27 January 2023
EMA/CVMP/EWP/483154/2019
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on the 'Reflection paper on resistance in ectoparasites' (EMA/CVMP/EWP/310225/2014)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope
2	EGGVP – European Group for Generic Veterinary Products; currently AccessVetMed

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment on this well written and comprehensive reflection paper. The reflection paper highlights the current knowledge shortfalls and therefore the need for further epidemiological research across Europe on several target parasites. Importantly, the need for resistance detection methods, especially those for routine, 'in clinic' or 'in farm'-use, is highlighted, paving the way for future research efforts in this direction. We note there is an apparent discrepancy between what is stated in the text as management strategies to delay the development of resistance with multi-active products and in the conclusion, which seems against fixed combination. Fixed combination products may be a solution to delay the development of resistance, for example those with IGRs, which could be better defined in this reflection paper. It would be helpful in the document to add a definition for tolerance and lack of efficacy in addition to resistance.	Thank you for the comments, which are partially accepted. The text has been overall revised and reworded, and it is considered that it currently makes a clear distinction between multi-active products (i.e. combining substances targeting the same parasite) and combinations of substances targeting different parasite groups. As it remains unclear how and to which extent multi-active products can be a tool in the fight against resistance, e.g. since the conditions of their optimal use remain to be established, the reference to these products in the recommendations to the CVMP has been removed. On the other hand, combinations with an extended spectrum should be used carefully to avoid unnecessary exposure, and this is still reflected in these recommendations. The particular case of IGRs is addressed below. The term "tolerance" is now explained under section 2 – Definition of resistance. The difference between resistance and lack of efficacy is now introduced in section 2 – Definition of resistance, and further explained under section 8.2 – Detection of resistance.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
61	1	Comments: The wording 'infestation' is more appropriate than 'infection'.	Accepted.
78-80	1	Comments: Stating the thresholds for resistance of Malaria vectors seems a rather extreme example, which does not appear to be directly applicable to the common veterinary indications which the paper is about. This might lead to rather inappropriate assumptions regarding definition of resistance. Is this a meaningful example at this place in the publication? Proposed change: Please delete.	Accepted.
79	1	Comments: The wording "a mortality >98% is considered susceptible, <90% is considered resistant" does not read well: mortality cannot be susceptible or resistant. Proposed change: A mortality >98% defines susceptibility, <90% defines resistance.	Not accepted. However, the paragraph has been deleted in accordance with the above comment.
80-84	1	Comments: To avoid misunderstandings it could be helpful to add some general guidance on the interpretation of RRs and the potential "caveats". In several of the following chapters specific RRs are mentioned while others	Partially accepted. The definition of RRs in section 2 has been clarified. The fact that an arthropod population might be qualified as "tolerant" rather than "resistant" in some RR window e.g.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		remain more vague. E.g., one could add that a certain natural variability in sensitivity of different isolates can be expected (but is not necessarily known) so that "low positive" RRs do not necessarily demonstrate resistance. In contrast "very high" RR factors may be more indicative of "truly developed" resistance with potentially relevant implications for resistance management. Proposed change: Please add some short sentence on the very general interpretation of resistance ratios.	from 1 to 10 has been mentioned, and so has the fact that there is no fixed RR threshold corresponding to clinical resistance. Further data on the interpretation of RRs is considered out of the scope of this review, all the more that it likely varies a lot depending on the test system, drug and parasite.
90-96	1	Comments: Following the first introductory statement, we suggest adding a further sentence specifying the geographical extent of the distribution of resistance in *Boophilus* spp. sub-genus ticks. Proposed change: "To date, acaricide resistance in *Rhipicephalus* (*Boophilus*) ticks (especially, but not exclusively, *R. microplus*), addressed towards several chemical classes of compounds (e.g. formamidines, pyrethroids, macrocyclic lactones and even fluazuron) has been recorded in several regions of the world such as Latin America (e.g. Brazil and Mexico), India, Australia (Abbas *et al*., 2014; Reck et al., 2014) and sub-Saharan Africa (Vudriko *et al*., 2016)". Additional references cited:	Partially accepted. The section has been largely rewritten, including the geographical distribution of resistance and the mention of other species. However, the proposed references were not all used, as more recent and extensive reviews were included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- Reck J, Klafke GM, Webster A, Dall'Agnol B, Scheffer R, Souza UA, Corassini VB, Vargas R, dos Santos JS, Martins JR. First report of fluazuron resistance in *Rhipicephalus microplus*: a field tick population resistant to six classes of acaricides. Vet Parasitol. 2014; 201: 128-136. - Vudriko P, Okwee-Acai J, Tayebwa DS, Byaruhanga J, Kakooza S, Wampande E, Omara R, Muhindo JB, Tweyongyere R, Owiny DO, Hatta T, Tsuji N, Umemiya-Shirafuji R, Xuan X, Kanameda M, Fujisaki K, Suzuki H. Emergence of multi-acaricide resistant *Rhipicephalus* ticks and its implication on chemical tick control in Uganda. Parasit Vectors. 2016; 9: 4.	
90-99	1	Comments: *Boophilus microplus* is the cattle tick and not "Australian" as it is the main tick also in Brazil, Argentina, and South Africa. : resistance to fipronil is published in Latin America and other sub-tropical and tropical countries and should be added.	Accepted. The word "Australian" was deleted and the geographical distribution of resistance was clarified, in line with the above comment. Resistance to fipronil is now mentioned in the reflection paper.
92	1	Comments: In addition to 'one animal species (i.e. 'one host life cycle')', it may help provide further clarity to add 'and individual animal'.	Accepted.
96	1	Comments: Do the authors mean '(B.)' instead of '(R.)', in *Rhipicephalus (R.) microplus*	Accepted. The initial letter has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
103	1	Comments: Add *Ixodes hexagonus*. Proposed change: Currently, there is no documented evidence of resistance in *Ixodes ricinus, I. hexagonus and Dermacentor reticulatus* to ectoparasiticides.	Accepted.
105-143	1	Comments: The only reference to the global situation is made for *Sarcoptes scabiei*. Proposed change: Please address global situation more fully.	Partially accepted. The section has been overall updated and this includes other geographical areas than Europe. However, the initial intention of the CVMP with this reflection paper was to focus mainly on the European situation, and therefore when extensive data are available for Europe, no detailed review was made for other parts of the world.
110	1	Comments: Reference is missing for "A survey in the former Czechoslovakia indicated resistance of *D. gallinae* to the synthetic pyrethroids permethrin and tetramethrin as well as to the organophosphate trichlorfon at few farms". Proposed change: Add reference.	Accepted. The reference is Zeman, 1987, which is already included further in the text. The full stop was replaced by a semicolon to clarify this.
120-133	1	Comments: One could consider adding some aspects that may be relevant and applicable to other ectoparasites too, e.g. "reversion to sensitivity": Milani and Vedova (2002, Apidologie 33, 417-422) found an approximate tenfold decline of "resistance" within 3 years	Partially accepted. The reference Milani and Vedova 2002 was replaced by a more recent one adding supplementary information (Elzer and Westervelt, 2004).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(determined by % surviving mites at a fixed diagnostic concentration of tau-fluvalinate in a bioassay). Also, similar to other sections in the paper one could add some previously observed RRs (10, 60 or >300; reported by Milani (1995 Apidologie 26, 415-429 ; Thompson et al. (2003, Bulletin of Insectology 56 (1), 175-181, or Watkins, (1997 Bee World, 78 (1), 15-22)].	It is not the intention of this reflection paper, and it would be hardly possible, to make a detailed overview for each parasite addressed. Therefore, it has been preferred not to add RRs as proposed, all the more that they come from rather old references.
141-142	1	Comments: We think that the case reports on *Sarcoptes scabiei* refractory to 300 µg/kg bw ivermectin should be geographically contextualised by adding "from Japan" after "case reports". Proposed change: Please amend as follows: Global: Case reports from Japan on two dogs treated with 300 µg/kg bw ivermectin suggested that *S. scabiei* in these dogs was clinically refractory to the treatment (Terada *et al.,* 2010).	Accepted (with slight modification).
170	1	Comments: Global situation for sucking lice not addressed. Proposed change: Please address.	Partially accepted. The text has been restructured and updated, but in accordance with the initial aim to focus on European data where available, it remains high-level regarding other parts of the world.
175	1	Comments: Ctenocephalides is more commonly abbreviated as C.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please consider replacing Ct. with C.	
180-184	1	Comments: For the sake of clarity, geographic locations of the cat flea's resistances to carbamates, organochlorine, organophosphates, pyrethrins and pyrethroids, cited in the paper by Coles and Dryden (2014) as well as Schenker *et al*. (2001) should be included.	Accepted. The text has been amended to reflect that, although it can be suspected from Coles and Dryden, 2014, that most of these cases are from the USA, their origin is not always easy to identify. The case reported by Schenker *et al.* is from the USA.
214	1	Comments: The term "cross-resistance" does not fit to the definition given in line 76-78. Proposed change: Please replace by "side resistance" (or adapt the definition in line 76-78).	Not accepted. The wording is the original wording from the publication, and compatible with the amended text of definitions in section 2.
224	1	Comments: Typo 'live stock' should be corrected as 'livestock'.	Accepted.
244 and 270	1	Comments: For consistency with this paragraph's title, 'sandflies' should be corrected with 'sand flies'.	Accepted.
270-273	1	Comments: For completion and further clarity, the names and concentrations of all three insecticides employed in the study (i.e. "DDT 2%, lambda-cyhalothrin 0.06% and permethrin 0.2%") should be included.	Partially accepted. The names of the substances were specified but it was not deemed necessary to mention the precise concentrations used in that specific test system.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
281-282	1	Comments: To improve clarity, we would suggest rephrasing the first sentence as follows: Proposed change: "Resistance can occur within the same chemical class due to a common mode of action shared by analog compounds".	Partially accepted. The whole sentence was deleted as it was deemed poorly informative and already covered by the *Definition* section.
293	1	Comments: Typo, full stop missing at the end of the sentence.	Accepted.
328	1	Comments: IGR should be better defined: IGRs are not insecticide/acaricide products (which are all neurotoxic). They are molecules interacting with hormonal or enzymatic systems which are key for the reproduction of insects. ○ It means that a mutation of these systems is usually not viable. ○ It explains why resistance to IGRs is exceptional and not at all at the same scale as resistance to insecticides. ○ It also explains why combination with IGR protects insecticide for a long time. ○ Examples of fipronil/S-methoprene and dinotefuran or imidacloprid/pyriproxyfen should be added.	Partially accepted. An introductory sentence was included on the mode of action of IGRs. However, in the CVMP's opinion it cannot be stated that a mutation of the target system is not viable - this exists at least for CSIs (see ref. Fotakis *et al.*, 2019) - and that IGR resistance is exceptional. Resistance to IGRs is not rarely reported (see for example, Junquera *et al.*, 2019), and its prevalence, which is quite difficult to compare to that of neurotoxic compounds, may in addition relate to the extent of their use and to the scope/indications for their use (i.e. mainly larvicidal). There seems to be no clear evidence at this time that combination with an IGR will particularly "protect" the associated neurotoxic insecticide, although this was hypothesized by some authors (see Rust, 2016); this was reflected in section 7.2.5.
401	1	Comments: Typo, 'glas' should be corrected to 'glass'.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
401	2	Comments: please correct spelling of "glas" to "glass".	Accepted.
412-414	1	Comments: It may be worth adding that, in the case of fleas, testing for IGR resistance can be performed by collecting eggs, directly from the fur of treated animals (and/or their litter, if they are kept in individual cages), and then keeping the eggs within a larval conducive medium at controlled conditions of temperature and humidity. Alternatively, adult fleas can also be exposed to given doses of the insecticide to be tested by using an artificial feeder system, from which flea eggs and fecal material are then collected to be monitored over time for hatching and then larval and pupal development.	Partly accepted. The concerned text has been moved to section 5.3. It has been slightly amended to better describe the possible testing procedures, and a literature reference has been added (Young *et al*., 2004); however, it is not considered that a high level of details is needed here.
442	1	Comments: We would suggest adding an ending line as follows: "However, molecular assays could be used for further confirmation and characterization of resistance mechanisms, following phenotypic assays".	Partially accepted. The text has been overall updated and reworded, and this concern was taken into account although the proposed sentence was not used as such.
448, 451, 456	1	Comments: Typo 'Varroa' should be in italics.	Accepted.
453	1	Comments: Typo FNOSAD should be "Apicoles" not "Apicole".	Accepted.
457-556	1	Comments: MISSING entomopathogenic fungi: *Beauveria, Metharhrizium* to be added.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			This was included into a new paragraph about possible alternative treatments based on entomopathogenic fungi and bacteria, and possibly on arthropod endosymbionts.
503-505	1	Comments: While more data on the practical benefit of rotation or the use of combination products may be desirable it does not seem appropriate to base the conclusion that "mitigation of resistance by these strategies has not been adequately demonstrated" on the citation of Cloyd 2010 as this paper actually refers to insecticide resistance in greenhouses. Also, the following paragraph gives an example for a benefit of rotation and an additional one for the same parasite would be Jonsson et al (2010) Vet Parasitology 169(1–2):157–164. Proposed change: Please delete the sentence.	Accepted. The sentence was deleted and the section on product rotation was completely reworded; it now includes among others, the reference Jonsson *et al.*, 2010.
510-520	1	Comments: Multi-actives combination: two types of combination should be differentiated: insecticide-insecticide and insecticide-IGR.	Partially accepted. Please see above, comments to line 328.
521-522	1	Comments: Although the Chapter title is plural only one synergist is mentioned. Proposed change: Please either amend the title to the singular or add further examples.	Accepted. The section has been reworded and made more general.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
524	1	Comments: We believe that this compound is an approved active substance by ECHA as a Biocide TP18 (insecticide/acaricide). It is therefore difficult in our opinion to state that this product has no intrinsic killing property.	Accepted. The section has been reworded and notable the word "intrinsic" has been replaced by "direct".
541-544	1	Comments: Expansion of this section with additional examples would be helpful.	Accepted. Further examples and recent references have been added in that section and in section 8.4 in the new paragraph about Integrated Pest Management.
541-542	1	Comments: We found this section a little unclear. *Amblyomma* spp. (please note the typo in the genus name) are usually three-host ticks. To which studies from Africa and South America does the paper refer? It may be worth clarifying and citing the supportive literature as appropriate.	Accepted. The sentence has been corrected.
543-544	1	Comments: "chorioptes mites Sarcoptes" also requires clarification.	Accepted. The sentence has been corrected.
547-546	1	Comments: This section should include also entomopathogenic fungi (*Metharizium* spp. and *Beauveria* spp. above all) with special regards to the control of ticks and the red poultry mite.	Accepted. This has been included into a new paragraph about possible alternative treatments based on entomopathogenic fungi and bacteria, and possibly on arthropod endosymbionts.
578-579	1	Comments: We suggest adding a mention of the "route of	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		administration" amongst the factors potentially influencing the development of resistance (e.g. plunge dip versus more localized topical applications, like hand-held spray apparatus, etc.) as evoked elsewhere (section 7.2.2) in this paper.	The first paragraph of section 8.4 has been amended; section 7.2.2 has also somewhat been reworded and expanded.
589-610	1	Comments: Some explanations given here *e.g.* "lack of efficacy" or "bad uses of a product" or "lack of observance" should be outlined in the Introduction and not introduced so far into the text of the reflection paper. Whilst the topic of this reflection paper is resistance it should be explained that resistance is one possible explanation for lack of efficacy in the field.	Accepted. A general sentence reflecting this has been included in section 2 (Definition of resistance) and section 8.2 (Detection of resistance).
590	1	Comments: Is there a globally accepted definition for lack of efficacy, in herds? Proposed change: Please consider adding definition.	Accepted. See previous comment.
613	1	Comments: Typo 'sea lice' not 'sealice'.	Accepted.
625	1	Comments: For improved readability please add a comma after 'selected'.	Accepted.
629	1	Comments: Unnecessary routine preventive use seems to be a bit dramatic. However, it should be clearly stated that in	Accepted. The paragraph has been completely reworded and the concerned sentence has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		areas with the occurrence of vector borne diseases the preventive use is not unnecessary. Proposed change: Instead of "unnecessary routine preventive use" just say "unnecessary use".	Please note the related sentence: *"Nevertheless, targeted treatment in a broad sense could be applied to ectoparasites, which would consist in avoiding unnecessary or systematic use and base treatment decisions on thorough clinical, epidemiological and parasitological assessment."*
641	1	Comments: Typo In 'Abbas *et a*l., 2014', 'al' should be all in italics.	Accepted. The reference has been deleted in this section, which is rather a summary/discussion of literature data presented above.
668-670	1	Comments: We welcome the idea of developing, when possible, "guidance information regarding scientifically supported risk mitigation measures to be included in the SPC of ectoparasiticides" to minimize the emergence of resistance in ectoparasites.	Noted. The CVMP guideline on the SPC for antiparasitic VMPs (including ectoparasiticides) has been developed and published (EMA/CVMP/EWP/170208/2005-Rev.1). This reflection paper has overall been amended accordingly.
681	1	Comments: For improved readability please add a comma after programmes.	Accepted.
690	1	Comments: **"**it might be prudent to include warnings on the SPC**"** caution should be exercised that due to the acknowledged incomplete knowledge, these warnings do not inadvertently worsen the situation.	Noted. The CVMP guideline on the SPC for antiparasitic VMPs (including ectoparasiticides) has been developed and published (EMA/CVMP/EWP/170208/2005-Rev.1). This reflection paper has overall been amended accordingly.
699-718	1	Comments: Chapter 10.1 CVMP recommendations: Fixed	Partially accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		combinations may be a solution, especially for combination with IGRs. "Restrict the use of fix combination product…" This is in opposition with the management strategy using multi-active products to delay selection (in chapter 7.2.4). In addition, combination with IGRs must be separated: IGR will protect the insecticide molecule as a mutant would not have any new generation.	Please see answer to comments on line 328 and to general comment no. 1.
702	1	Comments: As a very general statement without further specification this may be problematic, e.g. it would argue against preventive use as protection against vector borne diseases, with potential implications for animal wellbeing. Proposed change: Please consider amending the statement.	Accepted. That paragraph and the section relating to CVMP recommendations have been completely reworded. Notably it is now stated that treatment may be based on an appropriate assessment of the risk of infestation.
729	1	Comments: Although the abbreviation NCAs is generally well understood it may be best for clarity to explain the term. Proposed change: Encourage the NCAs (National Competent Authorities) to control.	Accepted.
740	1	Comments: In addition to 'farmers' we would also include 'veterinarians (*e.g.* companion animal veterinarians)'	Accepted. For simplicity we only included "veterinarians".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		as recipients of innovative 'ready-to-use' resistance detection tools suitable for routine employment.	
741	1	Comments: Whilst validation of tests is important and necessary and ring tests are an important tool in this validation. Nonetheless this testing is time consuming and resource intensive to organize and co-ordinate. Perhaps "continuous" is not the correct word to use. Proposed change: ~~Continuous validation of tests~~Ensure availability of valid test methods, e.g. by carrying out inter-laboratory ring tests as necessary.	Accepted.