



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CVMP/EWP/526298/2016-Rev.1
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on the ‘Reflection paper on anthelmintic resistance’ (EMA/CVMP/EWP/573536/2013)

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

Stakeholder no.	Name of organisation or individual
1	Tina Alstrup Hansen, University of Copenhagen
2	Sustainable Control of Parasites in Sheep (SCOPS)
3	Federation of Veterinarians of Europe (FVE)
4	European Group for Generic Veterinary Products (EGGVP)



1. General comments – overview

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2	1. Allele frequency and early action. The SCOPS group was set up in 2004 in recognition, across the UK sheep industry, that anthelmintic resistance (AR) was an increasing issue. One of the underpinning principles that drove this was that we could not wait before attempting to implement strategies to reduce the selection pressure on worm populations, because the sooner action is taken, the more likelihood of success. In scientific terms, this means acting while resistant allele frequency in the parasite population is still low. In particular, the success of refugia (dilution) strategies is critically important, but their effectiveness relies on having a susceptible population of worms. SCOPS does not feel that the current document reflects this need for early action. Irrespective of the prevalence of AR, sustainable practices are essential. Indeed, in countries or on individual farms where AR is not currently an issue, it is arguably the most important strategy for reducing the selection and spread of resistance. 2. Multi-resistant farms There are farms that have multiple resistance to all 3 broad-spectrum groups in the UK. The management of these is difficult, but not impossible, with very careful monitoring and use of management tools. The current paper does not make mention of this situation. 3. Use of groups 4-AD and 5-SI In the SCOPS paper given at the EMA workshop on 13 June, the importance of utilising these two 'new' groups as a quarantine treatment, and also as a single treatment mid/late season, was outlined. This is vital if we are to extend the useful life of the other three broad spectrum groups AND protect the future of the group 4	1. The point 'Effectiveness of refugia strategies relies on having susceptible worm populations' has been added to the reflection paper. The necessity of early implementation refugia strategies (when resistant allele frequency in the parasite population is still low) has been added in section 6.2. 2. The occurrence of multi-resistance on sheep farms is mentioned in section 3. 3. The described quarantine treatment given for sheep is too specific to be mentioned in such detail in a reflection paper. Quarantine as a management tool is shortly addressed in a general way (e.g. section 6.4 and section 7.3)." 4. The risk of inadvertent exposure of parasite populations to potential selection when some products are used e.g. combination products for the treatment of nematodes and trematodes infestations are now mentioned in the reflection paper (see section 6.1.).

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	and 5 from overuse should the others fail (as has been reported recently in the Netherlands). We would ask that the final document acknowledges that there is a positive and urgent role for these compounds to be used more widely. 4. Inadvertent Use of Actives At the workshop, we brought to the members' attention the issue of inadvertent exposure of parasite populations to potential selection when some products are used. In the UK, this applies to endectocides used for sheep scab control and to 'combinations' such as fluke and worm products. The use of combinations is acceptable when both parasites are the intended targets. However, when these products are used for the control of only one parasite there is still selection pressure on non-target parasite. The advice given with these products needs to be considered, as does the meat withhold periods which can be lower for some combinations than the individual actives, which encourages inappropriate use.	
3	FVE welcomes the updated reflection paper on anthelmintic resistance. Effective anthelmintics are essential to safeguard animal health, welfare and production. Anthelmintic resistance is a real problem, and in comparison with antibiotic resistance has been given hardly any attention. In order to keep them effective, they should not be used without careful thought being given to the risk that each use brings to the further development of resistance. The reflection paper fails to recognise the great lack of availability of anthelmintics. This means that very often off-label use is needed especially for species like goats, donkeys and alpacas where often no products are available at all. Also for some major species in some	The lack of availability of anthelmintics in goats, donkeys and alpacas as well as fish is now mentioned in the reflection paper. Other points (long-acting boluses, targeted strategic treatment, POM status) have been added or emphasised in the reflection paper.

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	countries and for some indications, products are not available. One other aspect not touched upon in the paper is the possible impact of climate change. It is expected that more rain will fall in certain regions which together with a higher temperature could create more favourable conditions for helminths to survive on pastures. During the meeting on the 13th June, a presentation was also given on the benefits and challenges of the different methods of administration (e.g. long acting boluses), we suggest adding this also in the reflection paper. Last but not least, the most important way to fight resistance is to try to reduce the number of unnecessary treatments. Seen the huge problems with resistance we have already it is urgently required to move away from the regular preventive worming we have done in the last 40 years and to move to a more targeted strategic treatment embedded in the whole herd health program. Therefore advertising should point to the need of getting veterinary advice before worming, POM status is important to allow the treatment to go along with veterinary advice.	
4	EGGVP appreciates the opportunity to comment on this draft concept paper. EGGVP welcomes and agrees on the contents of the concept paper generally. Special caution should be taken because parasitological efficacy tests are oftentimes not as exact as a bacteriological test. Furthermore lot of parasitological examinations can only be carried out in living animals and sometimes these are very difficult to perform. Nevertheless, the variance of parasitological infestation in	The difficulty of identification at species level in the field is now mentioned in the reflection paper (section 5.3.).

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	animals is high even at the same species. It would also be important to bear it in mind that in many cases the identification of parasites cannot be performed at species level, but only at genus or family level, although differences may be even at species level. In addition, sometimes the natural parasite infections do not show the same profile as in the artificial infections.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
039	3	Comment: Heavy infestations with helminths might lead to mortality. Proposed change: Add: <i>This might subsequently impact on performance (...), on production (...) and might even lead to increased mortality.</i>	Accepted.
044	3	Comment: Resistance is also seen in fish such as Salmon in which they see a reduced efficacy of praziquantel. Proposed change: Add sentence about resistance found in aquatic animals.	Not accepted. The literature on reduced efficacy of praziquantel in Salmon was not provided by this stakeholder and no information was given regarding the worm species. No literature could be found on this subject. Therefore this proposal will not be added. However, a remark has been made that anthelmintics should be available for fish.
080	1	Comment: <i>Oesophagostomum</i> spp. in pigs have also been reported to be resistant to LEV and BZs.	Accepted.
081	1	Reference 50 is not on resistance of parasitic nematodes in pigs.	Accepted.
081	1	Proposed change: Add the following to the text after pyrantel: “, benzimidazoles and levamisole” Include the following references: Gerwert S, Failing K, Bauer C. Prevalence of levamisole and benzimidazole resistance in <i>Oesophagostomum</i> populations of pig-breeding farms in North Rhine-Westphalia, Germany. <i>Parasitol Res</i> 2002;88(1):63-68.	Accepted.

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		Várady M, Bjørn H, Nansen P. <i>In vitro</i> characterization of anthelmintic susceptibility of field isolates of the pig nodular worm <i>Oesophagostomum</i> spp., susceptible or resistant to various anthelmintics. Int J Parasitol 1996;26(7):733-740. Bjoern H, Roepstorff A, Waller PJ, Nansen P. Resistance to levamisole and cross-resistance between pyrantel and levamisole in <i>Oesophagostomum-Quadrispinulatum</i> and <i>Oesophagostomum dentatum</i> of pigs. Vet Parasitol 1990;37(1):21-30. Roepstorff A, Bjorn H, Nansen P. Resistance of <i>Oesophagostomum</i> spp. in pigs to pyrantel citrate. Vet Parasitol 1987;24(3-4):229-239.	
126	3	Comment: The pharmacovigilance system has serious limitations to be used as a system to detect resistance. Indeed often it is uncertain whether what is seen is really a lack of efficacy, so seldom it will be reported. In addition, if a product seems not to work well, vets will simply not use it anymore, hence no reports will come in. If we want to use the pharmacovigilance system to find out about anthelmintic resistance, a more pro-active system should be envisaged, e.g. pharmaceutical representatives visiting vets could ask for regular feedback.	Partly accepted. The sentence has been amended as proposed without addition of “serious”.

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		Proposed change: However, the system has serious limitations as resistance is difficult to recognised in the field and ...	
144	1	Comment: Ref. 8: not original, ref. 30: Human reference	Accepted.
166	1	Comment: It is not only for cattle nematodes that eggs are not species specific.	Accepted.
222-223	3	Comment: <i>'... or a too frequent use of anthelmintics belonging to the same class will increase the risk for selection of resistance.'</i> Listening to the debates between the experts on the EMA meeting on 13 June I was not sure whether an agreement was reached on this. Some pleaded more in favour of using the same class (being afraid for multi-resistance when rotating), while others suggested rotation might be better. Proposed change: Make sure we are certain about this statement, otherwise we should recognise that no scientific evidence exists on whether rotation is better than keeping the same class and ask for more research in this.	Accepted. See comment below. Rotation is mentioned in the reflection paper but it also is pointed out that there is no scientific evidence of benefit.
224	2	Annual rotation of anthelmintic classes was a practice historically recommended in the UK to help delay the development of AR. However, this has now been superseded by advice to use the <u>most appropriate</u> chemical group for the target parasite(s). This increasingly involves the use of several actives in one	Accepted. The benefit of rotation has not been scientifically demonstrated and the strategy for reaching a delay in resistance development is controversial. This is now pointed out in the reflection paper.

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		season and, while this can be considered as 'within season rotation', this would be a misleading term, since the chemicals used cannot easily be predicted as 'rotation' would suggest.	
230-233	2	De-worming cannot be based simply on 'confirmation of burden', unless this term also includes predicted burden as determined, for example, by parasite forecasting (e.g. Nematodirus – add link) or previous knowledge of the contamination history of the grazing area.	Accepted. See section 9.
255	3	Comment: Use of multi-active anthelmintic products. The use of multi-active products can be beneficial but only used at the right moment. Often this is not the case and therefore this could lead to multiple resistance. It is very important to clearly put in the SPC and the PIL when this product can be used and when it should not be used. The same also counts for long-acting boluses. Proposed change: Add sentence to emphasise the importance of timing to use these multi-active products in pil/spc.	Partly accepted. For multi-active anthelmintic products: More research is needed before formulating any recommendation on the prudent use of such products even if it is evident that the same recommendations as mono-products also apply.
256-263	2	The SCOPS group has discussed the situation with multi-actives and our overall opinion is that these do offer the potential to delay resistance to the component actives. However, we also acknowledge that their value is at its greatest when allele frequency for resistance in the worm population is still low to the	Partly accepted. More research is needed to determine benefit/risk balance of such products and thus recommendations for prudent use of such products.

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		constituent actives AND there is a refugia-based strategy in place. We, therefore, suggest that, while there is a need to bring multi-actives to market, there is equally a need to better quantify the likely benefits to the European sheep industry and define the combinations that are likely to bring these to fruition. There is also a need to provide practical guidelines to prescribers on the situations when such multi-actives should be prescribed.	
288	3	Comment: Treatment strategies. We miss in the treatment strategy the work that needs doing to <u>reduce the reliance on anthelmintic</u>. This can be done by done by methods such as using alternative grazing strategies, good nutrition and acquired immunity, quarantine protocols to prevent import, monitoring and contamination mapping and breeding for 'resistance'. Suggestion: Elaborate more line 301, 302.	Partly accepted. Pasture management added to delete in section 6.4. Good nutrition, acquired immunity and quarantine protocols added in section 7.3.
291	2	In line with our comment above, a 'confirmed worm burden' would imply that there are animals with clinical signs and/or a high FEC, indicating the presence of adult worms. In either case, there is already significant damage to animal performance and possibly welfare. Increasingly, we are using indicators such as growth rates to 'confirm a worm burden', which also allows for treatment of those animals in most need, or who would benefit most from treatment, leaving others untreated (this has the added benefit of providing a higher <i>refugia</i> population – TST treatments). Contamination mapping (linking FEC and mob data to	Partly accepted. See later in the text, first CVMP recommendation: "Treatment should be based on the confirmation of worm infestation, using appropriate diagnostic measures. If this is not possible, treatment should be based on local (regional) epidemiological information regarding helminth infestation, e.g. contamination mapping or estimation of contamination." And second CVMP recommendation "Promote targeted selective treatment at farm level which ideally should include post-treatment check-up."

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		grazing areas over time) is another tool being developed. Therefore, SCOPS would urge the EMA to encompass these tools and re-phrase this in the assessment of worm burden and need to treat section.	
292	2	Again with 'alternation', we would suggest that this is on the basis of the best choice for the target parasite.	Partly accepted. The term "alternation" was deleted. The rotation of anthelmintic classes is mentioned in section 6.1 as follows: "Although there is a lack of scientific evidence, rotation of anthelmintic classes is often recommended to delay the development of resistance."
321	1	There were reports on anthelmintic resistance in <i>Oesophagostumum</i> spp. in 2005 when the guidelines mentioned in line 318 were developed. (please see comments for line 80 and 81).	Accepted. Point noted. The sentence has been removed.
342-344	2	The SCOPS group would recommend to the EMA the SCOPS guidelines, which are contained in the pdf attached, and which have been validated over the last 12 years in the field.	Not accepted. SCOPS Guidelines have been written for the specific situation in the UK and can be only considered as a local guideline.
342-344	3	Comment: See earlier comment on line 222-224	See earlier comment on lines 222-224.
341	3	Comment: Currently very little evidence on anthelmintic resistance exist because the diagnosis is difficult but also as hardly ever diagnosis was done is recorded. To move forward improving diagnostics and starting a monitoring scheme is urgently needed. As suggested in the 13 July meeting, the suggestion to establishment an EU reference labs in this area so that they can establish and maintain the reference strain library, evaluate and validate monitoring tools and raise awareness and training in respect to anthelmintic	Accepted. See also recommendations.

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		resistance could be very useful. Proposed change: Include a line after 341 on the needs to start monitoring anthelmintic resistance. Suggest the establishment of an EU reference lab for anthelmintic resistance?	
355-356	2	The term 'diagnostic' is misleading in this context. Referring back to 291 above, the diagnosis of a worm burden before it has done damage is difficult. Strategies now being used on farms involve the use of a matrix of tools to help us predict the need for treatment more accurately.	Partly accepted. The recommendation has been extended: "Treatment should be based on the confirmation of worm infestation pressure, using appropriate diagnostic measures. If this is not possible, treatment should be based on local (regional) epidemiological information regarding the rate of helminth infestation, e.g. contamination mapping or estimation of contamination."
355-356	4	Comment: Treatment based on the confirmation of helminth infestation may not be feasible for each individual animal/herd. Available local/regional data may be used as a surrogate. Proposed change: Treatment should be based on the confirmation of helminth infestation using appropriate diagnostic measures e.g. Faecal egg counts. If this is not possible, therapy should be based on local (regional) epizootiological information about helminth infestation.	Accepted.
357-358	2	SCOPS agrees that it is vital that everyone involved is aware that reporting a lack of efficacy is important, so for the UK this would replace the word 'Persons qualified to prescribe veterinary medicinal products in accordance with applicable national law and the end	Accepted.

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		user (farmers/animals keepers). Reporting and subsequent data only have value when this is shared both up and down the chain. As such methods for disseminating key messages via groups such as SCOPS should be included in the recommendation to ensure that all parties see value in identifying and reporting any lack of efficacy.	
365	3	Comment: It is recognised that mandatory prescription may not be within the responsibility of the CVMP for nationally authorised products, nevertheless we would urge EMA to make a strong recommendation to the different countries to make it prescription only. Proposed change: add the part to the sentence: 'The proposal of mandatory prescription for nationally authorised products, nevertheless is strongly recommended.'	Accepted. See section 9.
366-367	2	Anthelmintics in the UK are already by prescription only through veterinarians and Suitably Qualified Persons (SQPs).	Point noted.
368-369	4	Comment: The term "large package sizes" is used, but no further definition of "large" is mentioned. Number of animals to be treated would vary between farms and appropriate package sizes would be needed. The alternative would be to use several "small" packages, but it might be less feasible for large farms. Nevertheless, it would be beneficial to recommend the use of the most appropriate package size for a single	Partly accepted. The text relating to package sizes has been changed and "too large" has been deleted.

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		treatment course. Proposed change: Too large package sizes may lead to unnecessary treatment. Package sizes could be assessed, keeping in mind the indication and number of animals to be treated. Appropriate package sizes should be recommended for use which will prevent the possibility of unnecessary treatment.	
370	3	Comment: Seen the enormous lack of availability of anthelmintics it is important to call to increase the availability of anthelmintics especially for species like goats, alpacas and donkeys. Proposed change: Add bullet point <i>To promote increasing the availability of anthelmintics especially for goats, alpacas and donkeys.</i>	Accepted.
380	3	Comment: Resistance to helminths in aquatic animals is another important issue to investigate. Proposed change: Add '<i>to investigate resistance to helminths in companion animals and aquatic animals.</i>'	Accepted.
381	3	Comment: not only survey but also start monitoring Proposed change: ...<i>to survey routinely and monitor the occurrence of resistance throughout Europe.</i>	Not accepted. The sentence is deleted now. The initiation of a monitoring system was moved under Member states responsibility and the text changed.
385-387	2	In the UK, the reference to veterinarians should be replaced by 'Persons qualified to prescribe veterinary	Accepted.

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		medicinal products in accordance with applicable national law.	