European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT REVISED GUIDELINE ON THE SPC FOR ANTIMICROBIAL PRODUCTS

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

	Name of Organisation or individual	Country
1	IFAH-Europe	EU

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
The CVMP and its SAGAM (Scientific Advisory Group on Antimicrobials) thanks IFAH-Europe for very thorough review of the draft SPC guideline, and for many useful comments and suggestions. Many of them have been taken into account, to improve the draft and to clarify the contents of the text. Where the CVMP/SAGAM could not agree with the IFAH suggestions, explanations have been given in the specific points.
IFAH Europe comment: *"We believe the guideline requires so much information to be included in the SPC that the veterinarian is likely to be confused rather than assisted in his/her decision making, and so the SPC may be counter-productive. For instance, the paragraph referring to resistance of food-borne bacteria (page 6, paragraph 3) and reference to epidemiological breakpoints is unlikely to be enlightening for the practitioner and should be, in our view, deleted. These data neither contribute to the efficacy of a product nor do they increase its safety. Moreover, data on food-borne pathogens are already covered by the registration dossier via requirements laid down in Guideline CVMP/VICH/644/01-Final."* **CVMP/SAGAM response:** Since adopting the previous SPC guideline, it has become evident that more guidance can and should be provided in the SPC, with the aim to address the optimal use of antimicrobials and to minimize antimicrobial resistance. The updated SPC guideline will include more detailed guidance, as compared with the previous one. Some of the contents of the new guideline may appear superfluous but the guideline is aimed to cover all different antimicrobial veterinary medicinal products, taking into account the substance, the type of use and target animal species. All requirements will not be applied routinely for all products. The level of knowledge of the users should not be underestimated, as many of them if not all may consider more information in the SPC useful. Furthermore, education of veterinarians in this field is being updated. The revised guideline provides the user with information to be applied when relevant for that particular product. The paragraph referring to resistance of food-borne bacteria (5.1., page 6, paragraph 3) reflects the developments in veterinary antimicrobial therapy and resistance, and the recent initiatives by different bodies and authorities. VICH GL 27 gives the principles of data requirements for new antimicrobial products for food producing animals, with respect to antimicrobial resistance. It is applied for products with potential exposure of food-borne pathogens and risk for selection of resistant bacteria of human health concern. If the applicant provides additional data which contains important information relating to potential exposure to animal gut flora and possible selection of resistance, this information could be available also in the SPC. We cannot agree with IFAH-Europe that these data would not contribute to the safety of the product. The reference to epidemiological breakpoints is given here as they are used for these studies and not the clinical breakpoints which apply for the clinical use of the product. The paragraph text is reserved for specific products for which this type of information would be necessary, as said in the text "if relevant in the approved conditions of use"; it is not applied routinely. Finally, it can be emphasized that this is a guideline document, from which deviations can be made but they shall be justified.

IFAH Europe comment:
"We suggest that the phrasing regarding selection of different generations of cephalosporins (page 4, paragraph 5) should be deleted. This is a highly complex subject which is being addressed by SAGAM. It therefore appears premature and unacceptable to include the present wording at this stage. IFAH-Europe therefore recommends that consideration of such phrasing is postponed to a time point after the adoption of the Report on cephalosporins."

CVMP/SAGAM response:
The term "3rd generation cephalosporin" has been replaced with some more general term, as the basic idea of this paragraph (page 4, paragraph 5) is valid: the potential of broad spectrum antimicrobials to select for resistance is higher that that of narrow-spectrum antimicrobials. This paragraph is related to the general rule to prefer narrow-spectrum treatment, as agreed in many international guidance documents for prudent use of veterinary medicines.

SPECIFIC COMMENTS ON THE TEXT
GUIDELINE SECTION TITLE

Line no[1]. + paragraph no.	Comment and Rationale	Outcome
INTRODUCTION 1st paragraph Page 3	***IFAH-Europe comment:*** Recently the Public Statement on the use of (fluoro)quinolones (EMEA/CVMP/SAGAM/184651/2005) was published. *IFAH-Europe suggests this Public Statement is quoted in the introduction.*	Agreed.
SCOPE Page 3	"This guideline provides additional instructions about the information which should be included in the SPC of the veterinary medicinal products which contain antimicrobial substances." *"…should be included in the SPC of ~~the~~ veterinary medicinal products **containing** antimicrobial substances."*	Agreed.
Section 4.5 1st paragraph Page 4	***IFAH-Europe comment:*** IFAH-Europe strongly endorses prudent use principles for all classes of antimicrobial compounds. Though further statements in this paragraph about Good Veterinary Practice and hygiene regarding food and companion animals, are very true and as such strongly supported by IFAH-Europe, it is noted that it is not the responsibility of the animal health industry and these are assumed not to be in the scope of a SPC. Such non-product information diminishes the focus on product-specific information. *IFAH-Europe proposes to delete as a minimum the sentence "Information on measures to reduce such transfer could be included."*	CVMP/SAGAM considers that it is possible to give information related to prudent use in the SPC of antimicrobials. However, the last sentence can be deleted as proposed.

[1] Where available

Section 4.5 2nd paragraph Page 4	"If, in view of maintaining the efficacy of antimicrobials, the use of certain antimicrobials should be restricted, …….taking official and local antimicrobial policies into account." ***IFAH-Europe comment:*** It should be noted that the use of all classes of antimicrobials should be conducted prudently, not just *"certain antimicrobials"* Indiscriminate use of older molecules such as sulfonamides or tetracyclines, may affect the susceptibility of various bacterial species (and consequently efficacies) to medically essential classes such as cephalosporins and fluoroquinolones due to co-resistance mechanisms. *"If, in view of maintaining the efficacy of antimicrobials, the use of ~~certain~~ antimicrobials may be restricted, ……taking official and* ***national*** *antimicrobial policies into account."*	Agreed. The text has been changed accordingly.
Section 4.5 2nd paragraph Page 4	"This is particularly important for products with a high potential to select…." Proposal:*"This is particularly important for products* ***containing antimicrobials*** *with a ~~high~~ potential to select…."*	All antimicrobials have potential to select for resistance. Some of them have a higher potential for this.

Section 4.5 2nd paragraph Page 4	"This standard phrase……etc" ***IFAH-Europe comment:*** It is highly preferable to postpone this proposal regarding selection of cephalosporins, because a detailed analysis of this difficult issue is required. It is noted that SAGAM intends to address the question of resistance development to cephalosporins in a similar manner to that conducted for (fluoro)quinolones. Therefore, we ***kindly*** request to postpone this wording until CVMP/SAGAM have addressed this subject and the Report (reflection paper) about the 3rd and 4th generation cephalosporins has been adopted. We would also like to point out that cross-resistance of different generations of agents of a given class can be very complicated. In addition, scientific evidence is lacking that first generation cephalosporins select for less resistance than the higher generations. The current proposal ignores the fact that less active, poorly penetrating class members are often more adept at selecting resistance than their more active counterparts and that resistance to one member of a drug class often brings resistance to the whole class. Note that the spectrum of activity of the various generations differs considerably and, hence, can not be compared. *Pending the adoption of a cephalosporin Report from SAGAM, IFAH-Europe requests deletion of this paragraph.*	See the response above. The paragraph has been changed to become more general. The same has been done for the 1st example phrase.
Section 4.5 2nd paragraph Page 4	"Whenever possible, the *antimicrobial* should only be used based on susceptibility testing" ***IFAH-Europe comment:*** In acute cases, animals must be treated immediately before any susceptibility data are available. In some situations, for certain pathogen-antibiotic combinations there are no interpretive criteria or local epidemiological data are absent. Therefore, IFAH-Europe recommends adding a sentence as proposed. Please add*: "For acute situations where susceptibility can not be performed or results are not yet available, it may be necessary to initiate therapy based on local clinical information and the clinical experience of the veterinarian."*	This aspect is already covered in the 5th sentence, with a slightly shorter wording but meaning the same. These sentences are examples of the standard phrases used, and they are not restricted to those listed here. In all therapy, the clinical experience of the veterinarian has an important role

Section 4.5 2nd paragraph Page 5	"….. and may decrease the effectiveness of treatment with <*the following specified antimicrobials(s)*>, due to the potential for cross resistance." Proposal: …*with* ***products containing actives of the same class*** *due to the potential for cross-resistance."*	For clarification, the text has been changed to read <the following antimicrobials/classes of antimicrobials>
Section 4.5 3rd paragraph Page 5	"Depending on the application of VICH GL27, additional sentences could be included." ***IFAH-Europe comment:*** This sentence is unclear for us. Such an open statement is difficult to judge and to accept. *Can this be explained in more detail?*	The standard phrases to be incorporated in the SPC are not limited to the examples presented here, but more can be introduced. As the phrases very much are related to specific products, it is not possible to define all of them now. The reference to VICH GL27 can be deleted.
Section 4.9 1st paragraph Page 5	"All deviations from optimal dosing and treatment duration of the antimicrobial product should be avoided. Underdosing of antimicrobials is considered to increase the possibility for development of antimicrobial resistance in bacteria. Too short treatment can reduce the efficacy of the antimicrobial. Also, an unnecessarily long antimicrobial treatment can be a factor to promote the development of resistance." ***IFAH-Europe comment:*** The veterinarian's clinical judgement is the basis of antimicrobial treatment. In given situations the practitioner uses pharmacodynamic data to guide treatment that is not in accordance with the approved conditions, as correctly described in section 5 of the SPC. IFAH-Europe recommends therefore to slightly adapt the first sentence (see proposal). Proposals: *"All deviations from* ***approved*** *dosing and treatment duration of the antimicrobial product should be* ***minimized****."* *"…the possibility for* ***selection*** *of antimicrobial resistance in bacteria."* *"…a factor to promote the* ***selection*** *of resistance"*.	Agreed, the current text is: All deviations from approved dosing and treatment duration of the antimicrobial product should be minimized. Underdosing of antimicrobials is considered to increase the possibility for selection of antimicrobial resistance in bacteria. Too short treatment can reduce the efficacy of the antimicrobial. Also, an unnecessarily long antimicrobial treatment can be a factor to promote the selection of resistance.
Section 4.9 2nd paragraph Page 5	"To ensure a correct dosage body weight…." *It is noted that for large animals or in acute cases the current proposal may cause problems, because it can be difficult or unpractical to determine an accurate body weight.*	We agree that in case of large animals, body weight is often only estimated. However, as the guidance applies to all animals, we prefer the present wording, which ends "as accurately as possible".

Section 4.9 3rd paragraph Page 5	"For antimicrobials, administered through the drinking water or feed, the concentration in feed/water has …" ***IFAH-Europe comment***: Where oral intake is inadequate, changing the concentration dosed may be insufficient to improve the situation. Changing the route of administration would be preferable (where practicable). Proposal: *"For antimicrobials, administered through the drinking water or feed the concentration in* ***water/feed (or the route of administration)*** *has…"*	If the animals are too sick to take the medication in feed or water, it is definitely necessary to change the route of administration. That can be considered as part of good veterinary practice. The text has been amended to take into account the comment.
Section 4.9 3rd paragraph Page 5	"The uptake of medicated …" Proposal: *"The* ***in****take of medicated …"*	Agreed.
Section 5.1 2nd paragraph Page 5	"If appropriate, MIC data should be provided for a representative sample… ***IFAH-Europe comment:*** In this paragraph, MICs of the native population should be given; resistance rates are addressed in the next paragraph (page 6). Proposal: *"If appropriate, MIC data* ***of the wild-type population*** *should be provided for a representative sample…"*	Agreed. Wild-type term has been added to be more specific. Epidemiological data are not related to different regions, so the rest of the sentence has been deleted.
Section 5.1 1st paragraph Page 6	"Naturally resistant bacterial species should only be mentioned …." *Is this sentence needed ?*	The CVMP/SAGAM prefers to retain the sentence. There might be products for which it is useful.
Section 5.1 2rd paragraph Page 6	"Proportion of resistance in target pathogens should be reported" ***IFAH-Europe comment:*** It is unclear whether the proportion of resistance in target pathogens should be reported for various EU countries or only for those where the product is approved. Certain Member States may not have the capacity to operate susceptibility programs and such data are sometimes not available to sponsors.	This sentence has been deleted. There should not be information which is going to be outdated, i.e. proportions of resistance at a certain time. Thank you for that comment.

Section 5.1 2rd paragraph Page 6	"Clinical breakpoint MICs (µg/ml) should be used to categorise isolates as susceptible (S) or resistant (R). The source for the breakpoints used should be given." ***IFAH-Europe comment:*** Note that clinical breakpoints seem not to exist yet for all veterinary pathogens. IFAH-Europe suggests inserting "if available". Please also specify the meaning of "sources" of the clinical breakpoints. Proposal: *"Clinical breakpoint MICs**, if available,** should be used to categorise isolates as susceptible (S) or resistant (R). The source for the **clinical** breakpoints used should be given."*	Agreed. The source means the reference where these breakpoints are (published). The text has been clarified accordingly. It is true that clinical breakpoints are not available for all substances.
Section 5.1 2rd paragraph Page 6	"The known type(s) and mechanism(s) of acquired resistance in the target pathogens should be included." **IFAH-Europe comment:** This information is of more relevance to the CVMP reviewers than it will be to the veterinarian. For the veterinarian, having read that there is some proportion of target pathogens that are resistant, this will be interpreted as unlikely to respond clinically, it does not really matter whether this is due to specific resistance mechanisms or to unachievable drug concentrations at the site of infection. For some bacteria and antibiotics, there are no known resistance mechanisms, in spite of isolates with high MICs which are considered resistant. It would seem that even a general description of a mechanism might be more confusing than illuminating. For example, even with a general description such as an efflux pump or an altered target site mechanism, it does not seem as though this information would be of much use to the veterinarian to guide a decision about product use. Proposal: *to delete the sentence "The known type(s)……..be included."*	CVMP/SAGAM considers that this is useful information and should be retained. The text should not go to the specific molecular details but to remain on a more general level.
Section 5.1 2rd paragraph Page 6	"The existence of any cross-resistance within the class of antimicrobials and between classes of antimicrobials should also be stated." Proposal: *"The existence of any cross-resistance **(resistance within the class of antimicrobials)** and **co-resistance (resistance between classes of antimicrobials**) should also be stated"*.	Agreed.

Section 5.1 last paragraph Page 6	"Resistance among food-borne bacteria should be reported if relevant in the approved conditions of use. Epidemiological cut-off values (µg/ml) should be used to categorise isolates as susceptible (S) or resistant (R). The source for the epidemiological cut-off values used should be given." ***IFAH-Europe comment:*** Epidemiological cut-off values can be useful tools for resistance epidemiology, but they are not relevant to practitioners. In the context of the SPC they can be highly misleading to the veterinarians and counter-productive. A clinician choosing an antimicrobial agent to treat an animal needs to know that the compound chosen should be effective against the pathogen involved. Clinical breakpoints, therefore, are the essential information for the veterinarian, as explained in the preceding paragraph. Clinicians are not monitoring food-borne bacteria. Moreover, we consider the inclusion of epidemiological cut-offs outside the scope of the SPC for antimicrobial products. This information is only needed by epidemiologists. The inclusion of susceptibility data on food-borne bacteria is highly questionable to enhance appropriate use and these data will not provide guidance for the attending veterinarian to make an informed decision about whether to use the product or not. Other sections of the SPC such as the important suggestions on prudent use wording, make, in addition, this paragraph redundant. *IFAH-Europe strongly proposes that this paragraph is deleted.*	See the comment above.

Section 5.2 3rd paragraph Page 6	"If concentration in plasma is not applicable, free concentrations of the active substance…." ***IFAH-Europe comment:*** Generally, IFAH-Europe recommends not including too many details in the SPC. Here, there is a risk of misinterpretation because compounds with a very high protein binding and therefore low measurable free concentrations can be nevertheless clinically highly effective. In other sections of 5.2, free concentrations are not referred to. It is also doubted whether pharmacokinetic parameter such as volume of distribution (V_d) or clearance are useful to the veterinarian. *"If concentration in plasma is not applicable, ~~free~~ concentrations of the active substance…"* *IFAH-Europe suggests omitting the parameter V_d and clearance.*	The CVMP/SAGAM prefers to retain free concentrations, as they are most informative. As the same aspect is more or less expressed in the first paragraph, this sentence has been deleted and the word "free" added to the 4th sentence there. The degree of protein binding in plasma should be given separately. Vd and clearance are common pharmacokinetic parameters, and users may or should be familiar with them. The information should be available in the SPC.
Section 5.2 last paragraph Page 6	"Information on the excretion of the active substance at the defined dosage level into the gut of the animal where potential food borne pathogens may reside, if relevant in the approved conditions of use (antimicrobials for food-producing animals), should be given." ***IFAH-Europe comment:*** While excretion of drugs is a component of pharmacokinetics, it is not clear how this phrase is needed in the context of clinical use and efficacy. As many variables of this complex issue are unknown (drug concentrations, pH, binding, presence of food-borne bacteria) and this subject is not related to the target pathogens, it is suggested to delete "where food borne pathogens may reside." As above, the inclusion of too many details may distract the practitioner from concentrating on the intended therapeutic conditions that are appropriate. *"Information on the excretion of the active substance at the defined dosage level into the gut of the animal, if relevant ~~in~~ **to** the approved conditions…"* *IFAH-Europe prefers to delete the entire paragraph.*	The sentence has been revised to be more general. Reference to food borne pathogens has been deleted.

Editorial comments have not been included in the specific comments but taken into account.