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Guideline on the evaluation of the benefit-risk balance of veterinary medicinal products

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This guideline replaces the 'Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products' (EMA/CVMP/248499/2007).

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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Guideline on the evaluation of the benefit-risk balance of veterinary medicinal products

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Executive summary

This guideline was developed to facilitate the methodology for benefit-risk evaluations of the different pre-and post-authorisation applications of veterinary medicinal products, to provide a systematic approach, hence improving the consistency and transparency of decisions taken at CVMP level.

In light of the implementation of Regulation (EU) 2019/6 and experience gained over the years, the CVMP has revised the guideline.

1. Introduction (background)

According to Article 4 (19) of Regulation (EU) 2019/6 (hereinafter the Regulation) "benefit-risk balance" means an evaluation of the positive effects of the veterinary medicinal product in relation to the following risks relating to the use of the product:

(a) any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health;

(b) any risk of undesirable effects on the environment;

(c) any risk relating to the development of resistance.

The benefit-risk evaluation of a veterinary medicinal product is a complex process based on the intended use of each individual product in respect to its overall safety.

A positive benefit-risk balance must be demonstrated for a veterinary medicinal product to be granted a marketing authorisation and it may be subject to re-evaluation during the product life cycle to ensure it remains positive, so that the marketing authorisation can be maintained.

In this guideline, important points are highlighted related to the preparation and assessment of initial marketing authorisation and subsequent applications. The points in this guideline have to be read in conjunction with the Regulation and its Annex II in which the scientific dossier requirements for different types of products and marketing authorisation applications are provided.

Recognising the complexity of evaluating the varied information related to benefits and risks stemming from the quality, safety and efficacy evaluation of the product, this guideline proposes a methodology aimed at improving the transparency and the robustness of the decision-making process.

This guideline has to be read in conjunction with the European Commission’s Guidance to Applicants (Commission Notice C/2024/1443). In addition, relevant guidance documents prepared by the CVMP and/or the VICH should be taken into account, as applicable.

2. Scope

The guideline is intended to provide details on the conduct of the benefit-risk evaluation, to give guidance on when and how to perform a benefit-risk evaluation, and to be a basis for the elaboration of all assessment documents that include a section on the evaluation of the benefit-risk balance. It is addressed to those performing a benefit-risk evaluation of veterinary medicinal products, which includes regulators and applicants or marketing authorisation holders.

The principles of this guideline apply to all types of veterinary medicinal products.

The principles of this guideline apply whenever a benefit-risk evaluation is required under the Regulation, e.g. in the context of a marketing authorisation or variation application, pharmacovigilance or on request of a national competent authority (NCA) or the Agency (Article 58(9) of the Regulation).

3. Legal basis

This guideline takes into account the provisions of Regulation (EU) 2019/6 (including its Annex II) which provides the definition of benefit-risk balance, the scientific dossier requirements, criteria for refusing marketing authorisations and lays down the responsibilities of the marketing authorisation holders.

4. When to perform a benefit-risk evaluation

A benefit-risk evaluation is undertaken by competent authorities or the Agency before a new veterinary medicinal product is granted a marketing authorisation and throughout the life-cycle of authorised products, whenever new information is submitted or emerges that triggers a re-evaluation of the benefit-risk balance.

It is the responsibility of a marketing authorisation holder to provide data demonstrating that the benefit-risk balance remains positive, when required to do so by a competent authority or the Agency (Article 58(9) of the Regulation) or when new information emerges that might influence the assessment of the benefits and risks of the veterinary medicinal product concerned (Article 58(10)). The marketing authorisation holder is responsible for continuously evaluating the benefit-risk balance of the veterinary medicinal product and for taking appropriate action, when necessary, e.g. Articles 77(4) and 81(2).

4.1. Initial marketing authorisation application

4.1.1. Points to consider depending on the legal basis of the application

The amount and type of data to be provided in support of an application for a marketing authorisation vary depending on the legal basis of the marketing authorisation application and the type of product. Dossier requirements can be found in the Regulation and its Annex II. Although the dossier requirements (level of evidence needed) for quality, safety and efficacy may vary according to the legal basis of the application and depending on the type of product, the principles underpinning the benefit-risk balance evaluation do not differ, i.e. the benefits must always outweigh the risks, leading to a positive benefit-risk balance within the applicable context.

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 still be considered positive, subject to the satisfactory completion of any applicable post-authorisation measure 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.

For **limited market applications in accordance with Article 23**, the applicability of 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 during the marketing authorisation procedure, and it will be confirmed whether the dossier submitted in support of the marketing authorisation application is appropriate. 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 in accordance with CVMP guidance for limited market products eligible for Article 23.

For **applications under exceptional circumstances** (Article 25), the applicant will have to justify why certain quality, safety or efficacy documentation usually required according to Annex II cannot be provided (reasonable evidence that the benefit of immediate availability on the market of the product,

related to animal or public health, outweighs the risk linked to the fact that certain technical documentation cannot be provided by the applicant at the time of the evaluation and provided that there are exceptional circumstances related to animal or public health). The validity of the justification will be confirmed during the marketing authorisation procedure. 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 in accordance with CVMP guidance for applications under exceptional circumstances.

The benefit-risk balance of **generic products** (Article 18) should generally reflect that of the reference product. Where there are specific legal provisions in the Regulation (including Annex II) that foresee specific areas of assessment for generic products[1] (i.e. quality data, bibliographic information on antimicrobial/antiparasitic resistance (where applicable), data on local residues at the administration site and target animal tolerance (if relevant), user safety risk assessment (if relevant) or, if applicable, the outcome of the environmental risk assessment), these aspects should be taken into account in the evaluation of the benefit-risk balance. 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.

The benefit-risk balance of **hybrid products** (Article 19) should generally reflect that of the reference product apart from where there are differences compared to the reference product and where there are specific legal provisions (including Annex II) that foresee specific areas of assessment for hybrid products, e.g. pre-clinical/clinical data to cover differences with the reference product, risk of antimicrobial/antiparasitic resistance, comparability review for a biosimilar or demonstration of similarity between EU and non-EU reference product used for the conduct of any studies. 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.

The benefit-risk balance of products based on an **informed consent** application (Article 21), should reflect that of the cross-referred product[2] 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.

In case of applications for **combination veterinary medicinal products**[3] (Article 20), the need for and contribution of all active substances at the moment of treatment must be justified. The presentation of multiple active substances in a fixed combination product may present some specific risks (e.g. due to interactions between the active substances or cumulative toxicity, development of resistance). It should be justified that the benefits of the combination therapy outweigh its inherent potential risks such as additional or worsening of adverse effects, and the fact that fixed combination medicinal products may not always be easily adjusted to the need of an individual animal.

4.1.2. Points to consider for certain types of products

A. Novel therapy veterinary medicinal products

According to the specific nature of a novel therapy product, as defined in Article 4(43) of the Regulation, its use may potentially be associated with specific risks. Risks inherent to the specific product and the risk factors contributing to those risks should be identified in a risk analysis that may cover the entire development of the product. Based on the evaluation of the information on the identified risks and risk factors, a profile of each individual risk associated with a specific product shall

[1] See Annex II of Regulation (EU) 2019/6, Section IV.1.2.(e), i.e. "focusing on the differences between the generic and reference veterinary medicinal products (for example, composition in excipients".
[2] See Commission Notice C/2024/90009, Guidance to Applicants – Veterinary Medicinal Products.
[3] With reference to the 'Guideline on pharmaceutical fixed combination products' (EMA/CVMP/83804/2005-Rev.1*).

be established and factored into the benefit-risk evaluation. The adequacy of the applicant's risk management plan for novel therapy veterinary medicinal products will also be considered within the benefit-risk evaluation.

B. Antimicrobial veterinary medicinal products

Regulation (EU) 2019/6 places increased emphasis on the assessment of risk arising from antimicrobial resistance. For antimicrobial products, the applicant is required to address the direct or indirect risks to public or animal health, as well as risk mitigation measures to limit antimicrobial resistance development. In this respect the CVMP's dedicated guidance on antimicrobial resistance risk assessment should be taken into account. It should be noted that consideration of the environment within the context of antimicrobial risk assessment refers to the environment's potential role in acting as a vehicle for spreading the risk of antimicrobial resistance to humans.

The acceptability of the risk level is, as always, finally weighed into the context of the overall benefit-risk balance for the product, taking into account any agreed risk mitigation measures.

C. Antiparasitic veterinary medicinal products

The risk of development of resistance against antiparasitic veterinary medicinal products is of increasing concern and reflected in the Regulation as a risk to be taken into consideration in the benefit-risk evaluation.

Where an application concerns an antiparasitic veterinary medicinal product, applicants are required to provide appropriate data/information in regard to the potential of emergence of resistance of clinical relevance (if relevant for the type of procedure). This risk is generally assessed in regard to its potential impact on animal health, and data requirements as well as guidance on possible risk mitigation options are provided in Annex II to the Regulation and/or a number of guidance documents provided by the CVMP.

4.2. Variations

For all variations requiring assessment, where new/changed risks or new/changed benefits are identified, a benefit-risk evaluation by the competent authorities/the Agency is required in order to accept or reject the variation. Any new data provided in support of the variation will be assessed for their impact on the overall benefit-risk balance. Furthermore, any other relevant information identified during the procedure can be taken into account in the benefit-risk evaluation.

4.3. Pharmacovigilance

At the time of first granting of the authorisation, information on the safety of a veterinary medicinal product reflects data available in the marketing authorisation application. In the post-authorisation phase, when the veterinary medicinal product is used in larger populations as intended, new risks (including lack of expected efficacy) may be identified by data gathered during pharmacovigilance activities or from post-authorisation measures.

According to Article 77(4) of the Regulation marketing authorisation holders (MAHs) are responsible for the pharmacovigilance of their veterinary medicinal product(s). The continuous monitoring of the benefit-risk balance of the authorised veterinary medicinal product is an essential obligation of the MAH. MAHs shall record[4], at least annually, a conclusion on the benefit-risk balance in the Union

[4] Via electronic systems described in topic-specific guidance e.g. Signal management (veterinary medicines) | European Medicines Agency (EMA) (europa.eu)

pharmacovigilance database (Article 81(2)) and shall notify the competent authorities or the Agency where the outcome of the signal management process identifies a change to the benefit-risk balance or a new risk (Article 81(2)).

4.4. Union interest referrals

The assessment of a referral will address the benefit-risk balance of the veterinary medicinal product(s) that is (are) subject to the referral. The consideration of the benefit-risk balance will focus on the subject matter of the referral and specifically on issues that may change the benefit-risk balance or make risk mitigation measures, or amended risk mitigation measures, necessary. The outcome of the referral procedure may be, where duly justified, that the marketing authorisation(s) concerned are to be amended, suspended or revoked, or that temporary safety restrictions should be imposed.

5. Benefit-risk evaluation principles and methodology

The evaluation of the benefit-risk balance is a complex process as it generally includes multiple benefits and risks, as well as taking into account risk management options.

The benefit-risk evaluation should factually describe the observed effects and uncertainties, in terms of important benefits and risks, as well as their impact. The identified benefits and risks should initially be evaluated separately. The direct benefit(s) of the product must be clearly established for each target species and each indication. Each risk should be assessed taking into account all the elements present in the different parts of the dossier which should be accompanied, if appropriate, by proposals for risk mitigation measures. The aim is to objectively bring to light and critically discuss the benefits and risks described.

Finally, an overall conclusion should be drawn on the benefit-risk balance, recognising that zero risk does not exist and considering potential risk mitigation measures. The evaluation of the overall benefit-risk balance should clearly describe why the benefit-risk balance is considered as favourable (positive)or unfavourable (negative) explaining the reasoning leading to the conclusion. The outcome of the overall benefit-risk evaluation will be the basis of the scientific recommendations in the assessment and the regulatory decisions that follow. Benefits related to economic considerations will not be taken into account in the evaluation of the benefit-risk balance, for example, comparative cost-effectiveness of a veterinary medicinal product.

5.1. Methodology

A structured approach for the benefit-risk evaluation should be followed in order to ensure that the reasoning leads to a clear conclusion. It should comprise the following elements:

- The benefit-risk evaluation should include an introduction summarising the main characteristics of the veterinary medicinal product and outlining the legal basis of the marketing authorisation application which forms the framework of the assessment.
- The direct benefits of the product (see section below) should be clearly described for each target species and each indication. Any additional benefits (see section below) should be identified separately.
- The benefit-risk balance should take into account, in particular, dose-effect relationships if relevant, i.e. if higher doses give better therapeutic effects but also more frequent or severe adverse effects.

- The risk assessments should be performed for all relevant risks and information about each risk should be stated e.g. "adverse events related to treatment occurred in 25% of treated animals".
- Where relevant, risk mitigation options should be considered, and the potential residual risk discussed.
- The overall conclusions should describe on which basis the benefit-risk evaluation is considered as favourable or unfavourable.

The use of qualitative and quantitative approaches to benefit-risk assessment have been considered. While it could be hypothesized that a quantitative method could bring progress towards a more objective decision-making process, some (semi-)quantitative methods examined by the CVMP have not been found to be suitable due to difficulties to implement them and limited added value. In conclusion, the qualitative approach based on sound scientific judgement is deemed more fit for purpose at the current time.

5.2. Benefit assessment

It is important to distinguish between direct benefits which always impact the benefit-risk balance, versus additional benefits, which will not impact on the decision to reach a positive or negative benefit-risk balance but which may be relevant in other contexts, e.g. Article 40(5) of Regulation (EU) 2019/6 (see CVMP draft Reflection paper EMA/CVMP/64911/2021).

5.2.1. Direct benefits

Veterinary medicinal products are defined in Article 4(1) of the Regulation as any substance or combination of substances presented as having properties for treating or preventing disease in animals or which may be used in or administered to animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, to making a medical diagnosis or for euthanasia. Further guidance on the definition of a veterinary medicinal product is provided in the European Commission's Guidance to Applicants (Commission Notice C/2024/1443). 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 the demonstration of possible additional benefits cannot override this primary requirement.

In specific and well-justified cases, it is acceptable that the main benefit of treatment is demonstrated in other animals than the treated animal, for example when passive immunity is transferred to offspring or when the risk for transmission of disease to surrounding animals or humans is reduced. For products used for zootechnical purposes (as defined in the European Commission's Guidance to Applicants), for diagnosis or for euthanasia, it is accepted that no direct benefit of treatment may be demonstrated in the treated animal.

Benefits to the environment (e.g. reduced emission of greenhouse gasses) or to human health, apart from risk of transmission of zoonotic infections, fall outside the remit of the assessment of veterinary medicines.

The relevance and acceptability of specified direct benefits will need to be evaluated in each case in view of the nature of the disease. For example, an indication associated with production parameters such as reduced growth retardation for a vaccine to be used in growing pigs may not be accepted as a sole direct benefit but would need to be associated with a benefit in prevention/reduction of infection or disease. Furthermore, deficiencies in the demonstration of efficacy (e.g. study deficiencies, lack of statistical support and/or questionable clinical relevance for the proposed claims, dose, target

species/subpopulation) will be carefully considered as the granting of a marketing authorisation is precluded if efficacy is not sufficiently demonstrated[5].

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).

Examples of direct benefits taken into account in the evaluation of the benefit-risk balance include the following:

- Disease prevention or reduction, clinical or subclinical disease treatment,
- Improvement of, or recovery from, the clinical condition,
- Increase of survival rate or life expectancy, in relation to a recognised pathological condition,
- Reduction of the risks of transmission of a disease to the treated animal and potentially to other animals,
- Reduction in growth retardation in relation to a recognised pathological condition,
- Offering a diagnostic tool,
- Control of a zoonotic disease in animals,
- Appropriate alteration of physiology or disease status to derive a desired benefit in relation to a recognised pathological condition or in the context of zootechnical purposes e.g. oestrus synchronisation.

5.2.2. Additional benefits

Additional benefits are positive effects that are not specifically captured by the indication of the product but are associated to the use of the product in accordance with the terms of the marketing authorisation. These can be general benefits for the animal, the veterinarian, the farmer, the user, or relate to particular properties of the product and shall be relevant to the use of the product in the indications that have been specifically authorised; for example, economic considerations cannot be considered an additional benefit. Additional benefits cannot be the pivotal benefit demonstrated in the application, and would generally only be considered in the overall assessment of the benefit-risk balance where the direct benefits are already adequately established, i.e., the product must have shown a positive benefit-risk balance based on the direct therapeutic benefits before additional benefits would be acknowledged.

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,
- Possibility to Differentiate Vaccinated from Diseased Animals (DIVA) for vaccines,
- Better quality of life for the treated animal insofar as this is relevant in relation to the recognised pathological condition reflected in the primary indication.

[5] Article 37(2)(c) and (g) of Regulation (EU) 2019/6.

Additional benefits should be supported by appropriate information or data. Theoretical arguments that are not based on scientific evidence will generally not be sufficient to justify, e.g. palatability[6] or improvement of quality of life, and data from studies using the product evaluating the specific additional benefit may be needed for the benefit to be included in the product information.

Additional benefits are not included in section 3.2 of the SPC (indications for use[7]) but could be addressed in other sections describing the effects of the product, if relevant, if adequately supported in relation to the claimed indication(s) of the product, and, where applicable, in line with the CVMP Question and answer document on the information contained within section 5.1 of the SPC on pharmacodynamic properties for pharmaceutical products (EMA/CVMP/757903/2016).

5.3. Risk assessment

Risks relating to the use of the product are defined in the Regulation as 'any risk relating to the quality, safety and efficacy of the veterinary medicinal product as regards animal or human health, any risk of undesirable effects on the environment and any risk relating to the development of resistance'. 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 level of risk that is considered acceptable may vary, depending on intended use and on the possibility to identify and implement risk mitigation measures (which may include mentioning precautions and contraindications in the product information). When considering risks other than to the target animal (i.e. risks for the consumer, user, environment and development of resistance), the benefit(s) and risks cannot be directly compared. 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 relevant information in appropriate sections of the product information).

For the **quality** part, the risk assessment should consider whether the product is of appropriate quality throughout the life cycle of the product so as not to alter the conclusions made on safety and efficacy. The quality hazards that may have consequences in terms of safety or efficacy which may be assessed include, for example, degradation products or non-compatibility with other products, interaction between the finished product and the primary packaging, TSE risk, microbial contamination or extraneous agents, or the shelf-life of the product.

For the **safety** part, separate risk assessments are performed with regards to user safety, safety for the consumer, the environment and target animal safety. For these main risk assessments, guidelines are available.

The **user safety** will take into account the toxicological profile of the active ingredient(s) and excipients of the formulation, and the exposure scenarios depending on the type of product, use and pharmaceutical form. The assessment will also take into account whether the final user is a professional user or not.

In the case of **consumer safety**, the risk assessment has largely already been considered by the establishment of maximum residue limits (MRLs). In the marketing authorisation procedure, the assessment is limited to the establishment of the withdrawal period or other risk mitigation measures specific to the veterinary medicinal product.

[6] With reference to the 'Guideline on the demonstration of palatability of veterinary medicinal products' (EMA/CVMP/EWP/206024/2011-Rev.1*).
[7] SPC section 3.2 in QRD template v.9; SPC section 4.2 in QRD template v.8.

For the **environment**, the environmental risk assessment concludes on the risks associated to the use of the veterinary medicinal product in the proposed conditions. When a risk is identified for a certain taxonomic level it should be assumed that the whole environmental compartment represented is at risk. Regulation (EU) 2019/6 introduces new requirements with regard to products that meet the criteria for being considered (very) persistent, (very) bioaccumulative and toxic. It should be noted that the framework for environmental risk assessment of antimicrobials is not widened because there is no specific requirement for assessment of the risk of antimicrobial resistance to the environment (i.e. to ecosystems).

As regards **risk relating to the development of resistance**, for antiparasitics, Annex II has data requirements for development of resistance and related risk in animals (not humans), as well as measures to limit resistance in clinically relevant organisms. For antimicrobials (and specifically antibiotics), the data requirements are for development of resistance and related risk in humans and for development of resistance and related risk in animals (although cross-reference between both can be made where relevant), as well as measures to limit resistance development where necessary.

Nevertheless, for both antimicrobials and antiparasitics, a negative overall benefit-risk balance might be concluded where the risk of resistance to public health outweighs the benefits of the veterinary medicinal product to animal health. For antiparasitics, this situation is not common but could arise where a substance or class of substance is used to treat the same type of parasite in animals and humans (e.g. benzimidazoles / *Ascaris*), or where insufficient efficacy against an animal parasite could prevent adequate treatment of a zoonotic disease (e.g. *Echinococcus*) and thereby increase the risk of transmission in humans.

Regarding **target animal safety**, in studies conducted in the target species, secondary effects including adverse events in the target species can be identified. Such effects are relevant to the assessment of the target animal safety. A conclusion should be included on how the specific tolerance profile of the product fits into the larger context of the use of the product and the benefits of such use.

In addition, there may be **special risks** associated with a specific veterinary medicinal product. Each risk should be assessed taking into account all the elements present in the different parts of the scientific dossier. Specific risks, according to the nature of the product include (examples):

- Unintended spread of a vaccine strain;
- Reversion to virulence of a vaccine strain;
- Zoonotic potential:
  - the risk to humans from the use of live vaccine strains,
  - the risk to humans arising from lack of efficacy in the target animals,
- DNA vaccines: potential risk of migration of the DNA to gonadal tissues and potential DNA transfer into germ line cells of vaccinated male and female animals and thus potential transmission to offspring;
- GMOs: potential direct and indirect, immediate or delayed adverse effects of the GMO on human health and the environment (including plants and animals);
- Specific risks of novel therapies (see section V.1. of Annex II to the Regulation);
- Unintended interactions or differences in the pharmacokinetic properties between the active substances in fixed combination products;
- Risk of potential superfluous administration and inappropriate use of fixed combination products (especially with regard to antiparasitics).

5.4. Risk mitigation measures[8]

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. The summary of product characteristics (SPC) and the product literature (labelling and package leaflet) constitute an essential tool for this purpose. For example, an environmental risk may be identified if the product is used more than twice per year in the same chicken house and manure is spread on grassland. This may be addressed by including an explanation in the SPC on the limitation of use. For antimicrobial or antiparasitic products, appropriate prudent use warnings may be applied in the case of identified risks for the development of resistance.

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 proportionate to the level of risk and consistent with any specific scientific guidance.

If relevant, certain conditions or restrictions on the marketing authorisation might be applied.

5.5. Evaluation of the overall benefit-risk balance

After the analysis of benefits and risks, a clear discussion and conclusion should be reached. The evaluation of the benefit-risk balance should follow the benefit-risk evaluation principles (see section 5). It is not the intention of this section to repeat every benefit and risk. The aim is to discuss the benefits and risks and to explain the reasoning leading to the overall conclusion. Particular attention should be paid to the applicability and practicality of the risk mitigation measures proposed.

When specific conditions for authorisation, such as post-authorisation studies, have been included for a marketing authorisation, this should be stated and justified.

A positive benefit-risk balance can be concluded when the benefits of the product have been sufficiently substantiated and when the risks are considered as acceptable in relation to the proven benefits, taking into account any proposed measures to mitigate the risks. If applicable, and only in the case of an already positive benefit-risk balance, additional benefits may be mentioned at this stage.

[8] In this document, the terms 'risk management' and 'risk mitigation' measures are used interchangeably.

References

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- CVMP draft Reflection paper on the application of Article 40(5) of Regulation (EU) 2019/6 for certain categories of variations: potential criteria to support the demonstration of a reduction in the antimicrobial or antiparasitic resistance, or an improvement of the benefit-risk balance (EMA/CVMP/64911/2021).
- CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1).
- CVMP Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021).
- CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005-Rev1).
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- CVMP Guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011-Rev.1).
- CVMP Question and answer on the information contained within section 5.1 of the SPC on pharmacodynamic properties for pharmaceutical products (EMA/CVMP/757903/2016).
- 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 (Applications for limited markets) (EMA/CVMP/235292/2020).
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