbers of animals that are able to maintain high to low numbers of fleas.	Accepted
5.1.5	IFAH Europe: The comments on geometric means under section 4.1.7 also apply to this section. Amend to read: *"Arithmetic means are usually acceptable for this calculation. <u>However</u> ~~If~~ geometric means are <u>recommended by both WAAVP and VICH, but</u> ~~used, the transformation must be justified and~~ the arithmetic means <u>should</u> also <u>be</u> recorded."*	Not accepted (ref. to comment under 4.1.7)
5.1.5	IFAH Europe: Proposed efficacy for a flea product is listed as being at least 95%. For ticks it is 90%. Both should be aligned to 90%. This is the efficacy levels currently in effect for the US and would also match the VICH guidelines for anthelmintic efficacy. There are also arguments that: - using products that are >90% effective (rather than 95%) will slow down the level of resistance; -setting too high a specification will prevent some products reaching the market place. Again, to control the development of resistance it is important to have a range of products in the marketplace. To support our comment we attach a recent published article: "The World Association for the Advancement of Veterinary Parasitology	It should be noted that in response to repeated critique from the industry the required level of efficacy towards fleas was set at 95% or more. In contrast to ticks which are temporary parasites leaving the host after having taken a blood meal, adult fleas are permanent parasites. In principle, 100% efficacy is deemed necessary, because flea allergy dermatitis might be caused by a single flea only. Moreover, surviving fleas may continue egg laying and perpetuate the live cycle in the home environment. It should be noted that, up to date, no problems arose in MA applications regarding the high level of efficacy. However, while at least 95% efficacy should be reached under laboratory conditions, this approach can not be strictly followed in field trials, especially due to the permanent re-infestation pressure from the home

4. STUDY DESIGN – TICKS		
Paragraph No.	**Comment and Rationale**	**Outcome**
	(W.A.A.V.P) guidelines for evaluating the efficacy of parasiticides for the treatment, prevention and control of flea and tick infestation on dogs and cats" (please refer to paragraph 4.5 'Efficacy thresholds against flea and tick species'). Amend to read: *"The efficacy of the proposed product should be at least ~~95~~90%, based on geometric means, for adult fleas at each counting during the claimed efficacy period."*	environment. Moreover, for products with persistent efficacy claim for several weeks, efficacy may drop a little at the end of the period, with single surviving fleas. Therefore, and reflecting the assessment of recent MA procedures for pulicidal products, the limit was set at 95% and above. It is noted that according to WAAVP (2007) a reduction in flea number of only 90% may be expected to provide immediate relief from irritation and blood loss, ameliorate clinical signs in hypersensitive animals and in close environments provides benefit in reducing future parasite challenge. However, higher level of control may be indicated for the management of FAD in highly sensitive animals or to prevent transmission of pathogenic organisms. This statement reflects the dilemma of the authors, having in mind that, indeed, no owner wishes surviving fleas on its pet after the treatment. Thus, it is believed that the proposed level of 95% is in line with the consideration of the WAAVP. As regards the geometric mean, it is referred to the comment under 4.1.7.
5.1.7 **Warning line**	IFAH Europe: The common sense should be that: "the absence of evidence is not evidence of absence". It is therefore preferable to state what has been demonstrated and what has not been tested, rather than state suppositions in the absence of evidence. Amend to read: *"Avoid frequent swimming or shampooing the animal or remove collar beforehand because the maintenance of effectiveness of the product in these cases has not been tested ~~there may be a reduction of the effectiveness~~."*	Accepted.
5.2.3 **1st sentence**	IFAH Europe: In a field study using client owned animals enrolled through veterinarians, if the product claims a monthly treatment interval, why would flea counts need to be performed every 2 weeks? Also, for how many consecutive months should the treatments and the flea counts continue? Since the flea season in most temperate regions will be about	Accepted.

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	3 months, this time period would seem appropriate (3 consecutive monthly treatments with corresponding flea counts just prior to each subsequent treatment. Amend to read: "Actual flea counts e.g. through combing should be performed every two weeks *or alternative appropriate intervals for counts will be proposed by the applicant dependent on the specific product characteristics, particularly its recommended duration of efficacy*."	
5.2.3 **5th sentence**	IFAH Europe: Explicit reference to prevention of FAD or Dipylidium transmission at this stage only in the guideline and in this context seems questionable, since no clear cut-off point is mentioned and since to get such claim requires the provision of adequate supportive data. Please remove this sentence: "~~*Considering that the treatment and prevention of flea infestations is also directed towards the reduction of flea allergy dermatitis and the prevention of transmission of Dipylidium caninum, it is relevant to identify the number of animals that remain infested, despite treatment.*~~" If FAD and prevention of Dipylidium transmission are to be included in this guideline, they might need to be referred to in the scope section.	Accepted.
5.2.4 **Last sentence**	IFAH Europe: Should the control group be listed as a positive control group? It would seem inhumane to ask a pet owner to not treat their pet for fleas for up to 3 months.	Accepted. The sentence is changed as follows: *It is recommended to include a positive control group.*
5.2.5.	AVC: A field study conducted to GCP will have to cover all of these items and therefore the ANNEX may not be needed at all. The terminology in this guideline that Annex I represents a field study protocol is misleading, as a study protocol is not simply some questions but has a large amount of additional detail as it will be conducted to GCP standards and thus follow the recommendations of GCP guidelines	Accepted. Indeed the terminology is wrong and the given example in Annex I is an individual animal record rather than a study protocol (see also comment to **4.2.5 and 5.3.2).**

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5.3 **Heading**	IFAH Europe: From the rest of the text, it is obvious that the scope of the section is limited to assessment of the flea efficacy of IGRs. Please amend the heading to make clearer the scope: *"Specific recommendations for efficacy testing of veterinary medicinal products containing IGRs against flea infestation"*. Please remove the wording: "~~*Note*~~".	Accepted. Since IGRs act on the ovicidal/ larvicidal development but not the infestation of fleas, the heading is changed to *"Specific recommendations for efficacy testing of veterinary medicinal products containing insect-growth regulators (IGRs) against fleas"*.
5.3	IFAH Europe: The proposed sentence here, as an introduction of section 5.3, might provide a useful clarification on the 5.3 whole section. Please add the following sentence: *"Laboratory and field studies demonstrating the IGR properties should be provided. The applicant should justify the type of study (ovicidal/larvicidal activity)."*	Accepted.
5.3.1.1	IFAH Europe: We have still doubts that it is relevant to run separate studies on *Ct. felis* and *Ct. canis*. The two species are certainly showing the same response and it will be very difficult to conduct lab studies on *Ct. canis*. Limited laboratory tests should be accepted to prove that the efficacy against *Ct. canis* is identical to the efficacy against *Ct. felis*. To avoid repeating all dose titration and confirmation studies with *Ct. canis*, we would suggest comparing the activity of the tested drug in vitro against both species (*Ct. felis* and *canis*). Considering the two species are closely related and that their appearance, physiology, life-cycle, and behaviour on the host are almost identical, it should be possible to extrapolate the studies conducted with *Ct. felis* to *Ct. canis*.	Accepted. According to the recently published WAAVP-guidelines (2007) it cannot be assumed, that other species occurring on dogs or cats (*Ct. canis*) are equally susceptible to treatment and consequently supporting data are required for a label claim. Consequently, reference to *Ct. felis* is deleted in section 5.3.1.
5.3.1.2 (*In vivo* studies, IGR's **3 and 4th paragraph**	ClinVet International: **Recommendation:** *In vitro* studies on IGR's in combination with adulticides should be conducted according to the approaches as outlined in the WAAVP guidelines (Marchiondo *et al*., 2007).	Accepted. During the revision of the CVMP guidelines the guidelines of the WAAVP for the evaluating the efficacy of parasiticides for the treatment, prevention and control of flea and tick infestation on dogs and cats (Marchiondo et al., 2007) have been published. To consider the specific approaches made for controlled studies using fixed combination

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	Motivation: The suggested approach, namely a simulated home environment study, to evaluate the ovicidal/larvicidal efficacy of an IGR in a fixed combination with an adulticide is not feasible. Such simulated home environment studies need to be conducted over extended periods of time, special facilities are required and many factors can influence the development of fleas under such conditions, which may compromise the results of the study. The reference to the emerged adults from all harvested eggs during the study period, as stated, is also difficult to comprehend since my understanding is that shed flea eggs develop in the pen environment in simulated home environment studies. In a fixed combination the IGR normally has a more extended residual period of activity than the adulticide. This is the whole idea behind such combinations. Although few or no flea eggs may be collected during the initial period of high adulticidal activity, sufficient numbers of eggs may be collected during the adulticidal efficacy decline period to evaluate ovicidal/larvicidal activity. As stated in the WAAVP guidelines the treated animals may be infested with 200 or more fleas to potentially increase the number of eggs that can be harvested and evaluated for ovicidal/larvicidal activity of the IGR using the standard petri dish method (Young *et al.*, 2004). In conclusion, since flea eggs are sensitive and many factors can affect hatching success it is important to conduct laboratory studies under well controlled conditions and not to adopt approaches which may introduce a large degree of variability. It is thus logical to stick to the proven method which is used worldwide with great success by contract research organizations. **References:** Marchiondo, A.A., Holdsworth, P.A., Green, P., Blagburn, B.L. & Jacobs, D.E. 2007. World Association for the Advancement of	products containing an adulticidal and an IGR section 5.3.1.2, in vivo studies, 3rd paragraph is amended as below. However, the approach as proposed by WAAVP could not be followed completely. Infestation of dogs with up to 600 fleas is not acceptable from an animal welfare point of view and would not generate higher egg numbers if the combination product contains a highly effective adulticide (which is the normal case). Considering that the residual activity may decrease with time, it is useful to increase the number of fleas for reinfestations at the end of the claimed period of persistency or extend the observation period. The following paragraph has been added: *In case of a combination product containing both an IGR and an adulticidal, the demonstration of the IGR efficacy may be markedly impeded by the rapid killing effect of the adulticidal compound. In such a case it may be necessary to increase the number of fleas for infestations in the controlled study according to the WAAVP guidelines* (e.g. 200/animal) and/or extend the study period in order to generate adequate numbers of eggs for the calculation of the ovicidal activity. Reinfestations should preferably be carried out at the end of the claimed persistent period, where it can be anticipated that the residual activity declines, resulting in a sufficient number of surviving egg laying fleas. Alternatively, a controlled study under simulated home environmental condition may also be appropriate to compare both the effect of the adulticidal product alone and the adulticidal compound in fixed combination with the insect growth regulator.* *Marchiondo et al. (2007): WAAVP guidelines for evaluating the efficacy of parasiticides for the treatment, prevention and control of flea and tick infestation on dogs and cats (Veterinary Parasitology, 145, 322-344.)

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	Veterinary Parasitology (W.A.A.V.P.) guidelines for evaluating the efficacy of parasiticides for the treatment, prevention and control of flea and tick infestations on dogs and cats. *Vet. Parasitol*, 145 (3-4):332-44 Young, D.R., Jeannin, P.C. & Beockh, A. 2004. Efficacy of fipronil/(S) – methoprene combination spot-on for dogs against shed eggs, emerging and existing adult cat fleas (*Ctenocephalides felis*, Bouché). *Veterinary Parasitology*, 125:397-407	
5.3.1.2 Last paragraph, 1st and 2nd sentence	IFAH Europe: The comments on geometric means under section 4.1.7 and 5.1.5 also apply to this section. Amend to read: *"Arithmetic means are usually acceptable for this calculation. However ~~If~~ geometric means are recommended by both WAAVP and VICH, but ~~used, the transformation must be justified and~~ the arithmetic means should also be recorded."*	Not accepted (ref. to comment under 4.1.7).
5.3.1.2. Last paragraph, 3rd sentence	IFAH Europe: This section does not separate clearly the recommendations /efficacy threshold for VMP containing IGRs alone or for combined IGR with adulticidal product. In particular, it is not clear what level of efficacy is expected for simple IGR product. The section needs to be clarified. Please modify this sentence as follows: *"The efficacy of the proposed product should be:* *- at least 90% of inhibition of the emergence to adults in case of a IGR as mono-preparation;* *- at least 90% of efficacy vs. ~~for~~ adult fleas and at least 90% for the inhibition of the emergence to adults in case of combination products (IGR+adulticidal).*	Not accepted. We refer to the comment given under section 5.1.5.
5.3.2.	AVC: A field study conducted to GCP will have to cover all of these items and therefore the ANNEX may not be needed at all. The terminology in this guideline that Annex I represents a field study protocol is misleading, as a study protocol is not simply some questions but has a large amount of additional detail as it will be conducted to GCP standards and thus follow the recommendations of GCP guidelines.	Accepted. Indeed the terminology is wrong and the given example in Annex I is an individual animal record rather than a study protocol (see als comment to **4.2.5 and 5.2.5)**

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	AVC: The current Annex I is relevant for a study in dog only, (bodyweight range, swimming, etc.) and if maintained with the GL, it would need further adaptation. Adapt point 1 to include a weight range suitable for cats ad specify points 5 and 6 only apply to dogs.	The term "study protocol" has been replaced with the correct term "individual animal record" It is appended to the guideline as an example, which may be used by Applicants. Applicants are free to modify it. In order to meet the concern as regards the inappropriateness of weight range for cats, the weight range has been deleted.
	Although the example of a field study protocol has been updated based on recent applications, the outline of the questions is very limited and does not address several problems by either being to general or otherwise asking questions that tend to be misleading. Therefore we propose asking for specific data regarding: 1. animal data including historical data relevant to target ectoparasite infestations including relevant recent treatments 2. general health and clinical observations 3. ectoparasite counts including differentiation of alive and dead and attached and non-attached, prior to treatment and at follow up visits 4. Treatment related data (start, dose, frequency) 5. Husbandry, management, environmental control measures, water contact, shampooing, 6. adverse events The flexibility, in order to remain relevant to all the products tested, must be kept. Questions like "Does the animal swim in open waters (lake)?" needs to be modified as this implies that other water exposure eg walking in heavy rainfall or swimming in the sea are unimportant or somehow have different consequences.	The individual animal record appended to the guideline is considered a useful example. It is not binding. Applicants can use and amended it, as appropriate.