European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE SPC FOR ANTHELMINTICS

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

	Name of Organisation or individual	Country
1	International Federation for Animal Health (IFAH) Europe	Belgium
2	Fort Dodge Animal Health (FDAH)	United Kingdom
3	European Group for Generic Veterinary Products (EGGVP)	Belgium
4	Tom Kennedy (Central Life Sciences, Phoenix, AZ 85013)	USA
5	Association of Veterinary Consultants (AVC)	Belgium

Annex:
Feed-back from Focus Group Meeting on anthelmintic resistance, 23 February 2006, EMEA, London

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW

Comment	Outcome
IFAH-Europe: IFAH-Europe believes that the SPC is not the suitable tool to reduce anthelmintic resistance but that the reduction of anthelmintic resistance is possible if a consensus is reached between regulators, experts and industry, trying to avoid the risk of loss of products.	A focus group meeting was organised on 23 February 2006 in order to reach consensus on the subject between regulators, parasitological experts and industry. Consensus was generally achieved on the standard warnings which are proposed in the guideline (see Annex below). As discussed during the focus group meeting, the SPC can certainly be considered as one of the tools to be used to warn the users of anthelmintics about the (potential) existence of resistance. In contrast, it was agreed that the SPC was not the appropriate tool to refer to (herd) management strategies (such as e.g., quarantine treatments, see below). It should be noted that warnings on anthelmintic resistance are already mentioned in the SPC of many anthelmintics authorized through the European procedures. The objective is to increase the user awareness of the (possible) existence of resistance to the active substance contained in the Veterinary Medicinal Product (VMP), or to another active substance belonging to the same pharmacological class. It was also agreed during this meeting that the awareness of the Veterinarians (and farmers) on the anthelmintic resistance was insufficient, with apparently great differences among the member states; this was highlighted by both the parasitological experts as well as the Federation of European Veterinarians.

Comment	Outcome
IFAH-Europe: **Major concerns** The generalisation of a warning on class resistance.	Side resistance within the same class of anthelmintics appears to be the rule rather than the exception. Side resistance has been reported to occur within the benzimidazoles and the acetylcholine receptor agonists (Imidazothiazoles & tetrahydropyrimidines) (Wolstenholme et al, 2004). Concerning the Macrocyclic lactones, as discussed during the focus group meeting, side resistance appears less automatic: there are indications that a distinction between avermectins, on one hand, and milbemycins, on the other hand, is justified (see below).
It has to be clarified what criteria have to be investigated to demonstrate resistance.	The (revised) definition of resistance cited in the guideline does not refer to criteria to be used to demonstrate resistance. Efficacy thresholds and tests recommended to detect resistance are described elsewhere (WAAVP Guidelines), which are likely to be revised in the future (Coles et al., Vet Parasitol, 2006). Such efficacy thresholds (e.g., less than "x" % reduction in FEC "y" days after treatment) are commonly used to consider helminths as resistant in the scientific literature. The warnings are expected to be referred to when there is a clear indication of resistance (e.g., publication in a specialised journal, describing a clear decline in efficacy using an appropriate study, with appropriate tests). It should be noted that a guideline should not be too prescriptive. No change is required.
Scientific literature should not be cited in a regulatory guideline. This is particularly true when this can be misleading; only a few selected publications out of a vast amount are cited here, they only highlight one aspect of a topic, and do not reflect the full picture. Additionally, new relevant articles will most likely be published during the time a guideline is valid and the guideline cannot be updated accordingly.	The references were considered useful in the context of the Guideline; they were limited to the definition of resistance, the description of a case of multiple resistance in Europe (which points out the need to increase the awareness of anthelmintics users on the issue) and a review on the topic. However, it is true that many publications deal with the subject and a Guideline can not be updated regularly. Therefore, the reference to the review has been deleted (Wolstenholme et al, 2004), as well as the description of the case of multi-resistance (Sargison et al, 2005). The text of the Guideline has been revised accordingly. Only the reference to the definition of resistance (pivotal) has been retained.

Comment	Outcome
The standard warning statement to be included in the SPC for anthelmintics could not be agreed by all Member States and it is still unclear how to include the statement in the SPCs of all nationally approved products.	The Guideline may reduce the discussions on which types of warnings should be placed in the SPC of anthelmintics, which can occur during, e.g., mutual recognition or decentralised procedures. Concerning the procedure on how to introduce the warnings in the nationally approved products, the same would apply for any SPC Guideline. CVMP Guidelines are intended to be used at the European, as well as at the national level.
Tom Kennedy. It would appear that the guide was written from the perspective of those who have only dealt with macrocyclic lactones, since most of the examples address issues seen with that particular class of compounds. Resistance and naturally occurring tolerances to chemicals existed before the macrocyclic lactones appeared.	Apart from the macrocyclic lactones, the guideline makes reference to the other classes of anthelmintics as well. The sentence "In Europe, scientific reports indicate an increase of helminth resistance, to different extents, to all three major classes of anthelmintics (benzimidazoles, acetylcholine receptor agonists [imidazothiazoles/tetrahydropyrimidines] and macrocyclic lactones [avermectins/milbemycins])" covers this issue. The guideline is intended to cover all the anthelmintics approved for ruminants and horses; the warnings refer to any of the pharmacological classes.
Tom Kennedy. The audience for this guideline has not been defined, making this reviewer question the tone, level of explanation and the brevity.	(EMEA) Guidelines are intended for the European pharmaceutical industry, as well as for the European assessors for the safety, quality and efficacy of medicinal products. They are published on the EMEA website. Some sections of the guideline have been expanded to better put the intention of the guideline into a general context (see below).

Comment	Outcome
Tom Kennedy. Perhaps the assumption that the label of a product is the place for a discussion of resistance should be questioned. Since all products will presumably carry the same warnings, there is simply no place for a discussion of alternative treatments, timing, frequency or even if a treatment is required. At the point of reading the label, it is possible that all of those decisions have already been made. If one were to look at the labels of any of the current products, it will be obvious that these discussions will be carried forward in a type size suitable for only those with corrected presbyopia. If the definition of labelling here also includes the literature that accompanies the product, perhaps more than a simple caution sentence could be developed, including a more descriptive view of resistance and possible remedies as so briefly defined in the rest of this document. The last assumption to address is that it is not mandatory to read this before purchase or use, even if Directives 2001/82/EC and 2004/28/EC make it mandatory labelling, so perhaps the exercise is high on hope and low on expectations. The Directives also assume that we know definitively what to do to limit the development of resistance, something that is still debatable in scientific circles. Finally, since the use of anthelmintics in food animals is mostly an economic proposition, there are probably competing agendas between use of products for value added use compared to conservation of useful anthelmintic molecules.	-The warnings proposed within the guideline will appear in the SPC, as well as on the leaflet which accompanies the product. The information contained in the package leaflet and labelling must be conform to the SPC. The SPC of anthelmintics can be considered as one of the places for warnings relative to resistance to those products. Expansion of the text, within the guideline, concerning a more descriptive view of resistance, as proposed in these comments, is supported. The warnings to be added in the SPC have also been expanded, taking into account the comments. -All the products are not expected to cover the same warnings. Indeed, the warnings are dependent on the target animal species, the active substance concerned and the helminths species (or gastro-intestinal nematodes as a whole) affected by resistance. -At the present time, the potential impact of those warnings on anthelmintic resistance can not be appreciated. Unfortunately, there is still no follow up on the impact of resistance warnings which already figure on the labelling of some anthelmintics in Europe. -The guideline does not assume definitive knowledge on what to do to limit the development of resistance. That was also addressed during the focus group meeting, and is reflected in the Guideline ("There are many factors that contribute to the selection of resistant helminths, **but currently, the most widely accepted ones…").**
EGGVP. Introduction Background) The timing of these considerations has not allowed the use of the large body of research that has been done in the last three years in New Zealand in ruminants. These studies which are published in a special feature in Volume 54 of the NZ Veterinary Joumal in December 2006 represent the most extensive and up to date research in this area. The most important concepts in preventing the development of anthelmintic resistant are not related to dosing rates and weights. They relate to the use of refugia as a means of maintaining sensitive populations and in the role of combinations anthelmintics and quarantine treatments to prevent the spread of resistance.	-The concept of refugia was thoroughly discussed in the focus group meeting and it was agreed that it was a valid one: selection and development of resistance appears to be associated with practices limiting the size of the subpopulation of worms in refugia, like systematic treatments of the whole herd/flock, dose and move onto a clean pasture, and animal treatment at the beginning of the pasture season. However, it was also stressed that trying to maintain a subpopulation of worms in refugia in order to reduce the selection pressure was a very complex issue (this is still highlighted in the publications provided with the comments, namely, Pomroy, 2006; Leathwick et al 2006 a et b), depending on many factors (of which, geography and local resistance

Comment	Outcome
While management practice in the EU may differ from New Zealand the science on which these conclusions are based is the same and they should be recognized.	situation) and difficult to put in practice. While the purpose of the recommendations to avoid systematic treatments of the whole herd/flock, dose and move onto a clean pasture and treatment at the beginning of the pasture season, were agreed during the focus group meeting, it was stressed that such strategies might not be relevant for all geographical areas and also dependant on the local resistance situation, and the herd management. It should also be noted that the criteria to apply targeted selective treatments in field conditions still need to be validated, particularly under European field conditions. Please note that the PARASOL project (http://www.parasol-project.org) may give answers on this specific issue. Furthermore, although strongly suggested to be beneficial - as far as resistance is concerned - it was stressed that the impact of refugia on the development of resistance to anthelmintics still needed to be carefully evaluated. Finally, the knowledge of the concept of refugia by the veterinarians was not expected to be high either, and could be difficult to explain within an SPC. -Combinations of anthelmintics: this topic was also discussed in the focus group meeting; however, no consensus was reached. It was stressed by some participants that using combinations might be of help only where there is no reported resistance against any of the active substances present in the combinations. This is also supported by scientific literature (e.g. Wolstenholme et al., 2004).Also, the combination approach may only have a limited life span of efficacy as worms with resistance to each compound are present and will mate to produce multi-resistant worms. Finally, recommending combinations is not product specific either. -Quarantine treatment: although it was recognized to be a very good practice strategy to avoid introducing resistant worms within a farm, it was also agreed that recommending such quarantine treatment should not to be part of a SPC: this is rather part of a herd management strategy than being specific of a product/active substance. No change is required.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Executive Summary	**Tom Kennedy.** The Executive summary is inadequate. At the very least, one should frame the issue at hand, suggest the general approach to correcting the issue and comment on the effect of implementation of the changes to the field. **Proposed change.** Nematodes resistant to the application of anthelmintics have been an issue since the first use of these products in ruminants and horses. The recognition of the existence or possible development of resistance to anthelmintics must be considered in the use of any of these products on animals. The intent of this guideline is to increase user awareness of the fact that the development of resistance is directly affected by the use of anthelmintics. One of the ways to increase user awareness may be the addition of language to all anthelmintic labelling that cautions users of the issue of resistance. This Guideline recommends the addition of standard warnings to the Summary of Product Characteristics (SPC) for all approved products.	Accepted. The executive summary has been modified taking into account these comments.
1. Introduction **1st §**	**Tom Kennedy.** The examples ignore the facts of the long history of resistance and that these examples of resistance are probably not the best ones. Characterization of the plight of animals infected with worms resistant to anthelmintics as "dramatic" leaves one to run for the thesaurus. Words like "serious" or "dire" might be more appropriate, given the economic issues as noted later. There is no obvious connection made in the text between the fact that some flocks have shown resistance to all three classes of anthelmintics	The guideline has been modified to make a clear link between the fact that multi-resistance threatens the economic viability of herds/flocks (as well as animal welfare). Also, the word "dramatic" has been deleted. As such situation of multi-resistance seems still limited in Europe (surely in comparison with other parts of the worlds, such as e.g. New-Zealand), the wording has been "attenuated". Also, whereas the multiple resistance is documented world-wide, the cited article referred to an European case, which was the most appropriate for such an (European) guideline. Adding a lot of literature on this issue would not be useful, and is not desirable. See also elsewhere concerning the references.

[1] Where applicable

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	and the threat of resistant worms to economic viability. The frequent use of anthelmintics also threatens the economic viability of flocks. Each of these points has a plethora of literature that could be referenced to complete these thoughts. The paucity and quality of the literature cited to document multiple resistance should be augmented. This is a world-wide issue, well documented on several continents. The statement on discovery of new actives repeats an oft-quoted mantra that serves no purpose here. **Proposed change**: "Resistance to anthelmintics has been recognized in helminths that populate cattle, sheep, goats and horses worldwide. Resistance has been reported in"	The statement "Given that development of new anthelmintics with a novel mode of action in the near future is unlikely to occur, maintaining the efficacy of established anthelmintics appears as a priority" has been kept, as it highlights the need to be aware of the problem. As a whole, the 1st paragraph of introduction has not been profoundly modified, as it is thought to be an adequate background on the subject.
1. Introduction **2nd §**	**IFAH EUROPE.** The following sentence from section 4.4 "*Selection of resistant genes leading to the development of resistance can ultimately result in ineffective anthelmintic therapy*" is too general to be a useful warning statement, but can usefully be included in section 1. **Proposed change:** Please insert the following sentence from section 4.4: "*Selection of resistant genes leading to the development of resistance can ultimately result in ineffective anthelmintic therapy*."	-The comment has been taken into account (see also comment above) and the introduction has been modified accordingly. -The warning in section 4.4. has been modified (see also comment below

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
1. Introduction. **2nd and 3rd §**	**Tom Kennedy.** The proposed audience for the document should be defined since is important for the level of detail used here. Instead of noting the frequency of some alleles and equating rarity or lack of rarity to the use of anthelmintics, relate the resistant gene selection process to the actual activities that users of anthelmintics employ. Also, "the way anthelmintics are used..." begs one to ask if the authors mean that injectables are different than drenches than topicals than…? Since the discussion is expanded (minimally) in the next paragraph, the sentence could be moved. Rewrite paragraphs 2 and 3. **Proposed change:** ~~In general, genes conferring resistance to a particular anthelmintic appear to exist as rare alleles within a helminth population prior to the first exposure to the anthelmintic. The way anthelmintics are used will determine effectiveness of selection pressure for these resistance genes, thereby favouring, or not, the development of resistance within a population.~~ ~~Currently, the most widely recognized factors contributing to the development of resistance are the too frequent and repeated use of anthelmintics from the same class over an extended period of time as well as underdosing (which may occur following incorrect administration, underestimation of bodyweight, etc.).~~ There are many factors that contribute to the selection of resistant helminths, but the most widely accepted ones are too frequent use, the exclusive use of a single chemical entity or lack of delivery of an effective dose. These actions are risk factors because the development of resistant organisms within a population relies on the selection for individual parasites that possess genes that confer survival fitness.	The audience for this guideline is typically the European Pharmaceutical Industry as well as European assessors. It is not usual to describe the audience within the EMEA guidelines. No change is required at this level. The sentence "The way anthelmintics are used…" referred to the selection pressure afforded by any anthelmintic treatment, whichever the route of administration or the formulation being used. However, the wording proposed is clearer; and the guideline has been modified accordingly. The "exclusive use of a single chemical entity" as a major factor contributing to anthelmintic resistance has not been taken (see comments below). The original wording on side resistance has also been kept (see comments elsewhere). The sentence "Other factors that contribute to selection pressures are geography, grazing conditions, the concept of refugia, season of the year and mixing of age groups" has not been included in the Guideline (see comments on these topics above).

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	These genes may or may not be rare when use of an anthelmintic starts, but the frequency may increase based on the amount of pressure placed on the population by use of anthelmintics. Unfortunately, helminths populations that develop under anthelmintic selection pressure usually show resistance to all compounds that employ the same chemical mode of action. Other factors that contribute to selection pressures are geography, grazing conditions, the concept of refugia, season of the year and mixing of age groups.	
1. Introduction **4th §**	**IFAH EUROPE.** Anthelmintics belonging to the same class with the same mode of action might have a different affinity to receptors (e.g. as the tetrahydropyrimidines). **Proposed change:** "*When resistance appears to one anthelmintic in a class, other anthelmintics in the same class (sharing the same mode of action)* ~~*will generally*~~ *may also be affected*."	Accepted. However, published literature usually refers to side resistance within the tetrahydropyrimidines (Varady et al, *Int J parasitol*, 1997) and between tetrahydropyrimidines and Levamisole (Sangster and Gill, 1999, *Parasitol Today*, Borgsteede, Int J Parasitol, 1991). The current sentence in the guideline is thought to adequately reflect the true picture. No change is required in this sentence. However, please note that the following sentence has been modified: "In Europe, scientific reports indicate an increase of helminth resistance, to different extents, to all three major classes of anthelmintics (benzimidazoles, acetylcholine receptor agonists [imidazothiazoles/tetrahydropyrimidines] and macrocyclic lactones [avermectins/milbemycins])." The draft guideline did not refer to the tetrahydropyrimidines: this has been corrected. See also comments on macrocyclic lactones below.
1. Introduction **4th §**	**FDAH. Classification of anthelmintic compounds** The introduction notes that 'When resistance appears to one anthelmintic in a class, other anthelmintics in the same class (sharing the same mode of action) will **generally** (our emphasis) also be	As noted above, one of the conclusions of the focus group meeting was that side resistance was less automatic within the macrocylic lactones class as compared to the benzimidazoles class. As commented, milbemycins and avermectins (which share the same mode of

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	affected.' This generalisation is then used as a key part of the strategy and the statements proposed in the main guideline text assume cross-resistance within any given 'class'. The document recognises three classes of anthelmintics: benzimidazoles, imidazothiazoles and macrocylic lactones. We believe that this classification is not sufficiently discriminating and would unnecessarily restrict access to effective treatment options. Within the macrocyclic lactones a distinction should be made between the milbemycins (represented by moxidectin) and the avermectins (represented by ivermectin, abamectin, doramectin, eprinomectin). Although structurally similar, moxidectin and ivermectin differ in a number of important aspects. Structurally moxidectin lacks a disaccharide group at position C13, includes a substituted olefinic side chain at C25 and a methoxime moiety at C23. More importantly, there are many studies in the refereed literature that demonstrate that this leads to distinct pharmacological properties for the two compounds and different patterns of resistance. Moxidectin has been shown to be effective against multiple strains of nematodes resistant to avermectins, including European parasites (*Bartley DJ et al Vet Parasitology 123, 3-4, 2004 Characterisation of two triple resistant field isolates of Teladorsagia from Scottish lowland sheep farms*). The converse has not been published. Although there have been reports of some level of cross-resistance, moxidectin usually remains highly effective against parasitic nematodes that are quite resistant to the recommended dose rate for ivermectin. In regions of the world where anthelmintic resistance is problematic, moxidectin often remains the only effective anthelmintic against species such as H contortus (*Pritchard R 18th International Conference of the World Association of the Advancement of Veterinary Parasitology 2001 Mode of Action and Mechanisms of Resistance:*	action) are structurally (although slightly) different. These differences account for different kinetic and efficacy properties, ecotoxicity, as well as pattern of resistance. Although there have been reports of "side" resistance (if we consider macrocyclic lactones as 1 class) or "cross" resistance (if we make further distinction between avermectins and milbemycins), moxidectin has been shown to remain effective against nematodes resistant to ivermectin, while the converse has not been reported until now. This could be due, partly, to the lesser affinity of moxidectin, compared to ivermectin, to P-glycoproteins, involved in the efflux of drugs outside the cells and expressed by resistant helminths (Prichard, 2001; Lespine et al., 2007). It is also noted that at least 1 VMP having Moxidectin as active substance is authorized in Europe with a claim of treatment against ivermectin and doramectin-resistant *Haemonchus contortus* in sheep. Further distinction has therefore been made within the Guideline in the introduction section and the wording has been modified accordingly. This is consistent with Sangster and Gill (1999), which comment that "macrocyclic lactone" is a broad generic chemical term, and have adopted the use of the term "avermectins/milbemycins" for this anthelmintic class. The sentence "When resistance appears to one anthelmintic in a class, other anthelmintics in the same class (sharing the same mode of action) will **generally** also **be affected**." is thought to adequately reflect the true picture. Finally, it should be noted that guidelines remain guidelines (i.e. non legally binding documents), and that they should not be too prescriptive; the Applicants have always the opportunity to justify their own point of view at the time of submitting any SPC.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	Moxidectin and the Macrocyclic Lactones). A recent, interim report from the Institute of Parasitology investigating mechanisms for the development of resistance in *Haemonchus contortus* and *Caemorhabditis elegans* concluded that there are substantial differences between the responses to moxidectin and ivermectin and that the two compounds could not be considered equivalent in this regard (*report provided to the Rapporteur, but will not be discussed further as confidential*). This is supported by recent research in France (Lespine *et al* 2007 [In Press]: Interaction of macrocyclic lactones with P-glycoprotein: Structure-affinity relationship). **Proposed change:** Within the macrocyclic lactones a distinction should be made between the milbemycins (represented by moxidectin) and the avermectins (represented by ivermectin, abamectin, doramectin, eprinomectin).	
2. Scope	This is a re-hash of the introduction, needs to be re-written. **Proposed change**: ~~This guideline focuses on the problem of anthelmintic resistance. The objective of it is to draw attention of anyone involved in the anthelmintic treatment of ruminants (sheep, goats and cattle) and horses to the problem of resistance and to help limiting resistance development. This guideline only applies to the SPC of veterinary medicinal products (VMP) containing anthelmintics authorised for (at least one of) the above-mentioned target animal species. .~~	Please note, as commented above, that referring to the SPC is sufficient. The first sentence has been modified as suggested, taking into account the proposal: It has however been added that the warnings relates to resistance.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	The scope of this guidance is to provide language to be added to the labelling of anthelmintic products governed as Veterinary Medical Products (VMP). The SPC for these products must contain this guidance as part of the legal language for the labelling subject to EMEA Directives. This guidance only applies to anthelmintics authorized for at least one of the afore-mentioned target species.	
3. Legal basis **2nd §**	**IFAH EUROPE.** Cross-refer to comments and proposal on "References". **Proposed change:** "*This guideline should be read in conjunction with Directive 2001/82/EC as amended by Directive 2004/28/EC [3], guidelines on the efficacy requirements for anthelmintics [4, 5, 6, 7, 8, 9] as well as the guideline on the SPC for pharmaceuticals [~~6~~10].*"	Accepted Anthelmintics Guidelines from Eudralex Vol 7 are indeed superseded by the corresponding VICH Guidelines. The section references have been modified accordingly. The MUMS Guideline has also been introduced in the references section (although not referring directly to the SPC of anthelmintics, as do the anthelmintic efficacy Guidelines). The new Guideline on the SPC for pharmaceuticals is also referred to.
4. Main guideline text **1st §**	**Tom Kennedy.** This paragraph parrots what was said in the intro and the scope. I would rewrite this to address the reason why this guide is being proposed. **Proposed change:** ~~"In order to draw attention to the possibility of resistance development when using anthelmintics and to help limiting the development of resistance, the following standard sentences are proposed to be included in the SPC of anthelmintics authorized for either sheep, goats, cattle or horses, where appropriate:"~~ The use of anthelmintics to control helminth diseases in cattle, sheep,	The wording proposed is generally beneficial to the Guideline as it replaces the context in which the warnings have been developed. The Guideline has generally been modified accordingly. However , the warnings proposed differ from the warnings that were included in the draft Guideline: -"Frequency of treatment based on set timing, rather than anticipated economic helminth burdens". Although widely practised, treatment at set timing does not necessarily imply a frequent treatment but may be, e.g. a preventative treatment at the beginning of the pasture season. To contra-indicate the latter practice, although being likely to increase the selection pressure and favour the development of resistance (few worms in refugia), was not agreed within the focus group meeting (see above).

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	goats, and horses is indicated for the health and well-being of the animals. This use must be judicious, however, and based on sound veterinary and scientific reasons. Knowledge of the epidemiology of the parasites to be treated, the effects of these parasites on the animals and the economic benefit that should be realized from the application of anthelmintics are all points to consider. Furthermore, as a good steward of the products, the application of treatments should always be done with an appreciation of the long term effects of the use of the products on the entire parasite and host populations. One of the consequences of the use of anthelmintics is the possible selection for individual parasites within a population that may not be susceptible to the anthelmintic. Over time, it may be possible to allow this subpopulation of parasites to be selected as the dominant parasite population, reducing the effectiveness of the particular anthelmintic. Strategies to limit this selection process should be practiced. To that end, special warnings have been developed to call attention to some specific principles that should be observed whenever these products are used. Anthelmintic use practices that should be avoided due to an increased risk of development of resistance and result in ineffective therapy include: Frequency of treatment based on set timing, rather than anticipated economic helminth burdens; Use of the same chemical class exclusively over an extended period of time; and Improper dosing, due to misapplication, loss of dose or improper weight estimation.	-"Use of the same chemical class **exclusively** over an extended period of time." This warning indirectly promotes rotation of anthelmintics; however, no consensus exists on the impact of such practice on the reduction of resistance development. Therefore, the word "exclusive" has not been included. -"Improper dosing, due to misapplication, loss of dose or improper weight estimation". "Improper dosing" either refers to under or over dosing. Underdosing (especially) should be avoided, as far as resistance is concerned. Underdosing may be due to underestimation of bodyweight, misadministration (e.g., by administration of a bolus on the front of the tongue, which may stimulate the closure of the oesophageal groove and by pass the rumen) or lack of calibration of the dosing device (if any). The warning has been modified to reflect this.
4. Main guideline text **Section 4.4. 1st bullet point**	**IFAH EUROPE.** Rewording of the paragraph leads to easier reading. **Proposed change:** "*To decrease the risk of anthelmintic resistance development ~~T~~the following warnings should always be included:*	See above

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	~~o *Strategies that should be avoided because they might lead to an increased risk of development of resistance to anthelmintic drugs include:*~~ *-Too frequent and repeated use of anthelmintics from the same class over an extended period of time should be avoided* *-Underdosing should be avoided*".	
4. Main guideline text **Section 4.4.** 1st bullet point, 2nd and 3rd §	**IFAH EUROPE.** (Cross-refer to the first specific comment). The statement is rather descriptive than being a warning statement and should therefore be transferred to the introduction (as last sentence of the 2nd paragraph) and should be deleted here. **Proposed change :** **"**~~*Selection of resistant genes leading to the development of resistance can ultimately result in ineffective anthelmintic therapy.*~~"	The comment is noted and part of this warning has been modified.
4. Main guideline text **Section 4.4.** 1st bullet point,	**Tom Kennedy**. Remove paragraph that starts "Selection of resistant genes…" Paragraph 1 should be modified as noted above. **Proposed change**: • *The following warnings should always be included:* o "~~Strategies~~ Anthelmintic use practices that should be avoided ~~because they might lead~~ due to an increased risk of development of resistance and result in ineffective therapy ~~to anthelmintic~~: ▪ ~~Too frequent and repeated use of anthelmintics from the same class over an extended period of time~~ Frequency of treatment based on set timing, rather than anticipated economic	The guideline has been modified as commented above.

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Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	helminth burdens ▪ Use of the same chemical class exclusively over an extended period of time ▪ ~~Underdosing~~Improper dosing, due to misapplication, loss of dose or improper weight estimation.	
4. Main guideline text **Section 4.4.** 1st bullet point,	**EGGVP.** More benefit could be gained by adding to these recommendations the use of refugia management practices, quarantine drenches and combination of anthelmintics (where available). These are more effective strategies than those outlined in the guidelines. **Proposed change:** Section 4.4 (Special warnings for each target species): For example warnings could be expended to include The following warnings should always be included. • Strategies that can be used to reduce the incidence and' spread of resistant parasites are: -maintaining sensitive populations of parasites by altering management practices by not treating adult animals or moving newly treated animals onto clean grazing -Using an effective quarantine drench of two of more drench actives when animals are moved onto properties • Strategies that should be avoided because they might lead to an increase risk of resistance development include unnecessary repeated use of anthelmintics and under dosing. (There is no evidence that the repeated use of one drug until it does not work	-See above for comments on the refugia, quarantine treatments and combinations of anthelmintics. -Faecal Egg Count Reduction Test (FECRT), although being labour-intensive, quite insensitive and time-consuming (and not applicable for liver fluke, where dose and slaughter trials are necessary), remains the best test to detect and monitor anthelmintic resistance in field conditions. It works with all anthelmintics (and is, at the time of the comments, the only satisfactory test to monitor macrocylic lactone resistance) and is easy to perform (Coles et al, Vet Parasitol, 2006). This is why it is referred to in the warning "Suspected clinical cases of resistance should be further investigated using appropriate tests (e.g. FECRT)…". No change is required.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	is any more or less effective in preventing resistance than altemating drugs.) • Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (e.g. Faecal Egg Count Reduction Test). Where the results of the test(s) suggest resistance (FEe tests suggest they under score rather than over score resistance - strongly is therefore not a wise concept to include) to a particular anthelmintic , preferably in available a combination anthelmintic of two actives of another pharmacological class should be used or at least a change to an effective active of another pharmacological class. • Selection of resistant genes leading to the development of resistance can result in ineffective therapy. The other statements would appear to be reasonable.	
4. Main guideline text **Section 4.4. 2nd and 3rd bullet points**	**IFAH EUROPE.** We do not see a need for separating the warning sentence into two. Furthermore, either one substance or a substance class should be referred to. As it is still not clear how resistance should be investigated, lack of efficacy reported in scientific literature is not necessarily based on a "true" resistance but might also be the result of e.g. incorrect dosing, incorrect application etc. Therefore, we prefer "reported" instead of "demonstrated". Because anthelmintic resistance is generally shown for distinct populations of helminths, not for all populations all over Europe, we prefer "reported" instead of "developed" in the warning sentence. The common prudent use statement "*Before using this product, seek professional advice on current use recommendations to ensure good control of helminths and to limit selection for resistance to*	The warnings were originally separated into two for the sake of clarity; however, it is agreed that there is no obvious need to do so: both warnings have been grouped together. It is also agreed that either the active substance (if resistance to the active substance contained in the VMP has been demonstrated in Europe) or the class to which the active substance contained in the VMP belongs (if resistance has been demonstrated against an active substance from the same class as the active substance contained in the VMP, but not against the active substance contained in the VMP) should be referred to, rather than substance from the same class. The warnings have been modified accordingly.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	anthelmintics" would provide much clearer guidance focussing on the local resistance situation rather than confusing the user with resistance cases for the whole of Europe. **Proposed change:** "*When resistance to (an) active substance(s) contained in the VMP or to (an) active substance(s) from the same class of anthelmintic ~~is demonstrated~~ has been reported in Europe, using appropriate tests, for at least one species of gastro-intestinal nematodes ~~in Europe~~ or for a particular helminth species (except gastro-intestinal nematodes) ~~the following standard sentence should be used~~, taking into account that the different species of gastro-intestinal nematodes are not distinguishable from each other under field conditions, and that many natural infections are mixed ones, and that "resistance" refers to at least to one species of gastrointestinal nematode;~~:~~ ~~When~~ resistance to (an) active substance(s) contained in the VMP or to (an) active substance(s) from the same class of anthelmintic has been reported, using appropriate tests, for a particular helminth species (except gastrointestinal nematodes) in Europe;* *The following standard sentence should be used* *"Resistance to <active(s) substance(s) ~~> or to <~~ /active substance(s) from the same class of anthelmintic> has been reported ~~developed~~ in <gastrointestinal nematodes /helminth species > in <target animal species> in some geographical areas in Europe. Before using this product, seek professional advice on current use recommendations to ensure good control of helminths and to limit further selection for resistance to anthelmintics."* *~~When resistance to (an) active substance(s) contained in the VMP or to (an) active substance(s) from the same class of anthelmintic is demonstrated, using appropriate tests, for a particular helminth species~~*	It is clear that resistance, if referred to, should be well substantiated, according to the criteria in force at that time, e.g. described in sufficient details (correct dosing, correct application,…) in peer-reviewed specialized literature. This was the meaning of using the word "demonstrated" and "using appropriate tests". No change is required at that level. However, in the warnings, the words "developed in Europe" were replaced by the word "reported", as the former was indeed quite confusing and might have implied that resistance had developed over Europe, i.e. in its entirety. A single mention that "before using this product, seek professional advice …" is considered useless if it was not coupled to indications of the helminthes species concerned by the resistance. The last proposition (adding "and that resistance refers to at least one species of gastro-intestinal nematodes") has also been retained.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	~~*(except gastrointestinal nematodes) in Europe, the following standard sentence should be used: "Resistance to <active(s) substance(s)> or to <active substance(s) from the same class of anthelmintic> has developed in <helminth species> in <target animal species> in Europe. Before using this product, seek professional advice on current use recommendations to ensure good control of helminths and to limit further selection for resistance to anthelmintics".*~~"	
Section 4.4. 2nd and 3rd bullet points	**FDAH** **Description of resistant species** When resistant species are described, they should be listed at species level rather than as genera e.g. *Trichostrongylus axei* rather than *Trichostrongylus* spp.	The warnings proposed in the Guideline do refer to "helminth <u>species</u>" (or gastro-intestinal nematodes as a whole), and not to genera. No change is required at this level. Please also note that a warning concerning resistance of *Trichostrongylus axei* to an active substance should be referred to as resistance of <u>gastro-intestinal nematodes</u> as a whole.
Section 4.4. 2nd and 3rd bullet points	**FDAH.** **Host species** In products approved for more than one host species, the wording needs to be host specific, since the pharmacokinetics of the products may vary between the species, with differing efficacy results e.g. " ivermectin resistant *Haemonchus contortus"* in sheep", rather than a blanket statement encompassing all host species.	The warnings, as suggested in section 4.4, are already host specific: indeed, the following sentence is mentioned: "Resistance…**in <target animal species>**". No modification is required. Please also note that a warning concerning resistance of *Haemonchus contortus* to an active substance should be referred to as resistance of <u>gastro-intestinal nematodes</u> as a whole.
Section 4.4. 2nd and 3rd bullet points	**AVC.** If we adopt the definition of resistance as fixed by Prichard and colleagues in 1980, it has no importance to introduce different special warnings, one for gastrointestinal nematodes and another for other helminths, as proposed at page 4/5 of the draft guideline.	Not accepted. As noted above, the warnings are expected to be referred to when there is a clear indication of resistance (e.g., appropriate study, using appropriate tests, showing a clear decline in efficacy).

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	Proposed change. A single sentence should then be sufficient and valid for all the SPCs of anthelmintics: "Resistance to <active(s) substance(s)> or to <active substance(s) from the same class of anthelmintic> may be already developed in <helminth species> in <target animal species> in Europe. Before using this anthelmintic product, seek professional advice on current use recommendations to ensure good control of helminths in <the animal> or <group of animals> which has to be treated and to limit further selection for resistance to anthelmintics".	The distinction of resistance between GIN, or other helminths (e.g. *Fasciola hepatica*) may be important from a clinical point of view. See above for the changes made to the guideline. No change is required.
4. Main guideline text **Section 4.9.**	**IFAH EUROPE.** It has sometimes been observed that the (dosing) guns are not properly calibrated. **Proposed change:** "*To ensure a correct dosage, body weight should be determined as accurately as possible, as well as the accuracy of the dosing device*."	Accepted. The warnings have been modified.
4. Main guideline text **Section 4.9.**	**IFAH.** The warning "*For the treatment of a group of animals of the same or of a similar age, the dosing should be done according to the heaviest animal of this group*" is in discrepancy to the warning statement above reminding the user to administer the correct dosage. Dosing done according to the heaviest animal of a group might lead to overdosing which could (dependent on the active substance) evoke major safety concerns. **Proposed change:** "~~*For the treatment of a group of animals of the same or of a similar age, the dosing should be done according to the heaviest animal of this group.*~~ *If animals are to be treated collectively*	A similar warning as originally proposed in the draft guideline can be found in the SPC of many anthelmintics. The reason for this is to avoid underdosing (in the context of anthelmintic resistance). However, it is true that overdosing should be avoided, too (both for target animal safety and consumer safety). This was the meaning of the addition of the mention "of the same or similar age" in comparison to some current SPC warnings. However, the wording proposed in these comments is clearer and agreed; the guideline has been changed accordingly.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	rather than individually, to avoid under- or over-dosing, they should be grouped according to their bodyweight and dosed accordingly".	
4. Main guideline text **Section 4.9.**	**AVC.** The procedure recommended for the treatment of a group of animals of the same or similar age may be hazardous for anthelmintics with low margin of safety and in groups with a high degree of heterogeneity in body weights. **Proposed change:** We recommend adding "when individual weighing is impossible" before "the dosing should be done according to the heaviest animal of this group"	See above for a modification of the warning.
Definitions	**IFAH.** A general question that should be clarified when dealing with the development of resistance is what criteria are to be taken to demonstrate resistance. **Proposed change:** Please add the following sentence: "*Further scientific debate is required to establish the criteria that should be used to demonstrate and measure anthelmintic resistance.*"	Not accepted. See above.
Definitions	**Tom Kennedy.** This definition is based on Roger Prichard's paper from 1980. That definition has been updated numerous times in the 26 years since, perhaps some of these would be more appropriate. One such possibility is shown below. It is difficult to imagine that this is the only definition needed for this	The original proposition was inferred from a very recent publication in a specialized journal (Coles et al, *Vet Parasitol*, 2006), stating that "The definition of resistance given by Prichard et al. (1980) still adequately describes the nature of resistance". Although the meaning is essentially similar, the definition has been modified

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	paper and if it is, then perhaps one could simply add it to the text in the Introduction or the Scope, since it is a pivotal part of the reason for the guideline. **Proposed change** ~~resistance in a given parasite population is a greater frequency of individuals that are able to tolerate treatment than in a normal population of the same parasite species and is inheritable. [7].~~ ***:…resistance is a genetically determined decline in the efficacy of an anthelmintic against a population of parasites that is generally susceptible to that drug. '*** *Sangster NC, Gill J.* Pharmacology of anthelmintic resistance. *Parasitology Today* 15, 141–6, 1999	taking into account the proposition. The guideline has been modified accordingly. As, indeed, the definition is pivotal, there will be a mention of "(see definition below)" in the introduction.
References	**IFAH.** The anthelmintic efficacy guidelines in EudraLex Vol. 7 are obsolete (thus are superseded by VICH guidelines) and should be deleted. All the guidelines on efficacy of anthelmintics should be mentioned. As caprines and horses are minor animal species, the MUMS efficacy guideline should also be mentioned. The old SPC guideline is cited and should be replaced by the new one. Scientific literature should not appear in regulatory guidelines (see general comments). **Proposed change:** Please amend the section of References as follows: ~~"*[4] Volume 7A: The Rules Governing Medicinal Products in the European Union, Guidelines "Veterinary Medicinal Products: General, efficacy, environment, risk assessment", European Commission, DG*~~	Accepted. The section has been modified

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	~~*Enterprise, 1999, pp. 153-190.*~~ ~~*[5]*~~ *CVMP/VICH/832/99-corr: Efficacy requirements for anthelmintics: overall guidelines.* *[5] CVMP/VICH/833/99: Efficacy of anthelmintics: specific recommendations for equines.* *[6] CVMP/VICH/839/99: Efficacy of anthelmintics: specific recommendations for bovines.* *[7] CVMP/VICH/840/99: Efficacy of anthelmintics: specific recommendations for ovines.* *[8] CVMP/VICH/839/99: Efficacy of anthelmintics: specific recommendations for caprines.* *[9] EMEA/CVMP/EWP/117899/2004: Guideline on Efficacy and Target Animal Safety data requirements for Veterinary Medicinal Products intended for Minor Uses or Minor Species.* *[6~~10~~] ~~DGENTR/F/2/AW D (2002): Guideline: Summary of the Product Characteristics (SPC) Pharmaceuticals~~ EMEA/CVMP/065/05: Guideline on the Summary of the Product Characteristics for Pharmaceutical Veterinary Medicinal Products.* ~~*[7] Prichard, R.K., Hall, C.A., Kelly, J.D., Martin, I.C.A., Donald, A.D. 'The problem of anthelmintic resistance in nematodes', Australian Veterinary Journal, Vol. 56, 1980, pp. 239-250.*~~"	
References	**Tom Kennedy.** The paucity of references and the probability that they are useful to the Guideline begs that one leave out all but the Legal references. These could be incorporated in the text as full references and remove the need for a Reference section.	See above.

Feed-back from Focus Group Meeting on anthelmintic resistance
23 February 2006, EMEA, London

Welcome
The chairman, M. Holzhauser-Alberti, welcomed the group and asked the participants to briefly introduce themselves. The meeting attendees came from regulatory authorities (EMEA, CVMP and EWP representatives), industry (IFAH Europe and EGGVP representatives), FVE and learned societies (university, EVPC). The meeting was held in view of a new guideline on the SPC for anthelmintic products to be prepared by the Efficacy Working Party (EWP) of the Committee for Medicinal Products for Veterinary Use (CVMP).

Current situation on anthelmintic resistance in Europe in grazing (ruminants and horses) and non-grazing animals (R. Cody, IFAH Europe)

Dr. Cody gave IFAH Europe's presentation entitled "Minimizing the development of anthelmintic resistance. A brief survey of reported anthelmintic resistance in different countries and species in the EU was followed by a statement that resistance management strategies were complex and that the SPC was not the ideal vector of information on this topic. For centralised or decentralised/mutual recognition products, the SPC has to be identical, but in the different countries, different geographical areas there are distinctions for instance in the climate and, consequently, in the frequency of the treatment, etc. A number of concerns by the industry were noted (too short a period of data protection, increased costs for resistance surveillance/lack of validated methods, risks for application/marketing authorisation withdrawal). The industry's position is that the SPC should be general, e.g. a statement that resistance occurs in a particular helminth / target species, that consensus on recommendations should be reached before specifying them in the SPC, and that combination products may be of interest in slowing down resistance emergence.

DISCUSSION
Drs. Kerboeuf and Coles confirmed that there were no validated methods to determine anthelmintic resistance. Furthermore, Dr. Coles felt that treating with combination of products when introducing new animals to an established herd or group had their place. The group supported Dr. Coles in noting that buying a new animal was a "good way" of introducing anthelmintic resistance to a herd. However, Dr. Vercruysse stressed that fixed combination products probably could be of aid only in the situation where there is no reported resistance. Dr. Corning confirmed this, quoting a recent study in sheep where neither the single use of 3 anthelmintic substances nor the combined use showed any efficacy. A brief discussion took place in which some felt that fixed combination therapy was only of short-term benefit and others who pointed towards the advantage of fixed combination products in which overlapping efficacy of the active substances contained with the combination product could be of particular benefit. Dr. Jennings indicated that one fixed combination product containing levamisole and fenbendazole was currently authorised in Ireland. Dr. Cody also mentioned sequential combination therapy (including levamisole and a macrocyclic lactone) in case of introducing new animals into a herd, which was further explained by Dr. Coles. The Chair mentioned, however, that this strategy was different from fixed combination products. Finally, it was agreed to not make the discussion on fixed combination products the focus of the day's discussions.
Dr. Vaarten wondered if SPC guidance would or could focus in on resistance problems at the farm level or at the regional level.

Dr. Descamps indicated that the document developed by the EWP would not include revising dossier requirements. He asked Dr. Cody why there was no mention of triclabendazole resistance in liver flukes and if there were resistances reported in pigs and companion animals.
Dr. Cody confirmed that triclabendazole resistance has been reported in Europe resulting e.g. in a warning sentence on the label of an anthelmintic product by his company (Novartis) in United Kingdom, Ireland, and Netherlands. (This warning sentence was later projected and compared to the warning sentence as proposed in Dr. Seinhorst's presentation.). The group noted that information on anthelmintic resistance in companion animals or poultry is only limited.
Dr. Cody indicated that determination of resistance under field conditions would be difficult to achieve. Lack of efficacy (decreased or low production) might be related to a number of reasons, e.g. poor herd

management. Dr Chartier stressed that many farmers might not be aware of the problem of anthelmintic resistance; ., however, other participants disagreed with that notion, indicating that the farmers knew about resistance.

Refugia: Is it really so important? (F. Descamps, EWP)

Dr. Descamps gave his presentation, which was prepared with the input of Dr. Vercruysse. The main topic of his presentation was the concept of refugia and its application in the field. The presentation focused on the definition, importance, and composition of refugia. Refugia can be defined as the subpopulation of (susceptible) helminths not exposed to anthelmintic treatment and hence to selection. Within the context of "dose and move", it was shown that this practice put high selection pressure on helminths and that it favoured resistance development. How refugia could be used was discussed in relation to the number of animals to treat as part of targeted treatment, the timing of treatment, the frequency of treatment, and pasture management:
-A number of diagnostic tools, which would allow targeted treatment, were discussed for their pros and cons (FAMACHA in sheep, milk production level in goats, *Ostertagia ostertagi* milk antibody levels in cattle, and faecal eggs counts in horses).
-Timing the treatment, while favouring refugia, so that treatment falls later in the grazing season and becomes truly curative, could be of help in lowering the selection pressure for drug resistance on helminths.
-Frequency of treatment
-More appropriate pasture management was said to essentially consist of avoiding "dose and move onto clean pastures".
The role of hypobiotic larvae in horse cyathostomes was discussed. The role of the wildlife reservoir was said to be low due to the fact that nematodes are generally very host-specific. Dr. Descamps indicated that refugia was mainly a concept admitted where animals are grazing, but that it could also exist for cats and dogs and in pigs (*Ascaris suum*).

The impact of the use of refugia would depend on many factors: climatic/geographic conditions, level of resistance already present, farm management practices, proportion of animals treated, presence of intramucosal larvae, and others. In conclusion, Dr. Descamps advocated balance between worm control and section of anthelmintic resistance.

DISCUSSION
Dr. Kerboeuf agreed that the preventative treatment in the spring, similar to dose and move, was favouring selection of anthelmintic resistance and that targeted treatment should be advocated. Dr. Vercruysse agreed that preventative treatment should be avoided but felt it was difficult to move away from the idea of prevention altogether.
Dr Chartier agreed that targeted treatment should be promoted but acknowledged the difficulties under field conditions. The group agreed that there are problems in trying to identify the most affected animals in the herd, a lack of tests sensitive enough particular in dairy animals, a lack of understanding in farmers and veterinarians on the idea of "refugia". Also, the costs for the farmer of frequent, routine use of generic products would probably be less than methods to achieve targeted treatment. Dr. Svoboda informed the group that the availability of anthelmintic products might also limit the choice for targeted treatment. For example, in the Czech Republic the same anthelmintics are used for the control of different parasites. Although e.g. nematodes would probably not require additional treatment, others such as moniezia would. This would result in unnecessary exposure of nematodes.
Dr. Cody indicated the need for better clearer standard warning sentences. He recommended encouraging animal owners to check if the treatment achieves the desired effect. Dr. Vercruysse agreed, indicating that SPC warnings could also increase the awareness of veterinarians for anthelmintic resistance.

Strategies resulting in an increased risk of selection and development of resistance to anthelmintics (C. Chartier, EFSSA)

Dr. Chartier presented the practices leading to an increase in the development of anthelmintic resistance in dairy goats. He gave a brief overview of dairy goat management in France and explained the regulatory context in which treatment of helminth infections is undertaken, pointing out the paucity of effective licensed products. He cited reports from all over France indicating resistance to benzimidazoles. Data from a recent survey in France indicate resistance to this class of anthelmintics ranging between 80-100% of the farms depending on the regions investigated. Dr. Chartier said that helminth infections in goats were not easy to identify clinically and that farmers and veterinarians had to rely on subtle signs such as poor body score and decreased milk production. At the herd level, decreasing efficacy due to resistance leads to an increase in anthelmintic use. Lack of efficacy is not always explained by resistance, but can be caused by underdosing. In the widespread benzimidazole resistance, the culprit, according to Dr. Chartier, was undoubtedly underdosing, which was a consequence of decreased bioavailability of benzimidazoles in goats when compared to sheep. In the case of oxfendazole, the bioavailability in goats is about 50% of what it is in sheep. Some recent work has been performed by Dr. Chartier on smart drenching where an oral pharmaceutical form is used in combination with reduction of the intestinal transit in treated goats. He concluded that under-dosing should be avoided, but that the relationship between under-dosing and selection pressure on nematodal populations was quite complex.

He mentioned that the refugia concept allowed a better understanding of resistance mechanisms at the herd level and made specific recommendations such as capping the quantity of treatments per year (2 to 4 treatments) and targeting individual animals in the herd for treatment. Identifying animals most heavily infected would benefit from cheap, simple, and rapid methods of diagnosis, which do not really exist. A number of criteria were nevertheless identified, such as faecal egg count, faecal scoring or a "clinical approach". Sometimes it was up to a "feeling" of which animals should be treated. Targeted treatment has been shown to be effective when treating higher milk producers and first lactating animals. Targeted treatment relying on a clinical approach (in Haemonchus infections, estimating anaemia by examination of the conjunctiva) appears not to be feasible in dairy goats under European conditions. Dr. Chartier underlined the need for proper herd management, such as the aid of a sheet kept by the farmer on which treated animals are listed, but conceded that the message of prudent use was not getting through enough. Reference was made to modelisation which can be used, less so in goats, to predict resistance development. Combining drugs has a special place in treating animals newly introduced to an established herd.

Dr. Chartier pointed towards benzimidazole resistance as a lesson of the past, which should be understood in order to avoid the same mistakes in the future. In goat practice, the therapeutic arsenal consisted of limited resources, which should be protected through short-term (such as appropriate dosing) and long-term objectives (such as decreasing the number of treatments, targeting treatment, avoiding the dose and move concept). He also recommended the use of alternate anthelmintics; however, currently there is only very limited choice for such products authorised for goats. The challenge is to find a proper balance between efficacy and sustainability.

DISCUSSION

The group discussed the problem of the limited number of anthelmintic products authorised for use in "minor species" such as goats. The general availability of medicines was also mentioned with reference to the MRL (maximum residue levels) regulation. Within the example of goats, Dr. Chartier spoke of two molecules not used in goats: levamisole (no MRL for milk, so forbidden) and pyrantel, not on the market in EU. Dr. Lens pointed out that for MRL development there was no data protection and that companies are reluctant to invest in an MRL procedure that could then used by other competitors. Dr. Seinhorst indicated that combined efforts, between industry and regulatory agencies, could be fruitful where there was special need for products.

Validated and standardised tests to identify resistance to particular anthelmintics (G. COLES, University Bristol)

Dr. Coles indicated his main interests and expertise in the detection and management of anthelmintic resistance with a particular interest in macrocylic lactones usage in horses.
He started his presentation summarising that there are no validated tests at this point to identify anthelmintic resistance. The only reliable method at present would be to "dose and slaughter", which is not a practicable method. Other tests are currently still under development. He introduced the faecal egg count reduction tests and how it is used in different species. Other tests were mentioned such as the egg hatch test, the larval development tests (liquid or microagar form), the larval migration test (avermectin resistance), PCR and pyrosequencing tests, and field surveys, which could all, be of use to various degree. Dr. Coles also informed about a EU funded project, parasite solutions consortium PARASOL (a group of laboratory teams working together) which is developing over the next years a set of management strategies and accompanying tests. He concluded that lots of work would have to be done especially on ivermectin resistance before there would be validated tests and that there are no tests for resistance in liver fluke and tape worms available yet.

DISCUSSION
During the discussion, Dr. Coles confirmed that the only available test that could currently be used would be the faecal egg test in sheep; however, since this test is not yet validated, data might vary from laboratory to laboratory. It was stressed that the lack of funding would make it unlikely that new products would be developed for anthelmintic treatment of farm animals especially in « minor species ». Money would rather be invested in products for companion animal.
Dr. Vercruysse indicated that the criteria for targeting treatment existed, which were not solely based on faecal egg count. He also said that PARASOL had started its work and would follow a well-defined timeline. However, the project is still in a very early stage and would need further funding.
Dr. Kerboeuf mentioned the similarities of multi-resistance in cancer cell. At the cellular level, the mechanisms of cancer cell efflux would resemble the mechanisms in nematodes. This could be of interest in the margins of the PARASOL investigations.
Dr. Vaarten mentioned the EU global technology platform, which is a forum for discussion between industry and the Commission in order to fund important research. Dr. Vercruysse said that he was representative in this forum, but that parasitology issues, especially in the wake of other more pressing items like bird flu, were not on the top of the agenda.
Dr. Coles indicated that refugia were a valid concept and effective in horses and sheep. This could be demonstrated for instance in sheep in the UK where different herd management strategies exist in different regions with e.g. a high prevalence of resistance in the south of England. When asked by Dr. Seinhorst what he would recommend to horse owners, Dr. Coles indicated that several cases of resistance in horses were brought into the UK horses imported from the U.S. where treatments are not the same as in the E.U. Horses should only newly be introduced into a stable when established that they are free of parasites.

Strategies for delaying resistance to anthelmintics that could be detailed in SPC recommendations (J.W. Seinhorst, EWP)

Dr. Seinhorst presented "Strategies for delaying resistance to anthelmintics that are general and independent of housing- and climate factors and could be detailed in SPC recommendations" in which he exposed the assessor's point of view. He situated the SPC as being prepared in accordance with the individual dossier provided for assessment, taking into account the regulatory requirements on safety and efficacy. He showed some of the limits of the current SPC and regulatory requirements while pointing towards general and specific recommendations such as nematode-specific dosing. On the last two slides, examples of possible SPC warnings were listed which formed the basis of the following discussion. SPC guidance could be divided into general and specific recommendation.
According to Dr. Seinhorst, the SPC is the only document in which, during the process of authorisation, the authority's point of view on the applicant's dossier data can be reflected and where statements (agreed on or not) can be included. There is no other document in which information can be included that is considered necessary for the user.

DISCUSSION

The group queried if strategies to delay development of resistance could be achieved by introducing warnings in the SPC. Warnings on the SPC should be specific for a particular product and not be generalised. Concerns were also expressed that any changes to the SPC made in terms of new warning statements would be time-consuming. The Chairman reminded industry that it is the responsibility of marketing authorisation holders to ensure that the SPC reflects the current state of the art . The industry representatives were asked on feedback if the introduction of new warnings on the product literature had shown any impact on the development of resistance. However, no information of such follow-up was available. Dr. Lens acknowledged that general statements could be applied for "old" products but questioned their use for "new" products.

Some of the proposed general recommendations to be introduced into the SPC of anthelmintic substances were discussed.

In addition to the proposed strategies by Dr. Seinhorst, further possible strategies to delay the development of resistance would be to use anthelmintic products in combination or to ensure that no new animals should be introduced into a herd carrying resistant nematodes.

Dr. Kerbouf queried that "Too frequent and repeated use of anthelmintics of same class" would indeed generally be the reason for resistance development. The group agreed that too frequent use would increase the selection pressure. However, Dr. Cody expressed concern that any recommendation to avoid "too frequent use" might restrict the availability of individual products. Other phrases were suggested such as limiting the sentences to " Too frequent use over an extended period of time …" or a statement such as "intensive use or misuse of anthelmintics can give rise to resistance".

The group was in agreement that "underdosing" might increase selection for anthelmintic resistance.
The recommendations for certain farm / herd management strategies were discussed controversially. Although, the purpose of the recommendations to avoid "Systematic treatment of the whole herd/flock", "Dose & Move onto a clean pasture" and "Treatment of animals at the beginning of the grazing season" was in principle agreed; difficulties to implement these into the SPC were highlighted. It was stressed that such strategies might not be relevant for all geographical regions and also dependant on the local resistance situation and the herd management.

The need to recommend in the SPC to apply quarantine treatments when purchasing new animals was raised by Dr. Coles; while it was recognized that such treatments are indeed very important, the group felt that the SPC would not be appropriate for this particular warning.

Dr. Törneke pointed out that refugia might be limited in her country (Sweden) due to the long winter and queried if the concept of refugia could lead to identifying clear management strategies that could be applied in all of Europe. The chairman asked for feedback from other European regions. In Spain, classic treatments at the beginning and at the end of the grazing season are practiced. Special management strategies with regard to anthelmintic resistance are not very well known. Dr. Velasco indicated that surveillance would be undertaken in cattle outside of the region of Léon already studied. In Czech Republic, systematic preventative treatment would be done in early spring and autumn. Treatment success is recommended to be controlled by faecal egg counts. The awareness of anthelmintic resistance is relatively high in veterinary professionals. There are not many sheep and the resistance situation is fairly good. However, repeated treatment of cestodes in horses seems to be responsible for increased resistance development in nematodes.

The proposed special recommendations to be introduced into the SPC of anthelmintic substances or classes with known resistance to a particular helminth species were generally accepted.

However, the recommendation was extensively discussed to "seek professional advice on current use recommendations to ensure good control of parasites and to limit further selection for resistance to anthelmintics". The group agreed that the veterinarian should be at the heart of therapeutic decisions; however, general practioners are often not sufficiently aware of resistance development and would not readily seek expert help when needed. Many veterinarians are not even aware of the existence of

benzimidazole resistance. Dr. Vaarten acknowledged that a lot of work remained on that front and indicated to be more active in professional education with his organization.
It was noted that depending on the national requirements, anthelmintic substances are not always prescribed by veterinarians but by other Health professionals. It was also mentioned by several participants that lack of efficacy and/or potential resistance problems were not sufficiently identified by the attending veterinarian and hence there was lack of information in the pharmacovigilance database.

The Chair further noted that though there was a European Directive governing veterinary medicinal products, the legal status and prescription measures varied in the European Union, thus having an varied impact on the possibility of resistance management within a given country.

Conclusion

General consensus was reached that two general recommendations could be retained subject to editorial changes:

-Too frequent and repeated use of anthelmintics of the same class.
-Underdosing (Although here, it appears that underdosing in some cases could actually slow down resistance development. The group agreed nevertheless to keep this general recommendation.)

The group agreed that it is the misuse that leads to increased resistance development though it was also agreed that the term misuse was rather vague and did not constitute as such optimal guidance when specifying that misuse should be avoided. Dr. Chartier added that any general overuse constituted misuse.

Dose and Move onto a clean pasture and Treatment of animals at the beginning of the grazing season seem to have fallen into disfavour (there was indirect evidence that this led to increased selection pressure) but to categorically forbid them in the SPC was not accepted by the group. Treatment of housed animals could be of interest. Systematic treatment of the whole herd/flock also seems to be in disfavour, though few participants were ready to indicate the need for targeted selective treatment in the SPC.

The group agreed on the last recommendation, which reads as follows:
Resistance to (substance/class) has developed in (helminth species (e.g. Fasciola hepatica)/gastrointestinal nematodes) in (target animal species) in Europe. Before using a product containing (active substance from this class of anthelmintic), seek professional advice on current use recommendations to ensure good control of parasites and to limit further selection for resistance to anthelmintics.

This sentence was discussed in regards to what was meant by class. Caution was expressed regarding a warning on class resistance : While side resistance within the benzimidazole class seems to be the rule, side resistance is less “automatic” in the case for macrocyclic lactones, for example.

It was also mentioned that until now specific treatment programmes had been avoided and that this general statement remained in the spirit of prior assessment.

The large consensus that was had on the concept of refugia did not translate into any direct, clear recommendations that could be taken up in the SPC. It would not be enough to include a definition of refugia without following it up by specific actions to be taken.