7 November 2024
EMA/CVMP/307496/2024
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on Guideline on the evaluation of the benefit-risk balance of veterinary medicinal products (EMA/CVMP/307496/2024 – Rev.1)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope
2	Access VetMed

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope would like to thank the CVMP for this Draft guideline and is grateful for the opportunity to comment. Please find some comments below. Should you have further questions, AnimalhealthEurope is happy to provide any clarification needed.	Noted.
1	The general tone used in this document, gives the impression that this draft GL over-emphasises the risks aspects, there is too much focus on risk/hazard vs benefit. The benefit:risk balance of the product is the key principle that needs to be safeguarded to avoid any lost opportunities around additional benefits with regards potential indications. AnimalhealthEurope urges CVMP to ensure that this GL is not more restrictive than regulation demands, thus assure appropriate availability for treatment and prevention options for all animal species and indications. Therefore, it would be advisable to adjust the wording throughout the document for that purpose.	Noted. As indicated in the executive summary of the guideline, the CVMP is revising the guideline in light of the implementation of Regulation (EU) 2019/6 and to account for the experience gained over the years. It is not the intention of the guideline to emphasise the risks, but rather provide clarity in areas where Regulation (EU) 2019/6 provides new or emphasised areas of assessment.
2	This is a very important guideline for CVMP and also for the industry. We are therefore very grateful for the many opportunities where the updated draft guideline has been presented to stakeholders during the last months, and also for the opportunity to comment. The provisions in the guideline do generally look clear and provide some useful examples of what could be expected in the drafting of benefits and risks. When compared with the previous version, the new risk-benefit guideline does not present major divergences (for instance the methodology in both documents seems to be the same and much of	Noted. See justification above. In addition, please note it is not within the scope of this guideline to deal with any potential disharmonisation within the network, but rather provide clarity to all interested parties on how to undertake a benefit-risk assessment.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	the approach to evaluation remains unchanged). However, in general this guideline gives the impression that much emphasys is made to the risks/hazards aspects versus the benefits. There is also a perception that the guideline may not address the possible differences on risk-benefit assessment throughout different Member States, leading to disharmonisation.	
2	From a practical standpoint, it is unclear where the B/R balance for VMPs should be included. Should a particular section be included at the end of part 3 for the safety part, that means in the 3a6 (era) section, and then repeated again in an overall conclusion at the end of the 4B section to gather safety and efficacy? Or should the benefit /risk assessment be written in a separate file in the part 4?	An applicant (or MAH) may wish to include a benefit-risk balance as part of their application. Section 1C would be the appropriate location within the dossier structure. A benefit-risk balance, being a subjective assessment, should be presented together with (or as part of) the critical expert reports (CER), either as a stand-alone document or as a separate section within an existing CER.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
100-104	1	**Comment:** Dossier requirements differ depending both on type of application and type of product. **Proposed change:** Please consider amending the text as follows: '*Although the dossier requirements (level of evidence needed) for quality, safety and efficacy may vary according to the legal basis of the application* ***~~or~~ and*** *depending on the type of product, the principles underpinning the benefit-risk balance evaluation do not differ depending on the legal basis of the application…*'	Accepted.
105-110	1	**Comment:** For the sake of consistency with the information provided on the EMA website (Post-authorisation measures (recommendations, conditions and specific obligations) | European Medicines Agency (europa.eu)), it is proposed to refer to 'post-authorisation measures' only. **Proposed change**: Please amend this § and delete 'studies' to read: "Where there are **minor** shortcomings in the data provided in support of an application (compared to the applicable dossier requirements), the benefit-risk balance may be considered positive, subject to the satisfactory completion of post-authorisation measures ***~~or studies~~*** to be agreed in advance with the applicant/marketing authorisation holder, and only when the product quality, safety and efficacy meet acceptable standards and if the identified risks are shown to not outweigh the expected benefit(s) after taking into account the risk mitigation measures."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
105-110	2	**Comment:** For minor shortcomings, pharmacovigilance activities shall reflect if there is a need for any post-authorisation change **Proposed change:** *"Where there are minor shortcomings in the data provided in support of an application (compared to the applicable dossier requirements), the benefit-risk balance may be considered positive, subject to the satisfactory completion of post-authorisation measures* ***~~or studies~~ or pharmacovigilance activities*** *to be agreed in advance with the applicant/marketing authorisation holder, and only when the product quality, safety and efficacy meet acceptable standards and if the identified risks are shown to not outweigh the expected benefit(s) after taking into account the risk mitigation measures."*	Partly accepted. The term 'post-authorisation measures' includes, among others, additional pharmacovigilance activities. Thus, it is preferred keep reference to the general 'post-authorisation measures' only, in line with the above comment.
111-118	1	**Comment:** For the sake of clarity and having useful information in one single document, we strongly recommend to include in the guideline the statement from the CVMP Reflection paper on classification of a product as intended for a limited market according to Article 4(29) and/or eligibility for authorisation according to Article 23 (EMA/CVMP/235292/2020), that "post-marketing authorisation conditions in relation to the data gaps are not foreseen in the legislation". **Proposed change**: Please add at the end of the § "The benefit-risk balance evaluation …in accordance with CVMP guidance for limited market products" the following sentence: "**Regulation 2019/6 does not foresee the option for competent authorities or the Commission to impose post-authorisation studies to close the efficacy**	Not accepted. Reference to 'post-authorisation measures' (PAMs) in the text is currently linked to minor shortcomings (…) compared to the applicable dossier requirements. The fact that proposed additional text mentions PAMs in a slightly different context could lead to confusion/misunderstanding rather than being of help. The current wording is considered sufficiently clear and only a small addition is proposed to refer to "(…) completion of <u>any applicable</u> post-authorisation measure (…)".

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		and/or safety data gaps agreed upon during the scientific assessment of the dossier."	
116-118	1	**Comment**: The current version on Article 23 application reads "The benefit-risk balance evaluation and its principles are not different from applications under other legal bases, other than allowing for a customised set of data requirements". This evokes the impression of similar requirements like full applications. See also Guidance to applicants (C/2024/1443). **Proposed change**: Suggested change in line 117 (**additional** text, delete text): *'… **~~other than~~** **except for** allowing for a customised set of data requirements, **lacking comprehensive safety or efficacy data**.'*	Not accepted. The definition of benefit-risk balance set out in point 19 of Article 4 of Regulation (EU) 2019/6 is applicable to all marketing authorisations, including those granted under Article 23. A customised set of data requirements is allowed for applications under Article 23. While the stakeholder is correct in indicating that such customised set refers to the lack of comprehensive safety or efficacy data, it is preferred to use the current wording. Please note that the statement to be included in the product information of veterinary medicinal products authorised under Article 23 also refers to 'customised requirements' (please refer to point 3.3.5 of Commission Notice C/2024/1443 – guidance to applicants). The current wording is considered sufficiently clear. For the sake of clarity, the first sentence in the paragraph is tweaked to refer to "(…) the provisions of Article 23 (limited market and benefit of availability outweighing the risks of the omission of certain safety or efficacy data) will be assessed (…)".
131-132	2	**Comment:** for generic products, information on antimicrobial/antiparasitic resistance is not product specific. If a risk in this topic is identified during evaluation of a generic product, this must be considered for the reference product too, so the risk-benefit balance of the reference product and the generic product is identical on this matter.	Not accepted. The stakeholder is correct in stating that, when something is not a product-specific issue, further regulatory action might need to be taken, i.e. outside of the ongoing application. However, that does not exclude that a benefit-risk conclusion will have to be reached within the procedure under assessment. The last sentence in the paragraph, which was introduced to

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
		Proposed change: Reference regarding reciprocity of requirements and standards between generics and reference products should be added	account for the specific legal provisions that foresee specific areas of assessment for generic (or hybrid) products, has been slightly modified to indicate that "it should be discussed in the evaluation whether any difference in the benefit-risk balance compared to the reference product arises as a consequence of the above-mentioned differences" (and in such cases it will be for the respective competent authority to decide on an appropriate course of action). Other non-product-specific issues are not discussed within this guideline text.
140-141	2	**Comment:** for hybrid products, information on antimicrobial/antiparasitic resistance generally will not be product specific, unless there is a difference with reference product which impacts on resistance. If a risk in this topic is identified during evaluation of a hybrid product, this must be considered for the reference product too, if relevant, so the risk-benefit balance of the reference product and the hybrid product is identical on this matter. **Proposed change:** Add a sentence regarding reciprocity of requirements and standards between hybrids and reference products	Not accepted. See justification above.
145-148	2	**Comment:** The requirement to conduct ERA is mentioned only in article 18(7) for generic product. In article 21, relevant to informed consent applications it is noted that the applicant should not be required to provide technical documentation.	Not accepted. As indicated in section 7.1 of Commission Notice C/2024/1443 (i.e. guidance to applicants), for applications submitted under Articles 18, 19 or 21 (…), the submission of an ERA is not required, unless the reference/cross-referred veterinary medicinal product has been authorised prior to 1 October 2005. The current text is thus correct.

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			The paragraph has been reordered to avoid misleading the reader.
147	1	**Comment**: Reference to Informed consent application should be corrected from 'Article 20' to 'Article 21' **Proposed change**: Amend the text to read: '*… informed consent application (Article ~~**20**~~ **21**)*'	Accepted.
147	2	**Comment:** Error in reference **Proposed change:** *"Without prejudice to the fact that, where the cross-referred product has been authorised prior to 1 October 2005, the applicant may be required to provide data on environmental aspects, the benefit risk balance of products based on an informed consent application (Article ~~**20**~~ **21**), should reflect that of the cross-referred product."*	Accepted.
149-158	1	**Comment**: When it comes to **combination veterinary medicinal products**, besides the assessment of the benefit of a combination compared to a "mono" product, the benefit/risk assessment should also consider the global landscape of already available (authorized and marketed) treatments and the current recommendations from technical expert groups on the therapeutic approach for the concerned diseases. Example: for the registration and assessment of a combined endectoparasiticide, the availability of monotherapies and the recommendation towards deworming and ectoparasite treatment should enter the assessment of the B/R balance for this combination product. Alternate treatment with a mono and a combination product may be considered to appropriately assess any risk of resistance emergence.	Not accepted. The guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005-Rev.1*) provides detailed guidance for the benefit-risk assessment of combination products. The benefit-risk guideline does not intend to provide detailed guidance for every scenario, but rather provide the general landscape for conducting a benefit-risk assessment. To provide further clarity to the reader, and for ease of reference, some text has been deleted and a footnote with reference to the guideline on pharmaceutical fixed combination products added. See also the response to the comment below.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
		Proposed change: to add a reference or mention to this concept in this section.	
149-158	1	**Comment**: The benefit of fixed dose combinations versus individual administration of mono-products typically lies less in the pharmacology, but in improved compliance and treatment feasibility. Especially in veterinary situations with sometimes uncooperative animal patients, this benefit can be decisive for treatment success. **Proposed change:** the addition of a further example is proposed in line 154: '… *the potential clinical advantages of combination therapy (e.g. improvement of activity or broadening of the activity spectrum,* ***improvement in treatment compliance resulting in better clinical outcome****)'*	Not accepted. As indicated above, the benefit-risk guideline does not intend to provide detailed guidance for every scenario. To provide clarity to the reader, and for ease of reference, some text has been deleted and a footnote with reference to the guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005-Rev.1*) is added, where the potential advantages are detailed in section 4.3.
154	2	**Comment:** Suggestion of an additional example. **Proposed change:** *"It is necessary to assess the potential clinical advantages of combination therapy (e.g. improvement of activity or broadening of the activity spectrum,* ***improvement in treatment compliance resulting in better clinical outcome****) against the use of monotherapies…"*	Not accepted. See justification above.
166	1	**Comment**: Although there is a subheading on 'Novel therapy veterinary medicinal products' it is not entirely clear that the mentioned 'risk management plan' relates only to this type of VMPs, but not VMPs in general. In case the Guideline on RMP of 2012 was updated to match Reg 2019/6 a cross-reference to that Guideline (RMPs for Novel therapy	Partly accepted. Commission Notice C/2024/1443 (i.e. guidance to applicants) states, in page 11 (marketing authorisations subject to obligations or conditions) that regardless of whether post-authorisation studies are imposed, applicants for such products should submit a risk management plan detailing measures envisaged to

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		VMPs) would be helpful. It should be clarified that different to Human Pharma there is no general obligation for an RMP. See also Guidance to applicants (C/2024/1443; '... *the applicants for such* [novel therapy products] *should submit a risk management plan* …'). **Proposed change**: addition of specifying wording: *'The adequacy of the applicant's risk management plan* ***for novel therapy VMPs, if submitted,*** *should also be considered within the benefit-risk evaluation'*	ensure appropriate follow-up of treated animals with a view to detecting early and delayed adverse reactions and to gain information on the long-term efficacy and safety profile of the concerned novel therapy veterinary medicinal product. It is thus expected that applicants will systematically submit a risk management plan for novel veterinary medicinal products. The clarification proposed by the stakeholder is partially accepted, i.e. 'if submitted' is not considered to appropriately reflect the direction given in the guidance to applicants document.
170-172 182-186	2	**Comment:** Since generics are also required to submit data on antimicrobial / antiparasitic resistance, if a risk in this topic is identified during evaluation of a generic product, this must be considered for the reference product too, so the risk-benefit balance of the reference product and the generic product is identical on this matter. **Proposed change:** References regarding reciprocity of requirements and standards between generics and reference products should be added.	Not accepted. See justification provided in previous comments. In addition, please note this section relates to types of products whereas the clarification requested by the stakeholder is considered more linked to the legal basis of the applications.
192-194	2	**Comment:** Providing proof for anything to do with antimicrobial resistance may be very difficult, due to geographic differences, even at a farm level. E.g., how to proof that some mitigation measures will limit the risk of antimicrobial resistance? **Proposed change:** Example of possible situations would be preferred or any additional explanation on this part.	Not accepted. The benefit-risk guideline does not intend to provide detailed guidance for every scenario and the addition of examples for specific situations is generally not preferred. With due note of the stakeholder's concern, the last sentence in this paragraph is deleted (i.e. "The burden of proof (…) is on the applicant").

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196-198	1	**Comment**: "Safety information available at the time when the initial marketing authorization was granted is relatively limited, as it is restricted to data on a limited population provided in the marketing authorisation application." Nevertheless, the product holds the largest part of the safety information by the time the initial MA is granted. This shows that the pre-authorization efforts are giving a good view on the B/R balance rendering the initial evidence of a good B/R is substantial. **Proposed change**: Please amend the sentence to read: "Safety information available at the time when the initial marketing authorization was granted is ~~**relatively limited**~~ **robust**, as it is **restricted to based on comprehensive data from controlled pivotal trials on safety and efficacy. on a limited population The safety information provided** in the marketing authorisation application **reflects the major part of safety information as post-marketing information does in general not reveal substantial additional safety information."**	Partially accepted. The original text accurately reflects the safety information at the time of the initial marketing authorisation, which does not reflect the use of the VMP, as intended, in the wider targeted population and this has not changed with implementation of Regulation (EU) 2019/6. The comment from the stakeholder is however noted, and a rewording of the paragraph is proposed while keeping the main message as was.
196-198	2	**Comment:** The proposed wording does not give enough relevance to the safety information submitted in the marketing authorisation application to substantiate safety of the VMP, a change in wording is suggested **Proposed change:** *"Safety information available at the time when the initial marketing authorization was granted is* ~~***relatively limited***~~ ***robust****, as it is* ~~***restricted to***~~ ***based on comprehensive data from controlled pivotal trials on safety and efficacy*** ~~***on a limited population***~~*"*	Partially accepted. See justification above.

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204-205	1	**Comment:** As of today, it is not technically possible for MAHs to enter/record annual conclusions on B/R balance in the Union pharmacovigilance database. Depending on future changes (IT) for the Union pharmacovigilance database accessibility it is proposed to adapt the wording for more options. **Proposed change:** Please add the following: *"MAHs shall record, at least annually a conclusion on the benefit-risk balance in the Union pharmacovigilance database (Article 81(2))* ***or an alternative (e.g. IRIS)…"***	Not accepted. It is now technically possible for MAHs to record the conclusions on the benefit-risk balance of their VMPs in the Union pharmacovigilance database (via IRIS). There appears to be a misunderstanding in the proposed change as the Union pharmacovigilance database comprises a number of electronic systems, including IRIS. A footnote with reference to relevant guidance is added for the reader's benefit.
205	2	**Comment:** IRIS is also an option **Proposed change:** *"MAHs shall record, at least annually a conclusion on the benefit-risk balance in the Union pharmacovigilance database (Article 81(2))* ***or IRIS****, and…"*	Not accepted. See justification above.
Section 5.1. (starting in line 234)	1	**Comment**: The currently active version of the guideline (EMEA/CVMP/248499/2007 of 20 April 2009) includes in section 5.3 (Benefit-risk evaluation principles and methodology) a last paragraph "Avoiding the risk-risk scenario", which is now missing in the new draft for consultation. "A 'risk-risk' scenario arises where a risk mitigation measure itself introduces a new, usually unexpected, risk. In the case of veterinary medicinal products this can arise, for example, where the risks of not authorising a product are greater than the risks of authorising it with less than a normal data set…." **Proposed change**: Keep this very relevant section in the new version of the guideline. It is very important to consider	Not accepted. It is considered that the section 'risk-risk scenario' that was present in the former recommendation provides general guidance, and it was decided not keeping it in the benefit-risk guideline. The scenario and example given in the former recommendation are very detailed for a guideline that intends to provide general guidance, without focusing on specific scenarios.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
		risks that arise if a new product is not authorised to mitigate potential risks. Please reinstate the risk-risk scenario, please add: ***"Avoiding the risk-risk scenario.*** ***A 'risk-risk' scenario arises where a risk mitigation measure itself introduces a new, usually unexpected, risk. In the case of veterinary medicinal products this can arise, for example, where the risks of not authorising a product are greater than the risks of authorising it with less than a normal data set. Such a situation can lead to authorisation under exceptional circumstances of vaccines against epizootic diseases in situations where no such vaccines are currently authorised. This provision should be taken into account in advance of benefit-risk evaluation."***	
Section 5.1. (starting in line 234)	1	**Comment**: The currently active version of the guideline (EMEA/CVMP/248499/2007 of 20 April 2009) includes in section 5.3 (Benefit-risk evaluation principles and methodology) a paragraph "Comparison with existing products" (page 11), which is now missing in the new draft for consultation. **Proposed change**: Please keep this paragraph in the new version of the guideline, because under practical conditions in veterinary medicine, the compared risk-benefit of treatment options is key for treatment decisions. Please add: ***"Comparisons with existing products*** ***For pharmaceutical products, several guidelines exist which state the lowest level of efficacy that is considered acceptable. This level of efficacy must always be achieved, irrespective of whether the product is associated with a high or low level of risk.***	Not accepted. It is considered that the section 'comparison with existing products' that was present in the former recommendation provided general guidance not so much targeted at benefit-risk assessment but rather on how to demonstrate efficacy, and it was decided not keeping it in the benefit-risk guideline. There is, however, a targeted sentence in section 5.2.1 of the current text (right before the bulleted examples) stating that an evaluation regarding the claimed benefits should be made on the basis of endpoints and outcomes from clinical GCP trials, laboratory studies or other studies/publications, as applicable, and taking into account existing scientific guidance stating requirements for efficacy assessment (e.g. level of effect, statistical requirements). It is considered that this text sufficiently

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		When products already exist on the market with a claim similar to that of a new product, clinical trials for efficacy are generally performed in comparison to a reference product in order to avoid the unnecessary suffering of untreated control animals. The choice of comparator is left to the applicant but is validated as part of the assessment of the dossier. The statistical hypothesis of such a trial normally requires that the test product is at least non-inferior in terms of efficacy. Products with lower efficacy than their comparator products may however still be accepted provided that their efficacy exceeds the minimum acceptable level, where this is defined, and provided that the benefit-risk balance is deemed positive due to lower risks, improved product delivery or better dosing compliance. This is a clear example of a situation where a sound benefit-risk evaluation provided by the applicant may be beneficial for the product. ***For immunological products a different approach is usually adopted. Firstly, the applicant must justify that the proposed claim (i.e. reduction or prevention of infection, mortality or clinical signs etc.) is relevant to the control of the disease and appropriate data must be provided to demonstrate that the product achieves the level of efficacy claimed. There is therefore no direct requirement to compare with previously authorised products and untreated control animals are usually necessary to prove efficacy. Another factor is that for vaccines, contrary to pharmaceuticals, the***	covers for the referenced former section by cross-referencing to the more explicit scientific guidelines.

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		European Pharmacopoeia monographs usually dictate minimum requirements for efficacy."	
242	1	**Comment**: '*Information about the extent and importance of each benefit should be stated'*: an example as in previous guideline version may be useful to figure out what type of information is awaited regarding 'extent' and 'importance'. **Proposal/Suggestion**: Please add an example to enable better understanding what type of information is awaited regarding 'extent' and 'importance'.	Partly accepted. The comment from the stakeholder is acknowledged and it is proposed the sentence be deleted as a whole. The remaining two sentences provide sufficient detail on what is expected.
242	2	**Comment:** Information about the extent and importance of each benefit should be stated. **Proposed change:** Further explanation/meaning or even definition on what is meant by "extent and importance" would be welcome.	Partly accepted. See justification above.
248-250	2	**Comment:** Remove last part of this paragraph **Proposed changed:** '*The risk assessments should be performed for all relevant risks and information about each risk should be stated e.g. "adverse reactions related to treatment occurred in 25% of treated animals;* ***~~this is a major factor~~…*****"** '	Accepted.
250	1	**Comment**: 'this is a major factor'. We have no definition to classify the risk in major, minor, as in Human Pharma/GVP. This is also not a request neither in VGVP nor in the template for a Signal Assessment Report. This part of the sentence/example should be deleted.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
		Proposed change: Please modify the sentence to read: *'The risk assessments should be performed for all relevant risks and information about each risk should be stated e.g. "adverse reactions related to treatment occurred in 25% of treated animals~~; **this is a major factor**~~…" '*	
255-259	1	**Comment**: CVMP does rely on quantitative methods with the ROR (reporting odds ratio) + number of animals reacting. This paragraph is too vague, and examples should be provided of qualitative methods and non-suitable (semi-) quantitative methods. **Proposed change:** Please add explanatory wording: *'In conclusion, the qualitative approach **based on sound scientific and medical judgement (e.g. disproportionality analysis)** is deemed more fit for purpose at the current time.'*	Partly accepted. As the text is a general statement it is preferred to not include examples. Some more general rewording is proposed, and the proposed reference to 'sound scientific judgement' has been included.
255-259	2	**Comment:** since a completely objective decision making process using qualitative approaches is not possible, there might be differences on risk-benefit assessment throughout different Member States, leading to disharmonization and inequality of access to veterinary medicines. Clinical judgement is very important to be also considered. **Proposed change:** The addition of an explanation on the possible outcome of the qualitative approach for MAHs would clarify the impact of this guideline section. In case the applicant does not agree with the risk-benefit assessment due to a non-objective decision-making process, this should be a relevant reason for requesting a re-examination process.	Not accepted. The qualitative approach has been used by the CVMP for years due to the difficulties encountered to implementing (semi-)quantitative methods. The revision of the former recommendation has not changed this approach. Some more general rewording is proposed, and reference to sound scientific judgement has been included in the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
272-275	1	**Comment**: The explanation about direct benefits of a VMP with reference to the target animal should also cover the concept of '*Serious or life-threatening disease/condition'* in context with Art 23. See Reflection paper EMA/CVMP/235292/2020: '*… when considering 'serious disease' in the context of veterinary medicines, there is a need for a veterinary specific definition which encompasses all relevant elements (impact on target population, possible impact on non-target populations (zoonosis) and economic impact).'* **Proposed change**: Please modify the text to read: "When considering the direct benefits of a veterinary medicinal product, those taken into account in the benefit-risk evaluation are linked to the proposed indications of the product, and generally the therapeutic or diagnostic benefits demonstrated in the treated animal. ~~**It also follows that**~~ **Nevertheless**, the demonstration of possible ~~**additional**~~ benefits ~~**cannot override**~~ **in addition to** this primary requirement **in context with serious diseases is possible (e.g. impact on target population, possible impact on non-target populations (zoonosis) and economic impact)**.	Not accepted. The additional text proposed by the stakeholder refers to the context of an unmet medical need, which is neither a direct benefit nor an addition benefit. Unmet medical need is a set of circumstances which, when meeting the specific criteria of the applicable legal bases, enable applicants to submit a marketing authorisation application with customised dossier requirements where there is a general lack of options for treatment/prevention (Art. 23) or where there is an emergency (Art. 25). This concept is reiterated in Commission Notice C/2024/1443 (i.e. guidance to applicants).
298	1	**Comment**: First example of benefits taken into account in the evaluation of the benefit-risk balance is "Disease prevention, clinical or subclinical treatment," Does this include protection (partial protection, since "prevention" was previously defined in (https://www.ema.europa.eu/en/documents/scientific-guideline/revised-position-paper-indications-veterinary-vaccines_en.pdf) as near 100% protection)?	Partly accepted. The word protection is not deemed appropriate for addition. Instead, 'or reduction' is added since 'prevention or reduction' is the terminology commonly used in this context.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
296 and 323	1	**Comment**: Examples of benefits taken into account in the evaluation of the benefit-risk balance **do not state any longer 'Better quality of life'** (recommendation document EMEA/CVMP/248499/2007 of 20 April 2009 listed it on 3rd position). The introduction of 'or recovery from' does not fully replace omission of 'Better quality of life'. As QoL might also be a primary Endpoint in pivotal studies, it should stay in the Direct benefits list and not be seen to be, if at all, an additional benefit. As defined in the draft guideline, "Additional benefits are benefits not directly linked to the main indication of the product." Unlike 'Facilitated animal handling', 'easier administration', 'improved palatability' … that are completely independent from a main clinical indication of a product, 'better quality of life (QoL)' does not fall within this scope since QoL may be a direct consequential benefit of the use of the product in the context of the clinical indication and might also be a primary endpoint in clinical trials. 'Better quality of life' should be removed from "Additional benefits list" and added to the "Direct benefits list". **Proposed change**: Please re-introduce 'Better quality of life': *"Examples of benefits taken into account in the evaluation of the benefit-risk balance include the following:* • *Disease prevention, clinical or subclinical disease treatment,* • *Improvement of, or recovery from, the clinical condition,* • ***Better quality of life for the treated animal insofar as this is relevant in relation to the recognized pathological condition reflected in the primary indication,***	Not accepted. A better quality of life (QoL) is usually not a direct benefit (with some exceptions for chronic or incurable diseases). QoL is listed under the examples given for additional benefits because in some cases it can be an endpoint in a clinical trial if it is valid to measure improvement in QoL as a surrogate endpoint which shows the state of activity of the disease.

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		• *Increase of survival rate or life expectancy, in relation to a recognised pathological condition,"*	
310-312	n/a	n/a	The first paragraph under section 5.2.2 has been modified. It was considered that the former text could lead to misinterpretation of what additional benefits are. The text in this paragraph has been aligned with the direction provided in the Guidance to Applicants document (C/2024/1443).
317-324	1	**Comments:** 1)Examples of 'additional benefits' provided in section 5.2.2 are about improvements in comparison with other available veterinary medicinal products. For example: 'facilitated' handling, 'easier' administration, 'improved' palatability. A new product or variation could also aim at improvements in term of reduction of risks and this is in line with the provisions of Article 40(5). However, if the reduction of risks is only considered within the 'risk' part of the assessment, the VMP properties leading to a risk reduction won't be described anywhere in the SPC. The negative impact would be for both the user (fewer information) and for innovation in veterinary medicines (decreased incentive to innovation if innovations cannot be part of the labelling). For this reason, it is important that the ability to reduce risks is recognized as an 'additional benefit'. 2) More specifically, and in line with above comment, vaccines and vaccination represent an example of possible (positive) impact on reduction of AM use (and/or AMR) which is supported by the following arguments: • EMA/CVMP explicit acknowledged the positive impact of vaccination on reduction of AMR in the EU:	Not accepted. There is a dedicated reflection paper developing on the provisions of Article 40(5) of Regulation (EU) 2019/6. As previously indicated, the benefit-risk guideline does not intend to provide detailed guidance for every scenario, but rather provide the general landscape for conducting a benefit-risk assessment. The additional examples proposed by the stakeholder are part of ongoing discussions and it is considered premature to state in this guidance document that those do qualify as additional benefits.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
		EMA/CVMP/143258/2021 *"Reflection paper on promoting the authorisation of alternatives to antimicrobial veterinary medicinal products"* • Having this explicitly mentioned in the R/B GL would be an incentive for Industry to invest in the area (generate relevant data). • Would fit the goal of developing and authorizing ATAMs in the EU (mentioned in the above CVMP RP) • We are not aware of regulatory/legal barriers precluding such claims in the EU (such potential claims are not unlike the existing "body weight losses reduction" claims for vaccines in the EU). **Proposed change:** Please add in section 5.2.2.: *Examples of additional benefits include the following:* • *Facilitated animal handling (e.g. long-acting substance requiring fewer administrations, or a fixed combination might reduce the total number of tablets to be given),* • *Easier administration (leading to e.g. improved owner compliance)* • *Improved palatability,* • **Reduction of any of the risks listed in Article 4(19) in comparison to other established therapeutic options.** • **Reduction *of use of antimicrobials in general and in particular the use of antibiotics by means of vaccination.***	
321 and 333	1	**Comment**: The list of Examples for additional benefits contains 'improved palatability'. As 'palatability' is addressed in a separate guideline (EMA/CVMP/EWP/206024/2011	Partly accepted. The proposed additional text is not deemed appropriate for this guideline since it is text that pertains to the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
		Rev.1) on studies for palatability claims in the product information texts, some clarification would be welcome to whether and how additional benefits could be reflected in the approved product information by adding a respective reference to that guideline. **Proposed change/suggestion**: Please add at the end of the paragraph in line 333: "… **For palatability claims additional benefits should be included in section 3.9 (Administration route(s) and dosage) according to Guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011 Rev.1)".**	referenced guideline. A foot note with a direct reference to this document has been added instead.
322	1	**Comment**: DIVA generally stands for Differentiate Infected from Vaccinated Animals. This fits with the use of the generally available DIVA vaccines. Example of DIVA vaccines are the IBR marker vaccines (negative marker vaccine). For eradication purpose it is essential to identify IBR infected animals (where these often do not become diseased), there is no need to identify if animals are vaccinated or not. In case it was intended to also include vaccines that allow confirmation that animals were indeed vaccinated (positive marker), but despite that become ill, a different definition/abbreviation might be considered. The '*Possibility to Differentiate Vaccinated from Diseased Animals (DIVA) for vaccines*' is listed as an additional benefit whereas it can be a major benefit in the context of outbreaks (as a control tool for disease outbreaks, allowing to alleviate special restrictions necessary for infected animals…). Compared to other examples of additional benefits listed in	Not accepted. As also suggested by the stakeholder, only in very specific cases DIVA vaccines would qualify as bringing direct benefit. In all other cases, the possibility to differentiate vaccinated animals will be an additional benefit. As the text indicates, the listed are examples (it is not a prescriptive list) and the current example is still considered appropriate.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
		the guideline (e.g. improved palatability), it seems disproportionate. It could be either considered as a direct benefit or at least precise that in specific diseases outbreaks, DIVA may be considered as a direct benefit. **Proposed change/suggestion**: DIVA may be considered as a direct benefit. Alternatively, add clarification to whether in specific diseases outbreaks, DIVA may be considered as a direct benefit.	
325	2	**Comment:** clarification for the term "theoretical arguments" would be appreciated.	Accepted. Clarification is added, as requested, by meant of detailing that theoretical arguments are those 'not based on scientific evidence'.
340-343	1	**Comment**: The level of risk that is considered acceptable may also vary in case no other therapeutic option exists for life-threatening diseases, etc. See also comment above (8/ 272-275). **Proposed change/suggestion**: Add clarification to the level of risk that might vary in case of unmet medical need situation or *Serious or life-threatening disease/condition.*	Not accepted. The current text clearly indicates that for a specific veterinary medicinal product, each kind of risk should be assessed carefully in relation to the different part of the dossier (quality, safety, environmental safety, residues, resistance development, efficacy) in line with the existing guidelines. The situations highlighted by the stakeholder would correspond to specific scenarios for which there exist separate guidance elaborating on the different dossier requirements. As previously indicated, the benefit-risk guideline does not intend to provide detailed guidance for every scenario, but rather provide the general landscape for conducting a benefit-risk assessment. Any further clarification is thus deemed unnecessary.

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340-343	2	**Comment:** Add clarification to the level of risk that might vary in case of unmet medical need situation or serious or life-threatening disease or condition.	Not accepted. See justification above.
345-347	1	**Comment**: The 'different' risks could also be mitigated by addressing/mentioning them in respective sections in the product information. As in line 342 risk mitigations for the target animals are explicitly mentioned to comprise *precautions and contraindications in the product information* the same should be explicitly stated for the 'different risks'. **Proposed change**: Please add the suggested text: *"These different risks should be considered individually, and a conclusion should be reached in the benefit-risk evaluation whether or not these risks are overall acceptable in relation to the benefits, taking into account possible risk mitigation measures* ***(which may include mentioning precautions and contraindications in the product information)****."*	Accepted with minor changes.
376-378	2	**Comment:** for generic and hybrid products, in case there is a negative benefit-risk balance because of the risk of resistance, this should be the same for the reference product, since this is not a product specific issue. **Proposed change:** Reciprocity principle to be reflected in the document.	Not accepted. See justification in comments above.
394	1	**Comment**: The following bullet point is mentioned under Zoonotic potential. '- *the risk of lack of efficacy in the target animals'* **Suggestion**: The reference should be explained as it is not clear.	Accepted. The text has been expanded to explain that this example refers to 'the risk to humans arising from lack of efficacy in the target animal'.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome)
414-415	1	**Comment**: The draft guideline states that "For each relevant risk, an assessment should be provided which should be accompanied, if appropriate, by proposals for risk mitigation measures to address these risks.". It is expected that the risk mitigation measures should be commensurate with the level of risk, and it is suggested to add this clarification, which is applicable to each type of risk management, to guide the users in defining appropriate mitigation measures. **Proposed change**: Please add the suggested text: "When risk mitigation measures are proposed by the applicant or required by the competent authority, care should be taken to ensure that they are realistic and practicable. **They should also be commensurate with the level of risk."**	Partly accepted. While it is accepted to add text as suggested by the stakeholder, the work 'commensurate' is replaced by 'proportionate'.
417-429	1	**Comment**: Could EMA clarify where this overall benefit-risk balance should be presented in the Marketing Authorisation Application?	Please refer to section 1 – general comments – for a response.
End of the document (i.e. after page 13)	1	**Comment**: Annex I of the previous recommendation document EMEA/CVMP/248499/2007 of 20 April 2009 listed **Definitions for B/R analysis for VMPs**, which were considered helpful guidance. **Proposed change**: Re-introduce definitions for B/R analysis for VMPs as a glossary / annex. Some adaptations will be needed as reference should be to Reg 2019/06, not Directive 2001/82/EC.	Not accepted. Upon review of the guideline it was considered that the terms included in the definitions section were outdated or mostly of a general nature used also in other contexts (e.g. risk assessment) and that a glossary therefore would not be of added value in this specific guideline. The revised text of the guideline is intended to be sufficiently clear to allow understanding without a glossary.