European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON PHARMACEUTICAL FIXED COMBINATION PRODUCTS

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

	Name of Organisation or individual	Country
1	IFAH Europe	Belgium
2	Association of Veterinary Consultants	Belgium

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW

Comment	Outcome
IFAH-Europe: In veterinary medicine, **ease of administration and owner compliance** are critical to ensure success of treatment. Economic limitations, particularly for farm-animals, do not generally allow the use of sophisticated diagnostic tools. Intensive livestock rearing, and epidemiological considerations or zoonotic risks require the control of those diseases, which can be avoided **by the preventive approach**. Consequently, the guideline should also consider disease prevention. A single animal diagnosis cannot be the sole criteria for treating an animal. Epidemiological evidence should apply, e.g. prevention of mixed bacterial infections or parasite infestation at certain risk periods (such as weaning) or at time of parasite exposure under certain climatic or husbandry conditions. It is not economically feasible to wait for the disease to occur so that samples can be taken for a precise diagnosis of the infective organism. The convenience and compliance features of a combination should be emphasized, especially in veterinary medicine where severely ill animals are not brought to the hospital as in intensive care medicine, where all investigational tools are available. In summary, we believe that combinations cannot be restricted only for the treatment of well-characterized conditions. They can avoid repeat administrations of individual products, to treat acute cases in the absence of a complete or conclusive diagnosis, and to avoid disease transmission. Combinations are also particularly useful to reduce stress in manipulating farm animals, when they require multiple applications of drugs. They guarantee also a better accuracy of dosing than the application of several products*. Finally, multiple injections may be responsible for extended lesions. These are good examples showing that animal welfare should be taken into consideration for the justification of combinations. These aspects are acknowledged in the last paragraph of section 4.3, but need to also be explicitly mentioned in section 4. It has to be stressed that many non-fixed combinations are currently prescribed by the clinicians, without precise regulatory and scientific-based knowledge/demonstration of possible galenical, pharmacological and/or	It should be emphasised that the responsibility of a company should be distinguished from that of a clinician, which falls under the scope of GVP. Ease of administration and owner compliance may depend on e.g. formulation, packaging, volume, dosage, etc, but are not specifically linked to fixed combination products. The same applies for any "preventive approach". It is felt that "disease prevention" and "metaphylactic treatment" are being confused. For animals kept in groups it is common that only a few animals within the group will show clinical signs of a disease. Nevertheless, group-treatment is considered effective, provided that animals are infected. Treatment of uninfected animals does not prevent such animals from falling ill; it may only postpone the onset of a disease. The advantage and efficacy of a fixed combination product cannot be demonstrated by the applicant, if the disease condition is not well-characterized. Potential advantages of treatment with combination products versus co-medication with single substance products have now been introduced under a new heading 4.3.3. There is no reason why these advantages, opposed to other potential advantages, should be explicitly highlighted in section 4.

Comment	Outcome
toxicological interactions of the different medicines. In this respect fixed combination products should be encouraged where they are appropriate, particularly if this could improve safety, and they should not be blocked by overrestrictive criteria.	
IFAH-Europe: **Major concerns** The major concerns identified within our general comments can be pin-pointed to the following sections of the guideline: • **Section 4 - Justification of the combination**: this section is too restrictive. Furthermore, from the combination of phrases, it could be strictly interpreted to conclude that each active ingredient has to be indicated at the time of treatment. This must be avoided as it might lead to the requirement that a definitive diagnosis is needed before treatment. It is not always possible to diagnose with certainty all diseases, because the exploratory methods are not available or not accurate enough, or are too time consuming or too expensive. In case of acute diseases (i.e. infections, life-threatening conditions…) requiring an urgent treatment, broad-spectrum combination treatments are often needed before further investigations that may take time (such as *in vitro* culture of the organisms). A proposed text change is made under "Specific comments" below.	The impossibility to accurately diagnose a disease does not imply the need for a fixed combination product. In case that the exploratory methods are not available, not accurate enough, too time consuming or too expensive, the clinician will still give consideration to a number of possible causes, with one being more likely than the other. However, it is up to an applicant to demonstrate that a fixed combination product is safe and effective in case of more than one cause being possible. The fact that a proper diagnosis cannot be made in practice does not alleviate a company from demonstrating efficacy and safety of a fixed combination product as a treatment for such a condition.
• **Section 4.3**: Routine hygiene measures such as endo- and ecto-parasite control in pets and farm animals require broad-spectrum combination products to cover the wide range of parasites that may infect the animals. Although a specific diagnostic of the presence and nature of the parasite can be made, it is not possible to perform diagnostic tests frequently, as it is not economically acceptable by the pet owners and the farmers. The penultimate paragraph under section 4.3 places too heavy an emphasis on 'proper diagnosis'.	The mentioned relationship between routine hygiene measures and broadspectrum combination products can be questioned. Single substance products can offer a broad-spectrum as well. With respect to the (routine) use of such broad-spectrum products, the incidence and prevalence of the condition must be considered in a risk-benefit analysis and taken into account in drafting recommendations for (routine) treatment. To confirm the simultaneous presence of several etiological factors, which would require the use of such a broad-spectrum combination product, the applicant must be able to diagnose the condition properly. Reliable information on incidence and prevalence of a condition is also based on diagnosis.

Comment	Outcome
• **Section 6.1.1 and Section 6.3**: The requirements for the demonstration of efficacy of combinations of known or well-established substances, which do not act synergistically or additively but complementarily, should be reduced significantly. More consideration of animal welfare should be given to reduce the number of studies where animals are sacrificed for confirming the activity of a combination of drugs for which efficacy has been well documented earlier as single ingredient. Although section 6.1.1 clearly differentiates combinations of approved active ingredients, for which pharmacological, safety and efficacy properties are well documented, from new active ingredients, this differentiation should also be clearly made in section 6.3.	Considering combinations of known substances, reference can be made to the NTA, Chapter 2, section 5.5. Information on the individual active substances does not have to be provided. For clarification regarding "additive", see section 4.3 of the guideline and the answer to comment on page 12..
IFAH-Europe: **Estimation of withdrawal periods for combination products** The issue of the estimation of withdrawal periods for combination products should be considered by the CVMP for inclusion in this guideline (see examples), to illustrate situations where the withdrawal periods are sufficiently different that it should be scientifically justifiable to limit the residue studies to just one of the active substances. In some broad circumstances such as these the approval of combination products might be expedited to reduce the number of test animals and to improve the availability of new products. It is agreed that withdrawal periods for combination products need to be reassessed. However, the degree to which this must be undertaken should vary depending on the specific situation. It is suggested that the CVMP re-examine some broad circumstances where the approval of combination products might be expedited and acknowledge these possibilities in the revised guideline. Some examples are given below. If adopted, the potential exists to improve the availability of new products and to substantially reduce the number of sacrificed animals and the cost hurdle for the development of combination products.	Residue studies must be conducted with the proposed formulation. However, applicants can submit a scientific justification to demonstrate that one of the active substances is not significant in determining the withdrawal period (WP), and would not be required to analyse for this substance in the samples taken. It is not considered that the CVMP needs to re-examine or review guidance for establishing withdrawal periods for combination products. Applicants have the opportunity to submit scientific justifications for omission of data: this is the current procedure, no change is proposed.

Comment	Outcome
Example 1: where both products are currently approved VMPs and a proposal is made for a combination. Both of the products have approved withdrawal times when used as single substances, but these withdrawal periods vary widely. This variation is such that it is clear that only one active will govern the withdrawal time in the combination product. For purposes of the residue depletion study with the combination, there should be some flexibility in the need to actually conduct such a study. If the Sponsor has pharmacokinetic data that suggests no interaction, the WDP for the longest depleting substance (as a single substance) could be adopted directly. However, if a study is required, then the need to have actual assay data for both actives, seems unnecessary, if the depletion will be governed by only one active. The Sponsor would only provide residue data (and incur the significant analytical and validation costs) for the one active determining the WDP. The above would not apply to combinations where the WDPs are inherently similar.	See comment above
Example 2: situation similar to the above where one product is currently approved but the other product represents a new chemical entity (not currently approved). This new chemical entity **(**NCE) is not to be sold (or formulated) alone but will only be sold in combination with the currently approved product. The Sponsor has pharmacokinetic data and possibly even preliminary total residue data indicating that the withdrawal period will clearly be determined by the currently approved product. While complete toxicology information would be required to evaluate an ADI, the NCE should, in principle, qualify automatically for Annex II with respect to the need for an MRL. Full residue depletion studies and full analytical method validations would not be required saving the Sponsor considerable investment, without compromising safety as the withdrawal time would be determined by the currently approved product.	All substances must have an MRL before use in a formulation, which is intended for use in food producing species. The NCE would require an MRL application, which would provide information on its pharmacokinetic profile and residues profile including, marker residue and target tissues and these data would be evaluated during the procedure to establish MRLs. A residues study would need to be conducted on the proposed formulation.
The best example of this can be based on history with amoxicillin and clavulanic acid. Amoxicillin is by far the slowest depleting compound of the two drugs in all formulations when in combination, yet the Sponsor was required to perform full analytical method validation studies and full residue depletion studies to obtain a full Annex I MRL for clavulanic acid, a compound which will never be sold on its own. The developed methods will never be used because surveillance will be focused exclusively on amoxicillin. This represents a large body of scientific work and significant expense having no value for protecting consumer safety.	The data referred to for clavulanic acid would have been required to establish the MRL: this is a separate procedure from the residues data required to set a WP for a formulation. The two procedures should be kept separate. The data generated for an MRL is only required once and is not repeated for each formulation proposed using the substances.

Comment	Outcome
AVC: The draft guideline is longer and more detailed than its predecessor and has increased the overall requirements. AVC is concerned that these requirements are prescriptive and do not take into account the practicalities of veterinary use of combination products, which are often used in in-contact animals in groups where only some animals have shown signs of disease, groups where not all animals may be suffering from the full range of diseases against which a combination might be used, or conditions where veterinary usage expects one or more pathogens to be present and complete diagnostic assessment is not, as a matter of practice or practicality, carried out. Examples might include enteric diseases or parasitic infections in livestock and companion animals, otitis externa in companion animals or conditions commonly caused by mixtures of bacteria.	See comment to IFAHs general point of concern.

SPECIFIC COMMENTS ON TEXT
GUIDELINE SECTION TITLE

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
Executive Summary and 1. Introduction (background)	**AVC:** The juxtaposition of the word "guideline" and the terms "data requirements" and "acceptable data requirements" is confusing. The guideline itself suggests that the methods described may be useful, and this is not consistent with the word "requirement" which suggests that the document is a prescriptive recipe: i.e. follow it and the end result is guaranteed. Increasing the transparency in this area is necessary to prevent the following of scientifically illogical plans in order to prescriptively follow the "guideline". The AVC recommends deleting the word "acceptable" prior to "data requirements" and re-phrasing the first sentence so that it reads "The aim of this guideline is to outline and clarify data requirements for efficacy, safety and residue documentation…".	"Requirement" was adopted from the original Guideline. It is agreed that the wording may appear prescriptive. However, the terms "guideline" "acceptable data requirements" and "define" are all used in other CVMP guidelines; in particular in the recently adopted MUMS guideline. It is noted that the AVC did not comment on the use of these terms for this Guideline. Therefore, these terms do not need to be amended.
2. Scope	**AVC:** The first sentence "This Guideline outlines the conditions and data requirements" suggests that the items stipulated in the guideline are mandatory, and this does not clearly allow alternatively derived data to be submitted. Indeed we suggest that the mandatory requirements are given in the EU legislation and the role of this document is to provide guidance for a possible route to approval. The word "requirements" is repeated in the second bullet point, again the AVC disagrees with the use of this word within a guideline.	See previous comment.
4. Justification of the combination Paragraph 1, 2nd	**AVC:** The AVC believes that the sentence "Fixed combination products will be only considered acceptable if the proposed combination is based on valid therapeutic principles" ignores the fact that a group of animals may be treated where some animals are in the clinical phase of a disease whilst others are not clinically affected, or	From the proposed wording it is felt that "therapeutic" is considered being similar to "curative". As used in the draft Guideline, "therapeutic" refers to the general interest and attention paid to a disease or disorder and implies both curative and prophylactic treatments and/or methods. See also the answer provided on "General Comments" in the introduction.

[1] Where applicable

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
sentence	indeed where a whole group is treated prophylactically. We therefore suggest the addition of the words “and prophylactic” prior to principles. **IFAH-Europe:** See general comments. *“Fixed combination products will be only considered acceptable if the proposed combination is based on valid prophylactic or therapeutic principles. As an exception, patients suffering from acute serious infections may be treated with a fixed combination product prior to diagnosis if an adequate fast diagnostic tool is not available for animal welfare reasons.”*	The proposed sentence by IFAH is not endorsed. It is evident that animals suffering from acute infections may be treated prior to a definite bacteriological diagnosis. If the preference of a combination product in such acute disease is documented, the proposed combination is considered based on valid therapeutic principles.
Paragraph 2, 1st sentence	**AVC:** We believe that the phrase “an advantage in the clinical situation” could be further explained by the addition of “such as improved compliance and animal welfare” after “an advantage”. **IFAH-Europe:** The wording “clinical situation” is not clearly defined and could be interpreted as referring to clinical efficacy alone. It should be made clear that “clinical situation” includes animal welfare, improved safety, improved efficacy or reduced toxicity.	"Clinical" is meant as pertaining to the direct medical treatment of patients. It refers to those circumstances under which the fixed combination product is used. However, since the wording seems unclear to AVC and IFAH, the words “in the clinical situation” have been deleted. Possible advantages are outlined in section 4.3 and all the mentioned aspects are included.
Paragraph 2, 2nd sentence	**IFAH-Europe:** It is not clear what is meant by an “inadequate diagnosis”. If this means that, for example for parasite infections, the parasite always needs to be proven before treatment may be started, then this phrasing is not acceptable and should be modified. *It will also be critical to ensure everyone has the same understanding of the phrase “diagnosed properly” (bottom of page 4): Is it a common understanding that a proper diagnosis does not only cover proof of parasite/bacteria but also includes anamnesis, clinical picture, clinical relevance (e.g. zoonosis), etc.?*	The guideline is aimed for applicants and the sentence at hand does imply that products should not be developed to offer the clinician an unfounded “all-round” treatment, replacing diagnostic evaluation. The comments from AVC and IFAH are addressing use of the product under field conditions and GVP which is not the scope of the guideline Both examples below refer to situations that can be encountered by the clinician. Although the principles of GVP imply that any disease or disorder should be diagnosed before treatment is initiated, it is obvious that the possibilities for the clinician are limited. It is acknowledged that it will not always be possible to come to a definite diagnosis. Medicinal products should,

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	As illustrated in the table in Annex 2, it is well-known that a true diagnosis of parasites, such as anthelmintic or acaricidal infections, is often difficult to achieve due to the limitations of available detection methods which are currently and routinely used in veterinary practice (e.g. McMaster method, skin scrapings, etc.). The epidemiology of parasites has to be taken into account (e.g. long pre-patent periods, site of infection, intermittent egg shedding) as well as hygiene factors (e.g. risk of zoonosis) and not the proof of the presence of parasites alone. This problem is equally applicable for antiinfectives (see Annex 2 below); for example it is also well known that specific bacterial species (e.g. *Mycoplasma*) are difficult to isolate and that false negative results commonly occur due to limited detection methods. Please delete this sentence: *"~~Fixed combinations cannot be justified for reasons of compensating inadequate diagnosis.~~"*	however, not be administered or dispensed without giving consideration to the possible cause and the benefit of treatment. As pointed out by IFAH, the epidemiology, anamnesis, clinical picture and risk should be taken into account. In the event of e.g. helminth infections, the inability of properly diagnosing the infection should be balanced against the likelihood of the animal bearing a relevant parasitic load. The use of fixed combination products without giving consideration to aforementioned items bears the risk of routine use without a need for medication. It should also be pointed out that the responsibility of the clinician differs from that of the company. It is the company's responsibility to demonstrate efficacy, safety and advantage of a fixed combination product in agreement with the label claim, along with information on the risk-benefit deliberation, in order to provide relevant information to the clinician. The sentence is to be kept.
2nd paragraph, 2nd sentence	**IFAH-Europe:** **A diagnosis of anthelmintic infections is not always reliable due to the following reasons:** • Examination of faecal samples for helminth eggs bears the risk of false-negative results, because helminths frequently shed eggs only intermittently and eggs are not homogenously distributed throughout the faecal sample. • During the prepatent period of a helminth infection a diagnosis based on excreted eggs in faeces is impossible. • In some cases (e.g. *Toxocara* infection in bitches) the parasites are hidden in tissue and cannot be diagnosed properly. • Cestode infections are even more difficult to diagnose as proglottids are often macerated in faecal samples • It is very difficult to collect faecal samples from stray cats.	see above

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2nd paragraph, 2nd sentence	**A diagnosis of bacterial infections is not always possible or reliable due to:** • Technical difficulties of sampling leading to loss (false negative) or addition of the apparent pathogens (false positive). Timing of sampling in the course of the disease can have an influence on the composition of the sample • Time constraints imposed by emergency cases requiring immediate actions • Accessibility of the various tissues and body fluids can be very different e.g. lung tissue and milk Encapsulation of pathogen (S. aureus) in the udder tissue in the course of chronic mastitis (biofilms)	
Paragraph 3, 1st sentence	**IFAH-Europe:** See general comments. Please amend this sentence to read: *"Every active substance in a fixed combination ~~should be indicated for use at the moment of treatment~~ contributes to the intended therapeutic or prophylactic effect when ~~and~~ administered in the correct dose."*	It is evident that active substances in a fixed combination may contribute to the effect of such combination and that this is the intention of producing fixed combination products. However, if an active substance is administered as part of a fixed combination product, but without any "disease target" being present, the substance does not contribute to any therapeutic effect. On the contrary, it may pose a risk to the animal. Therefore active substances that are included in fixed combination products should be indicated at the moment of treatment. The sentence is to be kept.
Paragraph 3, last sentence	**AVC**: The AVC suggests to add "if known" at the end of the sentence "The mode of action…..be documented". **IFAH-Europe:**This sentence is not a justification but a requirement. Please delete this sentence: *"~~The mode of action of the combination should be documented.~~"*	It is considered unlikely to justify the recommendation a fixed combination product for a treatment, without any information on the efficacy and safety of such combination. Reference is also made to NTA, Chapter 2, section 5.5.
Section 4.1 Interactions	**AVC:** The AVC wonders what the rationale is behind the inclusion of "excipients" in the sentence "The possibility of interactions, *in-vitro* as well as *in-vivo* pharmacological interaction, between active substances and/or excipients". Moreover, the investigation of excipients may require an extensive battery of studies and the AVC is unconvinced of	In combining substances, interactions may occur, which are not limited to the active substances, but may involve excipients as well. Therefore "excipients" cannot be deleted and the wording should not be amended. Possible interactions should always be considered. It is acknowledged that the necessity to carry out studies depends on the impact and level of a possible interaction.

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	the value of such studies. The effect of any excipients will be reflected in the pharmacokinetic and pharmacodynamic data of the product. The AVC requests that the inclusion of excipients is clarified and consideration be given to removing the words "and/or excipients" altogether.	See also response to comment on third paragraph of 6.1.1 It should be noted that if new excipients are used in a formulation data are required in accordance with Directive 2001/82EC as amended by Directive 2004/28 EC.
Section 4.2 Indications	**AVC:** The proposed use of the word "all" in the proposed guideline may create problems where only the combination formulation is available but a particular clinical indication makes use of one single ingredient e.g. insecticide and acaricidal combinations. The AVC suggests the deletion of the single sentence second paragraph "The indications…….of the product", as it is not believed to add anything to the document. **IFAH-Europe:** By definition, the indication reflects the proper use of the product; this sentence is superfluous. Please delete this sentence: *"~~The indication(s) should reflect the proper use of the product.~~"*	Considering the example, it is likely that a clinician may use a combination product for only a part of the indicated use. However, this does not exempt the applicant from demonstrating the efficacy, safety and benefit for the combination product, meaning that this should be justified for all active substances in the fixed combination product. The Guideline addresses the authorised use of a fixed combination product. Regarding the previous paragraph, the sentence can be removed.
Section 4.3 - Potential Advantages 1st sentence	**IFAH-Europe:** This list is not exhaustive and other valid advantages should also be accepted if justified, even if not listed in the GL. Please amend this sentence to read: *"Potential advantages of fixed combination include <u>but are not limited to</u> one of the following <u>examples</u>:"*	From a pharmacological point of view the potential advantages of combinations of substances are limited. This should not be mixed up with the reasons for which fixed combination products are used in practice. A new heading 4.3.3 has also been included.
Improvement of activity Paragraph 4, 1st sentence	**IFAH-Europe:** It is not clear why two substances have to exert additive activity against the "same target". In our view the part "*for the same target and*" should be deleted: amend to read: *"In case of an additive activity, the pharmacodynamic effect of one substance adds to that of another ~~for the same target and~~ in a more*	If acting on different targets, the effect would have to be addressed as broadening of the spectrum.

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	or less linear way, without substances interacting."	
	AVC: The AVC requests an example and clarification of the "additive activity" described in the fourth paragraph.	By additive activity it is meant that one active substance can be replaced by another one, without the total efficacy being affected. Substances are interchangeable. The effect usually applies to a limited number of "targets. The alternative wording could be "complementary" Additive activity can apply to e.g. various sulphonamides or a combination of chloramphenicol and neomycin for *Shigella* infections in dogs..
Broadening the spectrum of activity	**AVC:** The AVC believes that the words "have been confirmed" in the statement "several aetiological factors which have been confirmed to occur simultaneously" precludes diseases where it is generally known that several factors are involved but where absolute scientific proof is lacking. The AVC is concerned that some diseases are treated early in a pre-patent or prophylactic way, before clinical signs are seen and a specific diagnosis is possible. Parasitic infections such as coccidiosis or lungworms are examples. Also clinical disease may occur in the prepatent period with some parasitic diseases such as ostertagiosis and cooperiosis in cattle, where diagnosis would not be possible without killing an animal, clearly an undesirable method.	"Generally known" may imply the absence of a need for documentation.
	IFAH-Europe: There is too much emphasis on proper diagnosis (what does that mean anyway?), when it is known that this is not always achievable. Please amend to read: *"Broadening the activity spectrum by combining more than one active substance often relies on the presence of several etiological factors which ~~have been confirmed to~~ may occur simultaneously, and are of clinical relevance ~~and can be diagnosed properly~~."*	The Guideline is not drafted for the practitioner. It should be pointed out that the responsibility of the clinician differs from that of the applicant. It is the applicant's responsibility to demonstrate efficacy, safety and advantage of a fixed combination product, along with information on the risk-benefit deliberation, in order to provide relevant information to the clinician. The text has been reworded with changes to the order of the words: *Broadening the activity spectrum by combining more than one active substance often relies on the presence of several etiological factors which can be diagnosed properly, have been confirmed to occur simultaneously, and are of clinical relevance*

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		See also answer provided under "general comment 4.3 (page 3) and specific comment 4. justification, Paragraph 2, 2nd sentence (page 9).
Section 4.3	**AVC:** The AVC believes that there is an additional benefit of combination products that is not mentioned. There is good evidence that mixtures of anthelmintics and antimicrobials can delay the onset of resistance to a single anthelmintic or antimicrobial, or sustain useful activity when there is resistance to single active components. Under the heading "broadening the spectrum of activity", the second paragraph appears to be a separate sub-section. The AVC suggests that the paragraph is headed "improvement of compliance and animal welfare", especially the avoidance of multiple administrations to very sick animals. This should be included. **IFAH-Europe:** Two new headings should be added. **Improvement of compliance** As mentioned earlier, compliance is critical for the success of the treatments applied to animals. Some species are difficult to dose (e.g. cats), husbandry conditions may make treatment application very difficult (sheep or cattle on high pasture), medication of large numbers of animals (pigs) is cumbersome. Therefore it is essential to be able to combine drugs. In addition, if the combinations are not licensed, they will be used anyway, with increased risks in terms of animal and food safety. Fixed combinations of different endo- and ecto-parasites, or combinations of both, intended for small animals should be exempted from the requirement to demonstrate the occurrence of mixed infections in the target species. There is clear epidemiological and etiological evidence that animals can be simultaneously infected with several parasite species, with species and infection rates varying over time. **Resistance breaking properties** For antibacterial and anthelmintic therapy of the future, resistance-breaking properties might become a key property of the drug profile.	A new heading has been introduced under "4.3.3", taking several of the AVC and IFAH comments into account. If substances are combined with respect to resistance breaking properties, this

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	Current examples show that such property is achieved when a combination such as amoxicillin and clavulanic acid is applied. Drug combinations that act synergistically to overcome resistance clearly add to the potential advantages of a fixed combination.	can be considered as improvement of activity i.e. synergism (4.3.1), as is pointed out in the example.
Section 5 Risk-benefit assessment	**IFAH-Europe:** Location in Dossier: No clear guidance is given where this risk benefit assessment should appear in the dossier. We recommend that this should be discussed in the clinical expert report, combined with the justification for the fixed combination.	Reference is made to Annex I of Directive 2001/82/EC for the requirements of the dossier, including a risk benefit assessment. Although the Guideline does address items following the requirements for a dossier, it does not deal with the way in which items should be included or addressed.
Paragraph 2 and 3	**IFAH-Europe:** Paragraph 3 is not very clear, particularly as it refers to a benchmark ("state of the art") that is progressive and consequently difficult to define. It should be combined with the 2nd paragraph. Delete paragraph 3 and amend paragraph 2 as follows: *"The risk-benefit assessment ~~for the individual fixed combination product~~ should determine whether the particular combinations of active substances is justified and should assess the potential advantages in the clinical situation against possible disadvantages compared to the therapeutic use of the single active substances.* *~~The risk-benefit assessment should determine whether the particular combination of active substances is justified and whether the product meets the requirements of the state of the art with respect to efficacy and safety~~."*	The proposal is considered and the text will be revised.
Paragraph 4	**IFAH-Europe:** It does not give any guidance, this is a statement with is not relevant if the dose is fixed. What does "critical dosage ranges" mean? In our view this is covered by "narrow therapeutic indices". Please delete this paragraph: *"~~A combination of substances with critical dosage ranges or with narrow therapeutic indices is unlikely to be suitable as a fixed combination.~~"*	This paragraph was included to indicate that fixed combinations containing substances having a narrow therapeutic index (= small safety margin) or critical dosage range (= one substance has to be dose accurately) limit their range for use. For clarification the text has been amended: A combination of substances with critical dosage ranges or narrow therapeutic indices is unlikely to be suitable in a fixed combination, as it would have a

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
	AVC: The AVC believes that the 4th paragraph that reads "A combination of substances with critical dosage ranges or with narrow therapeutic indices is unlikely to be suitable as a fixed combination" may contradict paragraph 5 in section 4.3 "Improvement of activity" where it is stated "tolerance can be improved in combination products, because the dose of individual substances with a narrow margin of safety can be reduced, without affecting the total level of efficacy." We also believe that the 4th paragraph would preclude the development of, for example, anti-cancer drug combinations, where the therapeutic margin may be narrow but the benefits outweigh disadvantage. AVC believes this paragraph should be amended so that these points are taken into account.	limited range of use and would require precise individual dosing. In particular, such combinations would be unsuitable for certain dose formulations/presentations with limited means of individual dosing e.g. tablets or one-dose presentations.
Last paragraph	**AVC:** The AVC agrees that superfluous administration is something to be avoided when possible but is concerned that the fifth paragraph as it is currently worded does not reflect reality. As we have already stated (section 4.3 broadening the spectrum of activity) some diseases are treated prior to clinical signs being present, and in a group of animals it may be the case that some individuals do not show clinical signs, but normal practice in many diseases would be to treat the whole group, as epidemiological factors have to be taken into consideration.	See comment on "General Comments".

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Section 6 Dossier requirements for combination products	**IFAH-Europe:** It is clear that a guideline cannot cover the requirements for all types of combinations, but it should give an outline helping the applicant. A decision tree or a tabular overview of dossier requirements (like in the Draft of the MUMS safety GL: EMEA/CVMP/66781-2005) in addition to the text, would facilitate the understanding of what is needed in each case. This table could help to categorize the requirements according to: • The type of application: generic, well established use, combination of approved ingredients, combination of not approved ingredients; • The type of combination: extended spectrum (same dose of the individual ingredients as in the single ingredient product) or additive/synergistic; • The presence or absence of pharmacokinetic or pharmacodynamic interaction; • The similarity or differences of the pharmacokinetic properties of the combination in comparison to individual ingredients.	This proposal was considered during the drafting of the guideline, but it was not possible to create a meaningful table because it was too difficult to generalise the types of applications, as there were many exceptions. However, all four types of application mentioned in the first bullet point have been addressed under 6.1 "general requirements " and it is made clear that for generic and well established use applications the respective requirements under article 13 and 13a of the Directive apply. The guideline should be read in conjunction with Annex I of Directive 2001/82/EC, as amended.
Section 6.1.1 *New fixed combinations*	**IFAH-Europe:** Section 6.1 identifies circumstances when data on the combination need not be supplied or can be substituted with data on the individual substances. However the link between section 6.1.1 and sections 6.2/6.3, where the data requirements are described, is difficult to make. The requirements for a fixed combination which ingredients have been fully tested separately are not clear at all. • Section 6.1.1 2nd paragraph, 3rd sentence: the CVMP has identified only very limited opportunities to avoid new studies on the combination, relating to pharmacological and toxicology data. Further opportunities should be considered, particularly for tissue residue studies and user safety studies (see comments later) and where synergistic or additive activity is excluded. • 3rd paragraph: 1st sentence: examining interference between and number of substances could quickly lead to a prohibitively large	According to the wording of Article 13b from the Directive, a full dossier has to be submitted for a fixed combination product. However, this is not required for the individual active substances, if known constituents. As is pointed out in the 3rd paragraph, combining active substances can lead to interactions. For new combinations a prediction on possible interactions, incl. range and impact, is difficult to make and will need further exploration. In developing new fixed combination products, consideration should be given to the fact that demonstration of efficacy, safety and benefit of such combinations requires adequate information and therefore studies. Depending the qualities of and the already existing information on substances to be included in a fixed combination product, missing information can be identified and studies to produce additional information designed. It is up to the applicant to justify the absence of data or to argue the validity of methods used. Specific data requirements are not given in the Guideline in order to allow for

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	number of studies. This must be avoided. How interference studies are designed needs careful consideration, and the possibility to use in-vitro data should be explored by the CVMP. • 3rd paragraph, last sentence: It is not clear what is meant with this sentence, particularly the phrase "all the studies". Which studies are referred to and should not be repeated? This should be further specified, and clarified, with more information on the type of studies and conditions to be met in order not to repeat certain studies. Guidance on reduction of studies would be useful, particularly in view of the European Commission's objectives to reduce animal testing. For example: o The minimum number of dose confirmation studies required should be indicated. o For combination against endo-parasites, a single study with the least susceptible species would be appropriate for an established active ingredient. o For approved active ingredients it should be sufficient to show that blood levels are similar to the reference approved product therefore no efficacy and TAS studies would be required. o For an established active ingredient it may not be necessary to conduct a field study if the drugs do not act synergistically or additively but independently (broader spectrum).	flexibility in the data submitted. Any indication on which kind of studies are needed and which not could also lead to a situation in which consent may be derived from the fact that such studies have been carried out, not from the results of such studies. However, it is agreed that the 3rd paragraph could be amended as follows to give better guidance; ~~Possible~~ "Interactions between active substances and/or excipients in the fixed combination product may, however, need to be further investigated in **pharmacological/toxicological** studies using the final ~~product~~ **formulation,** depending on the type and level of interaction ~~it will not be necessary to repeat all the studies using the combination~~."
	AVC: From paragraph 2 it appears that a new combination anthelmintic with a well-established active such as praziquantel, where praziquantel was acting as the sole active against cestodes, would still need to go through an entire set of cestocidal efficacy studies. AVC acknowledges that this is consistent with the Directive, but questions how is this justified on welfare grounds if it can be demonstrated that that there is no negative interaction between active ingredients and that praziquantel is effective against the dose-limiting cestode species? The relationship of third paragraph to the second is unclear to AVC. Perhaps it refers to the possibility of needing to provide	See previous comment.

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	pharmacological studies if there is the possibility of interactions? AVC is concerned about the repeated mention of excipients and refers to the Association's comments on excipients in section 4. Please clarify what is meant by "any new active substance" in the first paragraph. AVC considers that this paragraph requires a complete re-think and rewording, in the context of avoiding unnecessary use of animals and, where possible, deriving applicable conclusions from strategic studies; in this case, given appropriate scientific rigour, we believe 'less can be more'.	"Any new active substance" means any active substance not previously authorised in a veterinary medicinal product. Fixed combination products which use a new active substance will be required, in accordance with the Directive, to submit a complete Part III and Part IV and to justify any omissions of data. It should also be noted that if the new active substance is intended for use in food producing species, an MRL application would be required. In cases when the applicant is the same, the MRL dossier can be cross referred to for several sections of Part III.
	AVC: AVC requests clarification of the third paragraph.	In combining substances interactions may occur, which are not limited to the active substances, but may involve excipients as well. It should be pointed out that the designation "active substance" is arbitrary and depends on the intended use of a substance. The 3rd paragraph intends to draw attention to the possibility of interaction, which is the major issue for fixed combination products. It is acknowledged that the necessity to carry out studies depend on the impact and level of a possible interaction. The text will be revised. See answer given to IFAH comment
Section 6.1.3 - *Combination products that meet the criteria for generic application* Paragraph 3	**IFAH-Europe:** The 3rd paragraph should be amended to be consistent with current VICH anthelmintic efficacy guideline. Please amend to read: *"The new fixed combination product should have the same qualitative and quantitative composition with respect to the active substances ~~and the same pharmaceutical form~~ as the reference product and bioequivalence should be demonstrated to the reference product by appropriate bioavailability or other adequate studies, like e.g. dose confirmation studies."*	This is the wording in the Directive and the paragraph should not be amended. However, it is considered that this paragraph could be deleted because it is simply the wording from the Directive for Article 13.

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Section 6.2: Part 3 -Specific requirements for safety and residues documentation Paragraph 1 and 2	**AVC:** AVC notes the continued reference to excipients and refers to the Association's comments on section 4. AVC believes that it may be possible to examine for interactions during efficacy studies eg anthelmintic studies where it can be demonstrated that the two actives do not possess pharmacological activity in mammalian systems. AVC believes that the interaction between two parasiticides or antimicrobials, for example, may have a profound synergistic effect on parasites but no synergistic activity on the host. In this and other similar situations AVC believes that there is no need for more detailed toxicological data.	See previous comments on excipients Paragraph 1 and 2 relate to interactions between any of the substances in the proposed formulation, whether they are active substances or excipients. If interactions are observed then the Applicant must investigate this further and this may require additional toxicity studies. (It is acceptable that the efficacy studies are examined to look for interactions but if observed, they must be investigated further.) The Applicant would have the opportunity to submit a scientific justification for omitting toxicological data. It should also be pointed out that data imply bibliography as well.
Paragraph 1	**IFAH-Europe:** *In vivo* interactions may be identified in target animal safety studies. Please amend to read: *"<u>When relevant,</u> ~~I~~it is necessary to provide <u>in vitro</u> pharmacological data for the combination in order to ~~demonstrate the mode of action and~~ investigate the possibility of interactions."*	By nature interaction is always relevant for fixed combination products, unless it's absence has been demonstrated. All interactions must be investigated. The proposal to amend to "in vitro" pharmacological data has not been accepted because this is more specific and would exclude data from animal studies. Both *in vivo* and *in vitro* methods can be used.
Paragraph 2, 1st sentence	**IFAH-Europe:** Which kind of "toxicological data" is meant (all of part III)? What exactly is "data"? Scientific literature should be acceptable. If toxicological data are required, it might be enough to prove that there is not a toxicological synergistic effect even if a clinical synergistic effect exists; in that case, a simple acute toxicity test would be performed.	Data equals factual information, irrespective of its source. Toxicological data are all forms of information on toxicity of a substance or formulation. If interactions are observed then the Applicant must investigate these further and this may require additional toxicity studies.
Paragraph 2, 2nd sentence	**IFAH-Europe:** *In vitro* data and a safety assessment should be sufficient to address this point. Please amend to read: *"In all cases where there is a synergistic effect, a*	This amendment is not accepted. An assessment includes an interpretation of data. The dossier should also contain the original data. If there is a synergistic effect, the Applicant must investigate further and submit toxicological data; these data could be studies conducted by the

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	more detailed ~~toxicological data~~ safety assessment will be required".	applicant or published literature, or a scientific justification for omitting studies.
Paragraph 3	**AVC:** AVC is unclear whether paragraph 3 refers to studies or to a paper exercise to demonstrate the comparison between the safety of the individual components and the combination. AVC believes that studies should not be required when there are other valid methods of demonstrating safety.	If there are authorised single substance products, then the safety (user, environmental and consumer) should be considered in the assessment of the safety of the combination formulation. It would be expected that this would be a "paper exercise" as opposed to studies and these assessments would be included in the user risk assessment, the environmental risk assessment and the determination of withdrawal periods.
Paragraph 4	**IFAH-Europe:** User safety studies should not be systematically repeated if the combination formulation contains the same ingredients as an approved formulation, and there is no indication of enhanced toxicity. It should be possible to justify the omission of these studies.	It is agreed that user safety studies are not "systematically repeated". A user risk assessment should evaluate the toxicity data available on all the substances in the formulation. This may include data on the individual substances or the formulation or both and an overall risk assessment is made of safety for the user. Guidance on user safety assessment is available in the CVMP User Safety Guideline.
	AVC: AVC is concerned that unnecessary delays may be caused by the requirement that user safety studies (paragraph 4) should always be carried out with final formulations. AVC suggests that close-to-final formulations would be equally appropriate. Furthermore, this paragraph should read "In cases where it is necessary to carry out user safety studies….." as the present wording might be taken to imply that such studies are necessary in all instances. In the Association's view such studies should only rarely be necessary as they raise serious ethical issues, especially in relation to studies being carried out in children as the present wording might be taken to imply. Blanket statements in the product literature keeping children away from treated animals are preferable alternatives. There is already an approved guideline for the assessment of user safety (EMEA/CVMP/543/03 – FINAL) and the Association suggests that references to details other than the fact that the assessment should relate to the combination are superfluous. For this and the above reasons, the comments on details	See comments above. It is agreed that the wording of the paragraph could be misinterpreted as to imply that studies should always be conducted. The paragraph will be amended and a reference to the CVMP User Safety Guideline will be added as follows: "User safety studies relating directly to effects on the person administering the product, or any other persons exposed during treatment and after treatment (e.g. children handling animals after treatment), such as skin and eye irritation, sensitisation and inhalation studies, should always be carried out with the final formulation. Therefore, in cases where user safety studies are required, they would be conducted using the fixed combination product and would be part of the dossier. Guidance on user safety studies and user safety assessment is given in the CVMP User Safety Guideline (EMEA/CVMP/543/03 – FINAL)." The comment on "studies being carried out in children" raises serious concerns that any applicant would consider such interpretation of the terminology "user safety studies". It should be noted that user safety studies are never carried out in humans.

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	should be removed.	
Paragraph 7	**IFAH-Europe:** If it can be demonstrated that one of the actives included in the fixed combination is the substance with the slowest depletion in the target animal and thus responsible for the withholding period of the fixed combination, it should be allowed to measure the residues of the respective active only. Measuring the other actives also, should not be required as they are not critical with regard to the withholding period.	Residues studies must be conducted on the proposed formulation. Applicants can submit a scientific justification to demonstrate that one of the active substances is not significant in determining the withdrawal period (WP) and therefore omit these data.
	AVC: AVC believes that there are occasions when it is not necessary to conduct residue studies with fixed combinations, for example if residue data has been established for the individual active components and pharmacokinetic bioequivalence has been demonstrated for each active versus the combination, or if two ingredients are metabolised and excreted separately or if one active substance has a markedly longer excretion period than the other. In the latter case, the longest excretion period could be adopted. The guidelines should recognise the possibility that there can be a valid scientific rationale for not carrying out residue studies on the combination. AVC would like it stated that any residue investigations should only be conducted on residues of the combination once it has been determined that there is no analytical or pharmacokinetic interaction between the residues that might confound the analysis.	See comments earlier under General Overview to "IFAH-Europe: Estimation of withdrawal periods for combination products" In addition applications made in accordance with Article 13 as a "generic" application may be exempt from submitting residues depletion data in accordance with the Directive and Bioequivalence Guidelines. Applicants have the opportunity to submit a scientific justification for the omission of residues data. This is the current procedure, no change is proposed. With respect to the last comment made, the SWP Rapporteur does not understand this comment/request. Residues depletion studies are especially required if an interaction is observed between active substances that may affect the expected residues profiles. In such cases suitable analytical methods must be developed (and validated) that will detect the marker residues of the active substances and any other interactions between residues.

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Section 6.3: *Part 4: Specific requirements for preclinical and clinical documentation*	**IFAH-Europe:**	
Section 6.3: Part 4 - Preclinical data – Paragraph 1	**IFAH-Europe:** The mode of action cannot be changed in a combination, but the pharmacodynamics can be modified. Please amend to read: *"It is necessary to provide preclinical data (pharmacokinetic and/or pharmacodynamic) for the combination product to ~~demonstrate the modified mode of action~~ document pharmacodynamic properties, investigate possible interactions or clearly establish that interactions do not occur."*	Mode of action refers to the (alleged) way in which the active substance(s) in a product is (are) thought to display an activity, in agreement with the indicated use. Pharmacodynamics describe the effect(s) of a substance or a combination of substances, studied or observed in various systems, irrespective of any intended use. The sentence has been amended to read: It is necessary to provide preclinical data (pharmacokinetic and/or pharmacodynamic) for the combination product to demonstrate its mode of action (e.g. additive/ synergistic), investigate possible interactions or clearly establish that interactions do not occur.

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	AVC:	
	AVC: AVC requests clarification of what is meant by "mode of action" as in some cases it is impossible to determine the mechanism for synergism.	Mode of action refers to the (alleged) way in which the active substance(s) in a product is (are) thought to display an activity, in agreement with the indicated use. Such information is needed, not only to explain the efficacy and safety of the combination, but also to justify the possible benefit. In documenting synergism, the mode of action is demonstrated, even if the exact mechanism has not been determined.
Section 6.3: Part 4 - Dose finding	**IFAH-Europe:** The requirement for setting the dose of a synergistic or additive combination is exaggerated if studies have to be conducted ***in vivo***, in the absence of in vitro test. It will be not possible to have a sufficient number of animals to tests the combinations. Assuming 3 dose groups per substance and a placebo, 16 groups are needed to test all combinations of doses. With a minimum number of 10 subjects per group, 160 subjects will be required!	In case of synergistic or additive activity, the doses for the single substances cannot be applied to the fixed combination product. Hence, new dose levels for each substance should be established. In developing new fixed combination products, consideration should be given to the fact that demonstration of efficacy, safety and benefit of such combinations may require the production of additional information and therefore studies. Depending on the qualities of and the already existing information on substances to be included in a fixed combination product, missing information can be identified and studies to produce additional information designed. It is foreseen that the applicant will use exiting information on the single substances and results from pharmacokinetic/pharmacodynamic studies with the combination, to limit the groups required. It is up to the applicant to justify the absence of data or to argue the validity of methods used. If it is the applicant's opinion that such information can be produced by *in vitro* studies, the validity of results for the *in vivo* situation

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		should be demonstrated.
	AVC: AVC suggests that it may be possible to carry out dose-finding *in-vitro*, particularly where experimental *in-vivo* models do not exist for disease conditions.	If validated, *in vitro* methods for dose finding can be possible.
Section 6.3: Part 4 - Clinical data Paragraph 2	**IFAH-Europe:** This paragraph implies, that in any case for all clinical studies and for the TAS study there have to be separate treatment groups receiving the single substance products in addition to a group receiving the fixed combination. If this is really the intention of this paragraph, this is not acceptable also with regard to animal welfare. The whole paragraph should be deleted. If this is not the intention of this paragraph, it should be reworded to be more precise.	The way in which such information is not specified. It can be added that the information can be based on documentation. If not available, studies will have to be carried out indeed. Giving consideration to animal welfare it is also regarded as inappropriate to promote a fixed combination product as being effective and safe, without having demonstrated it.
	AVC: AVC believes that it is not necessary to carry out all studies comparing the combination, the single products and the two (or more)* actives found in the combination, as single products co-medicated. In the case of a month-long anthelmintic study this would increase the cost of the study and the number of animals used, without necessarily increasing the quality or quantity of useful data. Moreover, where it is not possible to establish co-infections there may be separate studies for each disease entity (eg parasite species) which rapidly increases the number of animals used in the studies. AVC requests that this section be expanded and thus clarified.	The need for carrying out clinical studies depends on the availability of existing information as well as the nature of the fixed combination product. In case sufficient preclinical information is available, the need for additional clinical trials will be less or absent. The text in brackets (alone and as co-medication) has been deleted.
	AVC: The Association does not believe that it is necessary to include the individual components of a combination product in target animal safety studies. It is the tolerance of the combination which is critical. Tolerance of the individual components will not contribute relevant data and there is also the ethical issue of unnecessary animal use and animal welfare.	In assessing the tolerance the need for a reference is present. The need for such reference treatment specifically applies to claim on improved tolerance. It is considered unlikely that a conclusion on improved tolerance can be made on the observation of the tolerance of the fixed combination product only.