European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON THE DRAFT RECOMMENDATION ON THE EVALUATION OF THE BENEFIT-RISK BALANCE OF VETERINARY MEDICINAL PRODUCTS

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

	Name of organisation or individual	Country
1	IFAH-Europe	Belgium
2	EGGVP	Belgium

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
IFAH-Europe The revised version of the document EMEA/CVMP/248499/2007 can be considered a major improvement. The IFAH-Europe recommendations on the structure of the "guideline" have been taken over. The document is greatly improved in readability and it is much clearer in giving guidance on the benefit-risk evaluation process. Industry is glad to read that this recommendation document is not intended to apply retrospectively as stated in the *Executive Summary* (line 62) and also that *"is not intended to add new requirements for marketing authorization holders"* (*2. Scope*, line 147). Some paragraphs of the document seem to be repetitions (in a slightly different wording) of earlier paragraphs (compare e.g. lines 169-172 and 180-182, lines 193-199 and 214-217, lines 603-605 and 618-620). Although not strictly necessary from a readability point of view, these paragraphs might be shortened as the size of the document can indirectly affect readability (repetitions may create apparent contradictions, and it would be beneficial to the guideline to avoid unnecessary rephrasing at different places). With respect to the definitions given in the Annex of the document, the order in which these are given is improved. The definitions themselves are however not updated and some of these are still not clear (see also specific comments). Whereas definitions of risk management and benefit-risk management are more comparable, other related definitions are still very distinct (e.g. please compare definition of risk assessment with definition of benefit-risk assessment and likewise those of risk communication and benefit-risk communication). - Whenever it is stated in the document that "data must be provided", this data should be called "data relevant to the SmPC". - The recommendation to update or renew the benefit-risk evaluation when a dossier is opened threats industry, since this could be triggered by a generic application that would end up with the originator having to provide an updated benefit-risk assessment.
EGGVP would like to complement CVMP with their work. Compared to the last version of the document, the readability and clarity has improved a lot due to the use of examples. However, one serious risk remains. In the text it is now clear that the intention is to evaluate each product on its own merits. But due to the fact that no quantitative values are given, the qualification ´a positive BR balance´ remains subjective. In the case the new product is used in clinical trials with a positive control, the BR balance of the new product (if efficacy is lower) can only be positive ´due to lower risks´. This still means that the date of application can affect the outcome of the BR assessment as a product can only be authorised as it is at least as effective as existing products or has a lower risk profile. Even products with lower efficacy and acceptable risks should be available to the veterinarians as they can be useful in specific cases (allergies, resistance, interaction with other medication, etc.).

SPECIFIC COMMENTS ON TEXT		
SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Table of contents	IFAH-Europe: The Annex is not clearly indicated in the Table of Contents and also a reference to the definitions is lacking. It would be useful if these could be added please. Please include a reference to the Annex between lines 39 and 40 (between *"6.2 Presentation ..."* and *"Principles of ...."*). And add the following in line 40: *PRINCIPLES AND DEFINITIONS OF BENEFIT-RISK ANALYSIS FOR VETERINARY MEDICINAL PRODUCTS 15*	Table of contents has been updated. The reference to the Annex has been updated. Accepted
2. Scope Line 139	IFAH-Europe: In order to allow for other availability issues, we suggest adding *'for example'* in brackets: *"The risk-benefit principle defined by the legislation takes into account issues relating to availability (e.g. minor use/minor species)."*	Accepted.
Line 168/169	IFAH-Europe: To improve readability we suggest a paragraph break is inserted before 'For applicants or marketing authorization holders …'.	Accepted

[1] Where applicable

4. When to perform a benefit-risk evaluation	IFAH-Europe: The overall structure of section 4 could be improved in order to avoid redundancies (which may lead to apparent contradictions between various sections of the GL). In addition, for formal reasons, having a 4.1 subsection without any 4.2 is not satisfactory.	Accepted
Lines - all	To improve the structure and readability, two clear sections should be created, and all text relating to new applications should be included in the 1st section, and all text relating to post-authorisation activities should be included in the second section.	Accepted
	The 2nd sentence in the first paragraph, although valuable in terms of general objective of the guideline, is general and does not apply directly to the 'when' of the B/R assessment.	Moved to Introduction
	The 2nd paragraph ("For applicants") repeats section 3 ("Who…")	Amended
	We suggest to split into 2 subsections: " **4. When to perform a benefit-risk evaluation** 4.1. <u>New applications</u>. In general, regulators should make a benefit-risk evaluation for all new applications. <u>In fact,</u> when a competent authority evaluates an application for a veterinary medicinal product, this has always comprised a weighing of the benefits against the risks before taking the decision to authorise the product. (*Relocate next sentence shown below in strikeout to end of 1st paragraph in section 2, i.e. line 135*) ~~The use of a structured, written benefit-risk evaluation will create more transparency and harmonisation of the regulatory decisions for the benefit of marketing authorisation holders, the regulatory system and the public.~~ For MA holders, the writing of a formal benefit-risk evaluation is up to the choice of the applicant, but may provide valuable summarized information to the assessors. (*move all text relating to post-authorisation activities to next section*) <u>4.2.</u> Post-authorisation benefit-risk assessment *(Add text moved from above).*	Accepted. Accepted

185 par 4	EGGVP: ´where new benefits or risks...´ The inclusion of benefits in this section is appropriate, however, considering the lack of resources on the side of both applicants and competent authorities it seems not necessary to perform a benefit/risk assessment in case only new benefits are identified. This new assessment would not lead to any change in the existing authorisation, unless new risks are identified. Any new benefits should be taken into account if a BR assessment was to be performed based on the identification of new risks. Proposal: ´where new risks...´	Not accepted. Transparency dictates that authorities will need to prepare a new or updated BR assessment even where only new benefits are identified.
Line 186	IFAH-Europe: Please provide definition or examples of *"important new information"* that could impact the benefit-risk assessment	Two examples given.
Line 189-190	IFAH-Europe: The sentence rather applies to section 5.1 (how to perform) than section 4 (when to perform) Suggest moving the sentence to section 5.1.	Moved to Scope (Section 2).
197-199 par 4.1	EGGVP: Even in cases the BR assessment update is the first BR assessment to be carried out, this should not open the possibility to reassess the BR balance of the whole product. EGGP proposes to delete the sentence.	Not accepted. This is a voluntary activity which could help the applicant's case.
Pharmaco-vigilance Line 215-216	IFAH-Europe: *Suspected adverse reactions or events* are not the only data gathered from the field. In this paragraph, we should also include a word on the post marketing trials as they may positively confirm the previous assessment of the product. Please amend line 216 as follows: "This should concentrate on the new information that has become available, <u>including published post-marketing clinical studies that contain pharmacovigilance information or confirmation of efficacy)</u>, and in particular whether this information has an impact on the marketing authorisation."	Accepted

Line 264	IFAH-Europe: This *Referrals* section deals with all types of referrals and they all may involve re-evaluation of the benefit-risk balance. For one type of referral, an extra risk assessment preceding this re-evaluation is necessary. This is the referral according to Article 33 of Directive 2001/82/EC ('mutual recognition and decentralised referral') which is subject to the requirement that a "potential serious risk" must be involved. Please add the following to the paragraph: *Situations that may result in referrals are indicated in Articles 33, 34, 35, 39 and 40 of Directive 2001/82/EC. The assessment of a referral may involve the evaluation of the benefit-risk balance of the issues related to the veterinary medicinal product(s) that is (are) subject to the referral. The consideration of the benefit-risk balance should, in principle focus on the subject matter for the referral.* *In the case of a referral according to Article 33 of Directive 2001/82/EC as amended ('mutual recognition and decentralised referral'), the CVMP first evaluate whether the risk that forms the basis of the referral meets the definition of 'potential serious risk' provided in EMEA/CVMP/2006/C 132/08 ('Guideline on the definition of a potential serious risk to human or animal health or for the environment in the context of Article 33(1) and (2) of Directive 2001/82/EC') into consideration. If the 'potential serious risk' fulfils the criteria of EMEA/ CVMP/2006/C 132/008, the benefit-risk balance is further re-evaluated in accordance with chapter 3 in Volume 6A of the Notice to Applicants.* *In the case of a referral according to Article 34 ('divergent decision referral', Article 35 ('community interest referral') or Articles 39 and 40 ('follow-up referrals') of Directive 2001/82/EC, the CVMP conducts a re-evaluation of the benefit risk balance of all the products concerned in accordance with Volume 6A Chapter 3 of the Notice to Applicants. In all cases, benefit-risk evaluations should … […].*	Accepted.

Line 277	IFAH-Europe: The example given on "innovator" should be replaced, since the term *innovator* has no legal basis for an application. Please replace: (e.g. ~~innovator~~ full application, generic…)	Accepted.
Line 281-285	IFAH-Europe: This paragraph should be deleted as it does not provide any useful information in the scope of this guideline.	Accepted
Lines 287-289	IFAH-Europe: The reference to Article 12 applications only does not make sense. It seems this should not be a standalone paragraph but should be merged with the following paragraph (lines 291-293). The combination of a merged first paragraph and the following paragraphs would then make sense. We would also suggest adding here a reference to Table 1. Please merge paragraphs 1 and 2 of this section (lines 288 to 293) and add a reference to Table 1. Please insert: *'For a summary of the legal basis, data requirements and basis for the benefit-risk evaluation, please refer to Table 1 in Annex. '*	Accepted
347-350 par 5.1	EGGVP: For immunological products the description how the BR assessment is different is missing. Only the derogation in the data to be submitted is described, but not how this effects the BR assessment.	Qualification sentence has been added.

359	IFAH-Europe: Surprisingly, although emphasis is put earlier in the text on post-authorisation re-evaluation of B/R, no specific mention is made in this section. In order to mirror the heading '5.1. for new marketing authorization' as well as '4.1. Post-authorisation benefit-risk evaluation', we suggest to add a '5.2 Post-approval' Insert new section 5.2 "**5.2 Post-approval**" (*add brief text*)	Accepted.
442 par 5.2	EGGVP: Efficacy levels for pharmaceuticals are stated only in a few guidelines. EGGVP proposes rephrasing as follows: ...are ~~frequently~~ some guidelines stating ...	Re-phrased to capture the comment.
443 par 5.2	EGGVP: Benefit is not a correct term in this sentence. EGGVP proposes rephrasing as follows: This level of ~~benefit~~ efficacy must always	Accepted
451 par 5.2	EGGVP: The statement that an ´inferior´ (eg less effective as the used reference product) product could only reach a positive BR balance due to lower risk should be refrased. BR balance of a product should be only on the products own merits. This is one of the cases in which an ´additional´ benefit (such as compliance enhancers, see next remark) could play a role as well.	Text has been expanded
5.3 Benefit assessment Line 478	IFAH-Europe:For clarity please insert: *"These benefits should not be part of the benefit assessment but may be used to support the final conclusion. They should be summarised in the introduction of the evaluation in the benefit-risk balance chapter."*	Accepted.

Direct therapeutic benefits Line 500	IFAH-Europe: The availability of an authorised product is clearly a direct benefit compared to the lack of a product. In the absence of a veterinary product vets and owners have to find an alternative way to manage the animal's illness. Otherwise, how can we justify the legislation (cf. article 10 of Directive)…? Moreover, increased owner or patient compliance should be regarded as a direct benefit. Factors of compliance have a direct impact on therapeutic benefit as they determine if a therapy is actually followed. This has direct impact on the health of the animal. Improved compliance and ease of administration can easily be measured by a questionnaire in a clinical trial We would therefore argue strongly for having these examples of direct benefits added to this paragraph. Please add at the end of this section: - *The authorisation of a product for a given indication where no other product is licensed in veterinary medicines,* - *The availability of an approved product which has been tested for safety and efficacy vs. off label use of a human product.* - *Improved ease of compliance with the intended therapeutic protocol.*	Relevant paragraph amended, however, the examples provided would be considered as additional benefits. Partly accepted – example concerning unmet medical need included as an additional benefit. Partly accepted –example concerning unmet medical need included as an additional benefit. Amended

502-506 par 5.3	EGGVP: ´Additional´ benefits that directly influence the efficacy of the product in the field (anything resulting in better compliance with the prescription as palatability, ease of administration etc.) should be taken into account in the BR assessment. A tablet for cats, administered in a trial setting by professionals, can be effective. However, if due to taste, administration is difficult for the animal owner, tablets will get lost during administration and the owner will be inclined to stop treatment premature as soon as symptoms are easing because of risks to human health (e.a. scratches; a additional risk that is not taken into account during assessment). Although we agree that these sorts of benefits are difficult to assess, they still should be part of the BR assessment. To take them into account only if the BR balance is already positive is not very usefull.	Paragraph now amended
Additional benefits Lines 505-506	IFAH-Europe: *These benefits cannot be easily assessed in the majority of cases and may be very subjective.* We consider that the sentence negatively prejudices the kind of benefits quoted in the paragraph. If the benefit can be demonstrated, it should be included in "Direct therapeutic benefits". Please delete the sentence.	Paragraph has been re-worded
5.4 Risk assessment Line 524-527	IFAH-Europe: *"The purpose of the quality assessment…"* A quality assessment has not the role to evaluate potential risks coming from degradation of products, since a pharmaceutical expert is not qualified to do such judgment. Please rephrase. IFAH-Europe proposal: *"~~The purpose of~~ For the quality part, the risk assessment should consider whether ~~is to ensure that the product is of appropriate quality and that~~ the conclusions made on…"*	Paragraph has been amended

5.5 Risk management or mitigation measures Lines 542 & 556	IFAH-Europe: We would like to insist on adding "relevant" to every reference to risk, as risks are taken in their more extensive definition, whereas there is a trend to limit benefits (indirect are separate). Please add: Line 542: *"Each relevant risk should be assessed taking into account…"* Line 556: *"For each relevant risk an assessment should be provided…"*	Text has been amended. Text has been amended.
6.1 Presentation of the benefit-risk evaluation in the dossier Line 591	IFAH-Europe: We would suggest including here a reference to new-Part 5 as well, since a reference to annual reports, which has no legal basis, is also made in section 3 (line 168). Please add this at the end of line 591	Not accepted. It has already been stated that benefit-risk assessments would not be a required for marketing authorisation holders as part of annual reports.
Line 582	IFAH-Europe: In order to avoid any apparent contradiction with lines 169-170, line 582 should be amended to avoid any inference that a benefit-risk assessment by the applicant is mandatory. Proposal: *"The benefit-risk evaluation may ~~should~~ be presented in the marketing authorisation application. If an applicant chooses to include a risk-benefit evaluation, it should be presented in Part I of the dossier…"*	Partly accepted - paragraph has been amended
(none)	IFAH-Europe: The presentation as part as post-authorisation re-assessment, including PSURs, is not mentioned. For PSURS in particular, it should be made clear that a simple statement that e.g. the benefit-risk balance remains unchanged may be sufficient.	Partly accepted, however, details concerning the structure and content of the benefit-risk assessment have already been described in the recommendation.

Annex Lines 686-689 and 691-693	IFAH-Europe: The definitions for benefit-risk assessment and communication would benefit from more clarity. IFAH-Europe would like to propose the following changes: ***Benefit-risk assessment:*** ~~*Benefit-risk assessment is the*~~ *A process of assessing benefits and risks in accordance to the benefit-risk assessment policy. This assessment includes the mitigation of risks from a proposal of benefit-risk management options. The benefit-risk balance is the outcome of the benefit-risk assessment.* ***Benefit-risk communication:*** *The exchange of information and opinions throughout the benefit-risk analysis process concerning benefit (direct and indirect or additional), risk, risk-related factors and risk perceptions, including the explanation of benefit-risk assessment findings and the basis of benefit-risk management decisions. Benefit-risk communication is an essential aspect involving all parties concerned and aiming to promote consistency, transparency and understanding of the benefit-risk analysis process.*	Partly accepted - definitions have been amended

Figure 1	IFAH-Europe: "Benefit-risk assessment of a specific VMP" consists of an evaluation of "benefit" and of "risk". It is not well understood what the asterisk is referring to (i.e. "* *of the product concerned as well as of similar products*"). Perhaps the original asterisk has become deleted. Please delete the word "risk" in the text box as shown below: *Benefit ~~- risk~~* *Assessment of the direct benefits* *(additional benefits)*	Accepted.