European Medicines Agency
Veterinary Medicines and Inspections

London, 20 April 2009
EMEA/CVMP/248499/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

RECOMMENDATION ON THE EVALUATION OF THE BENEFIT-RISK BALANCE OF VETERINARY MEDICINAL PRODUCTS

ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	12 September 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2008
ADOPTION BY CVMP FOR RELEASE FOR SECOND CONSULTATION	16 October 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2009
ADOPTION BY CVMP	17 April 2009
DATE FOR COMING INTO EFFECT	1 November 2009

KEYWORDS	*Benefit-risk, risk assessment, benefit*

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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TABLE OF CONTENTS

EXECUTIVE SUMMARY **3**

1. INTRODUCTION **4**

2. SCOPE **5**

3. WHO SHOULD PERFORM A BENEFIT-RISK EVALUATION **5**

4. WHEN TO PERFORM A BENEFIT-RISK EVALUATION **6**

4.1 NEW APPLICATIONS 6
4.2 POST-AUTHORISATION BENEFIT-RISK EVALUATION 6
Pharmacovigilance *6*
Variations and extensions *7*
Annual reports *7*
Renewals *7*
Referrals *7*

5. HOW TO PERFORM A BENEFIT-RISK EVALUATION **8**

5.1 NEW MARKETING AUTHORISATIONS 8
Data requirements according to the legal basis of the product *8*
Data requirements according to the nature of the product *9*
5.2 POST-AUTHORISATION CHANGES 9
5.3 BENEFIT-RISK EVALUATION PRINCIPLES AND METHODOLOGY 9
Quantitative versus qualitative benefit-risk evaluation *9*
Benefit-risk evaluation *10*
Principles of the evaluation of the overall benefit-risk balance *10*
Comparisons with existing products *11*
Avoiding the risk-risk scenario *11*
5.4 BENEFIT ASSESSMENT 11
Direct therapeutic benefits *11*
Additional benefits *12*
5.5 RISK ASSESSMENT 12
5.6 RISK MANAGEMENT OR MITIGATION MEASURES 13
5.7 EVALUATION OF THE OVERALL BENEFIT-RISK BALANCE 13

6. WHERE TO INCLUDE THE BENEFIT-RISK EVALUATION **13**

6.1 PRESENTATION OF THE BENEFIT-RISK EVALUATION IN APPLICATIONS AND PSURS 13
6.2 PRESENTATION OF THE BENEFIT-RISK EVALUATION IN THE ASSESSMENT REPORT 14

7. FUTURE STEPS **14**

REFERENCES AND LINKS TO WEBSITES **15**

ANNEX I: PRINCIPLES AND DEFINITIONS FOR BENEFIT-RISK ANALYSIS FOR VETERINARY MEDICINAL PRODUCTS **17**

ANNEX II: FIGURE 1 GENERAL SCHEME OF BENEFIT-RISK ANALYSIS FOR A VETERINARY MEDICINAL PRODUCT (VMP) **19**

ANNEX III: TABLE 1 SUMMARY OF THE BENEFIT-RISK EVALUATION APPROACHES IN RELATION TO THE BASIS FOR MARKETING AUTHORISATION APPLICATIONS **20**

ANNEX IV: EXAMPLE OF STRUCTURE AND SENTENCES THAT MAY BE INCLUDED IN A BENEFIT-RISK EVALUATION **22**

Executive Summary

The CVMP developed this recommendation document in order to improve the methodology for benefit-risk evaluations to provide a more systematic approach, hence improving the consistency and transparency of decisions taken at CVMP level, and also to provide guidance to CMD(v) and Member States.

The recommendation is intended to clarify the definition of a benefit-risk evaluation; to give guidance on when and how to perform a benefit-risk assessment; 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 regulators and applicants or marketing authorisation holders. For applicants or marketing authorisation holders a benefit-risk evaluation is required for PSURs. In addition, a benefit-risk evaluation may be required where new pharmacovigilance or other data impacts on the evaluation of the benefits and risks of the product. In general, regulators should make a benefit-risk evaluation for all new applications and PSURs. This recommendation is not intended to be applied retrospectively to authorised products, i.e. already authorised products have, by definition, a positive benefit-risk balance and a new written benefit-risk assessment is not expected as a result of this recommendation. However, a benefit-risk evaluation may be indicated where new benefits or risks have been identified in variations, extensions, renewals, referrals and when important new information emerges from pharmacovigilance or other data.

In order to clarify the concepts for benefit-risk evaluation contained in this paper, the CVMP has defined various terms with regard to benefit-risk analysis based on internationally agreed definitions for risk analysis in Annex I.

The benefit-risk analysis of a veterinary medicinal product is a complex process based on the intended use and the indications of that product in respect to its overall safety. The benefit-risk principle defined by the legislation takes into account issues relating to availability including minor use/minor species (MUMS). A structured approach should be followed to ensure the reasoning leads to a clear conclusion. The benefit-risk evaluation should describe factually the observed effects and uncertainties, in terms of important benefits and risks, as well as describe their impact. The direct therapeutic benefits of the products should be clearly described for each target species and each claim. If applicable, important additional benefits, which are benefits not directly linked to the claim of the product, could be mentioned separately. 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 management or risk mitigation measures. The aim is to objectively bring to light and critically discuss the benefits and risks described.

The goal of the benefit-risk evaluation is to draw an overall conclusion on the benefit-risk balance, recognising that zero risk does not exist and considering potential risk mitigation measures. The conclusion should explain explicitly why the benefit-risk evaluation is considered as favourable or unfavourable explaining the reasoning leading to the conclusion. The outcome of this benefit-risk evaluation will be the basis of the scientific recommendations and the regulatory decisions.

1. Introduction

The evaluation of the benefit-risk[1] balance is fundamental to the decision to grant a marketing authorisation of any veterinary medicinal product as well as to any re-evaluation of the product throughout its life cycle e.g. when pharmacovigilance data are provided or at renewal.

Whilst benefit-risk considerations have long been part of the decisions on marketing authorisations, the revised legislation, Directive 2001/82/EC with the amendments under Directive 2004/28/EC and Directive 2009/9/EC (hereafter referred to as Directive 2001/82/EC) places an increased emphasis on the evaluation of the benefit-risk balance. According to the preamble of Directive 2001/82/EC (Recital 11) the basic requirement is: "*The concepts of harmfulness and therapeutic efficacy can be examined only in relation to one another and have only a relative significance, depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization must demonstrate that potential hazards are outweighed by the benefits due to efficacy. Failing such demonstration, the application must be rejected.* "

With Directive 2004/28/EC further provisions were introduced requiring specifically consideration of the benefit-risk balance for regulatory authorities as well as applicants and marketing authorisation holders throughout the whole life cycle of a product, summarised in Recital 16 of the preamble: "*The criteria of quality, safety and efficacy should enable the risk-benefit balance of all veterinary medicinal products to be assessed both when they are placed on the market and at any other time the competent authority deems this appropriate*". This means that an authorised product has, by definition, a positive benefit-risk balance and only when new information or knowledge emerges, a re-evaluation of the benefit-risk balance is indicated.

In Article 1 of Directive 2001/82/EC definitions of risks relating to the use of the product and of the benefit-risk balance are given.

> 19. Risks relating to use of the product:
> - any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health;
> - any risk of undesirable effects on the environment.
>
> 20. Risk/benefit balance:
> An evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks as defined above.

As no guidance previously existed on how and when to perform and present an evaluation of a benefit-risk balance, the CVMP agreed to develop a specific recommendation in order to improve the methodology for benefit-risk analyses and to provide a more systematic approach, hence improving the consistency and transparency of decisions taken at CVMP level and also provide guidance to CMD(v) and Member States. The use of a structured, written benefit-risk evaluation is expected to create more transparency and harmonisation of the regulatory decisions for the benefit of marketing authorisation holders, the regulatory system and the public.

[1] The terms benefit-risk and risk-benefit are synonymous. Benefit-risk is used throughout out this document, and in similar documents relating to assessment of human medicines, to denote that the benefits must be considered to outweigh the risk in order for a product to be authorised.

2. Scope

This recommendation document is addressed to those responsible for benefit-risk evaluation, which includes regulators and applicants or marketing authorisation holders.

The benefit-risk analysis of a veterinary medicinal product is based on the intended use and the indications of that product in respect to its overall safety. The benefit-risk principle defined by the legislation takes into account issues relating to availability e.g. minor use/minor species (MUMS). The overall benefits and the general risks due to the use of that product have to be taken into account. The goal of this analysis is to draw an overall conclusion on the benefit-risk balance, recognising that zero risk does not exist and considering potential risk mitigation measures. The outcome of this benefit-risk analysis will be the basis of the scientific recommendations and the regulatory decisions.

Applicants or marketing authorisation holders are encouraged to prepare a benefit-risk evaluation for all procedures, however, at this point in time these are not considered obligatory, except in the case of periodic safety update reports (PSURs). This recommendation is not intended to add new requirements for marketing authorisation holders and no retrospective benefit-risk evaluation is foreseen for authorised products. It is not intended to require any redrafting of any existing benefit-risk assessment report or the creation of a report where one does not yet exist, as a result of the publication of this recommendation. However, when a product is renewed, has a pharmacovigilance issue, or the dossier is opened due to e.g. an extension, then an updated or new benefit-risk evaluation may be recommended.

Products on the market may be subject to a change in the benefit-risk balance due to variation, extension or new pharmacovigilance data. This is addressed in this recommendation.

The principles of the recommendation are intended to apply to all types of veterinary medicinal products (including pharmaceutical, immunological and homeopathic products) and for all marketing authorisation procedures (centralised, decentralised, mutual recognition and national). The recommendation does not apply to applications for maximum residue limits.

For a summary of the legal basis, data requirements and basis of the benefit-risk evaluation refer to Annex III.

3. Who should perform a benefit-risk evaluation

The recommendation is intended to be a basis for the elaboration of the application and assessment documents that include a section on the evaluation of the benefit-risk balance.

For competent authorities those who should perform a benefit-risk evaluation include personnel preparing assessment reports such as: Rapporteurs' assessment reports, CVMP assessment reports, European Public Assessment Reports (EPARs), assessment reports by Member States, Public Assessment Reports (PuARs), assessments of PSURs, annual reports, renewal assessments and referral assessments.

For applicants or marketing authorisation holders, it is expected that relevant experts will prepare the benefit-risk evaluation.

4. When to perform a benefit-risk evaluation

4.1 New applications

Regulators should make a benefit-risk evaluation for all new applications. In fact, when a competent authority evaluates an application for a veterinary medicinal product, it must always weigh the benefits against the risks before taking the decision to authorise the product.

For applicants or marketing authorisation holders, the writing of a formal benefit-risk evaluation is a matter of choice, but may provide valuable summarised information to the competent authorities.

4.2 Post-authorisation benefit-risk evaluation

During its life cycle, any authorised product is subject to an updated benefit-risk evaluation at different time points e.g. for pharmacovigilance purposes or when the marketing authorisation holder applies for a variation to the marketing authorisation, or in case of a referral.

Regulators should make a benefit-risk evaluation for all PSURs. In addition, a benefit-risk evaluation may be indicated where new benefits or risks have been identified in variations, extensions, renewals, referrals and when important new information emerges from pharmacovigilance or other data (e.g. significant increase in antimicrobial resistance or data which calls into question the validity of the withdrawal period).

For applicants or marketing authorisation holders a benefit-risk evaluation is obligatory for PSURs. In addition, where new pharmacovigilance or other data impacts on the benefit-risk balance of the product a new benefit-risk evaluation may be required. For products authorised before this recommendation document comes into effect, such activities may be the trigger for the first written benefit-risk evaluation. In that case, the applicant or marketing authorisation holder may elect to include a benefit-risk evaluation that comprises more than the actual update in order to explain the case more clearly. It may also be useful in particular where the applicant or marketing authorisation holder wishes to support or defend an application in clearer terms than just by submitting data.

Furthermore, as Article 27(3) of Directive 2001/82/EC (respectively Article 41 (4) of Regulation 726/2004) requires regular updating of the marketing authorisation dossier by obliging the applicant or marketing authorisation holder to submit new data that is pertinent to the benefit-risk evaluation, further assessment may be required at that time also.

Pharmacovigilance

It is recognised that at the time of first granting of the authorisation, information on the safety of a veterinary medicinal product is still relatively limited as it is restricted to the data available in the marketing authorisation application, therefore not all potential risks may have been identified. In the post-authorisation phase the review of the benefit-risk balance of an existing product may be triggered by several means.

A risk management plan may be put in place to complement pharmacovigilance procedures for detecting safety signals, if considered appropriate for specific products. Such a plan would be needed in situations where risks are identified that cannot be managed through routine pharmacovigilance. If it becomes apparent from the submitted safety information that the risk profile has changed unfavourably, an updated benefit-risk evaluation must be made, discussing the new or increased risk and the management options. Should new risk management measures or regulatory actions become necessary as a result of the evaluation conducted, an appropriate risk communication strategy must be initiated, as laid down in the relevant legal provisions.

Variations and extensions

For all extensions and for those variations where new risks and/or new benefits are identified a benefit-risk evaluation would be needed for the competent authorities or the CVMP to be able to accept or reject the extension or variation. There could also be situations when the new data provided have an impact on the overall benefit-risk profile for the global product. This would be the case if a new risk is identified during the variation or extension procedure where this risk is present independently of the new variation or extension. However, in most cases the benefit-risk evaluation for extensions and variations should be restricted to the scope of the variation or extension application and the associated data supplied.

Annual reports

For centrally authorised products, an annual report is produced by CVMP. This assessment is mainly a review of the benefit-risk balance according to potential new elements and taking into account the adverse events that have been reported. This annual report should refer to the last benefit-risk evaluation and consider if the benefit-risk balance remains unchanged or if any measure is to be taken. There is no requirement for the marketing authorisation holder to provide any benefit-risk evaluation in relation to the annual report.

Renewals

Article 28 (2) of Directive 2001/82/EC, respectively Article 39 (2) of Regulation 726/2004, indicates clearly that the authorisation may be renewed after five years on the basis of a re-evaluation of the benefit-risk balance by the competent authority. Generally only one renewal is required in the legislation unless there is a particular need. The marketing authorisation holder is recommended to provide a benefit-risk evaluation prepared in line with this recommendation and the Notice to Applicants Volume 6C. The re-evaluation should comprise the experience with the product since the time of authorisation or the previous renewal, and should take into account pharmacovigilance data and particularly the overview of all new information in the summary bridging report and PSUR/addendum report, as applicable.

For products authorised under exceptional circumstances subject to a yearly review, specific conditions are expected to apply.

Referrals

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 ('mutual recognition and decentralised referral'), the CVMP first evaluates whether the risk that forms the basis of the referral meets the definition of 'potential serious risk'[2]. If the 'potential serious risk' fulfils these criteria, the benefit-risk balance is further re-evaluated in accordance with Volume 6A Chapter 3 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 may conduct a re-evaluation of the benefit-risk balance of all of the products concerned in accordance with Volume 6A Chapter 3 of the Notice to Applicants. In all cases, benefit-risk evaluations should focus on issues that may change the benefit-risk balance or make risk mitigation measures necessary and should take into account any previous benefit-risk evaluations that may have been made.

[2] As defined in the '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' (Official Journal C 132, 7/6/2006 p. 32 - 35)

5. How to perform a benefit-risk evaluation

5.1 New marketing authorisations

Directive 2001/82/EC establishes the regulatory options for approval of a veterinary medicinal product (standard authorisation or authorisation under exceptional circumstances) and the provision of different data requirements according to the legal basis of the application (e.g. full application, generic, combination) and the nature of the product (pharmaceutical, immunological, homeopathic). Taken together, these elements provide the basis for different benefit-risk evaluation approaches.

Data requirements according to the legal basis of the product

Article 12 (3) of Directive 2001/82/EC describes the content of a standard dossier to be provided in order to obtain a marketing authorisation. Articles 13, 13a-d of Directive 2001/82/EC provide for various derogations from the standard data requirements. These specific dossier requirements for different categories of product imply tailored benefit-risk evaluation approaches. For a summary of the legal basis, data requirements and basis for the benefit-risk evaluation refer to Annex III.

Products presented according to Article 12 of Directive 2001/82/EC should benefit from a standard benefit-risk evaluation. This is also the case for well-established use products (Article 13a (1) of Directive 2001/82/EC), where the content of the dossier is based on bibliography. The same applies to combination products (Article 13b of Directive 2001/82/EC) even though it is not necessary to provide scientific references relating to each individual active substance.

For generics (Article 13 of Directive 2001/82/EC), bioequivalence with the reference product will be the keystone of the benefit-risk evaluation. The benefits and risks for the generic should generally be considered as being similar to the reference product. However, in exceptional cases there may be differences between the reference and generic products which may lead to a partial re-assessment of the benefit-risk balance. This could for example be new excipients, as there would be a new toxicity package.

For hybrid applications, it is clear that the new studies provided (Article 13a (3) of Directive 2001/82/EC) should lead to a re-evaluation of the benefits and risks and consequently the benefit-risk balance.

For informed-consent applications (Article 13c of Directive 2001/82/EC), as far as they are strictly identical to the reference product, the benefit-risk evaluation of the reference product would be applicable and no re-evaluation of the benefit-risk balance is required.

Article 26 (3) of Directive 2001/82/EC, respectively Article 39 (7) of Regulation 726/2004, indicates that in exceptional circumstances, the authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the veterinary medicinal product. Such authorisations may be granted only for objective, verifiable reasons. Continuation of the authorisation is linked to the annual re-assessment of these conditions.

For a marketing authorisation granted in exceptional circumstances, the benefit-risk evaluation should take into account that the marketing authorisation may be subject to specific management measures. Preferably, specific guidance should be established in advance in order to advise the applicant on the data needed to apply for this type of procedure and this guidance would form part of the benefit-risk evaluation principles.

The CVMP has applied these provisions in the past to certain categories of products particularly when specific veterinary medicinal products were not available on the market. For example, this approach has been followed for Avian Influenza vaccines in order to facilitate the availability of these immunological products. The main reason for this approach was the absence of authorised vaccines needed in case of a possible outbreak. A specific guideline on data requirements for this type of product has been issued.

For veterinary medicinal products for limited minor markets/MUMS certain specific guidelines on data requirements are available. These products will normally be authorised by the standard

authorisation procedure or, in particular cases, they may be authorised under exceptional circumstances.

Data requirements according to the nature of the product
The data requirements listed in Article 12 are detailed in Annex I of Directive 2001/82/EC according to the nature of the products (pharmaceutical, immunological or homeopathic).

However, Directive 2001/82/EC provides for certain derogations that lead to different approaches for the benefit-risk evaluation.

For immunological veterinary medicinal products (Article 13d of Directive 2001/82/EC), in exceptional circumstances, the results of certain field trials do not need to be provided if these trials cannot be carried out for duly substantiated reasons, in particular on account of other Community provisions. Clearly, the benefit-risk assessment must be tailored to take account of this situation.

The registration of homeopathics is also regulated by specific provisions that have an impact on the approach for the benefit-risk evaluation. For homeopathics, following a standard registration procedure, a Member State may introduce or retain on its territory specific rules for the safety tests, pre-clinical and clinical trials for those products intended for companion animal species and non-food-producing exotic animal species. The proof of the therapeutic effect is not required to be provided for homeopathics that follow a simplified registration procedure (Article 17 (2) of Directive 2001/82/EC). In this case, the benefit-risk evaluation would be limited to a risk assessment.

5.2 Post-authorisation changes

The benefit-risk balance of a veterinary medicinal product may be re-evaluated at any time of the product's life cycle, if occurrence of suspected adverse events makes it necessary. This should concentrate on the new information that has become available, including published post-marketing clinical studies that contain pharmacovigilance information or confirmation of efficacy, and in particular whether this information has an impact on the marketing authorisation.

5.3 Benefit-risk evaluation principles and methodology

The basic principles of the benefit-risk evaluation are defined by Directive 2001/82/EC and in its Annexes and apply not only to national, MRP, DCP, but also to centralised products (c.f. Recital 14 of Regulation 726/2004). These principles are complemented by various guidelines on data requirements and assessment of the dossier published by EMEA and the European Commission. For definitions regarding benefit-risk evaluation refer to Annex I.

A veterinary medicinal product should be authorised if it meets the requirements of Directive 2001/82/EC in terms of quality, safety and efficacy and the benefit-risk balance is positive.

Quantitative versus qualitative benefit-risk evaluation

The benefit-risk evaluation in the context of a new medicinal product application takes into account the conclusions of the different parts of the dossier submitted.

A recent review of the existing models for benefit-risk assessment has been done for medicinal products for human use. It appears that currently no solely quantitative methodology is available; semi-quantitative methods exist but are considered to be of limited value for veterinary medicinal products. For veterinary medicinal products the problem is even more complex compared to human medicinal products due to the nature of the various risks that should be taken into account (e.g. animal safety, consumer safety, user safety, environmental safety, antimicrobial resistance, dissemination and reversion to virulence for vaccines). Each general risk should also be assessed according to different exposure scenarios and should address different protection goals. Therefore, the benefit-risk evaluation will rely mainly on a qualitative approach.

Expert judgement remains the cornerstone of benefit-risk evaluation for the authorisation of veterinary medicinal products.

Benefit-risk evaluation

The benefit-risk evaluation for an individual veterinary medicinal product should be based on the established benefit-risk assessment principles. It should describe factually the observed effects and uncertainties in terms of important benefits and risks as well as describe their impact. A structured approach 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 characteristic of the product.
- The benefit-risk evaluation approach that is to be followed should be clearly stated (see 5.1).
- The direct therapeutic benefits of the product should be clearly described for each target species and each claim. Additional or indirect benefits should be identified separately. Some indication of the extent and importance of each benefit should be stated e.g. lifespan was increased by one year; this is the key benefit for this product.
- The risk assessments should be performed for all relevant risks. Some indication of the extent of each risk should be stated e.g. "adverse reactions related to treatment occurred in 25% of treated animals; this is a major factor...". For each risk, risk management options should be considered and the potential residual risk discussed.
- The benefit-risk balance should then be established taking 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 conclusion should explain why the benefit-risk evaluation is considered as favourable or unfavourable.

Principles of the evaluation of the overall benefit-risk balance

The evaluation of the benefit-risk balance is a complex process as it includes not only a single risk and a single benefit but multiple benefits and risks as well as taking into account risk management options.

A balance between the benefits and the risks for the animal can often be done directly, e.g.
- Demonstration of the efficacy (e.g. reduction of clinical signs) is based on pharmacology and on efficacy studies which include generally dose determination, dose confirmation and field trials.
- Adverse effects to the animal are also documented in particular in safety, tolerance and field studies.

A direct comparison can be performed between efficacy and tolerance; this could include considerations on the different doses used in the efficacy trials in terms of efficacy and safety for the animal. The level of risk that is considered acceptable may vary, depending on the nature of the disease to be treated, prevented or diagnosed e.g. treatment or prevention associated with severe adverse events may still be acceptable if the disease is also very severe.

When considering the other risks (including consumer safety, user safety, environmental safety, antimicrobial resistance development) the balance between benefits and risks cannot be assessed directly. These different risks should be considered individually and a conclusion should be reached whether or not these risks are acceptable, taking into account possible risk management measures.

If insufficient data are presented to assess risks that are potentially serious, or if risks are considered unacceptable even after taking into account the risk mitigation measures, precautions and contra-indications, the overall benefit-risk balance will be considered as unfavourable and the product will not be authorised. However, where there are only minor deficiencies in the data and an acceptable level of efficacy is shown, the benefit-risk balance may still be considered positive subject to satisfactory completion of post-authorisation commitments agreed in advance with the applicant or marketing authorisation holder. In defined circumstances a positive outcome to the benefit-risk evaluation may be linked to authorisation of a product under exceptional circumstances or may be subject to the satisfactory completion of a risk management plan. Separate guidance exists on the

criteria to be applied by the CVMP and regulators when deciding if either of these options should apply.

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. 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 European Pharmacopoeia monographs usually dictate minimum requirements for efficacy.

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.

5.4 Benefit assessment

The definition of the benefit-risk balance, given by Directive 2001/82/EC as mentioned before, relates to the positive therapeutic effects. In Recital 11 of Directive 2001/82/EC there is a specific reference to benefits due to efficacy.

It is important to distinguish between direct benefits and indirect or additional benefits. As mentioned earlier, certain benefits may already be identified early in the process. This is the case for example for the authorisations under exceptional circumstances where particular benefits are expected but cannot be fully demonstrated at the time of submission of the application. 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 of the benefit-risk balance.

Direct therapeutic benefits

Veterinary medicinal products are defined in Directive 2001/82/EC 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, or to making a medical diagnosis. When considering the benefits of the use of such products, those taken into account in the benefit-risk evaluation are the direct benefits that are linked to the intended use of a product. These are generally therapeutic, zootechnical or diagnostic benefits.

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

- Direct therapeutic benefits such as disease prevention, clinical or subclinical disease treatment,
- Improvement of the clinical condition,
- Better quality of life,
- Improvement of the physiological status of the animal,
- Increase of survival rate or life expectancy,
- Reduction of the risks of transmission of a disease to other animals,
- Offering a diagnostic tool,
- Control of an enzootic zoonotic disease, reduction of the risk of transmission to man,
- Appropriate alteration of physiology or disease status to derive a desired zootechnical benefit e.g. oestrus synchronisation, elimination or reduction of a specific microorganism.

Additional benefits

Additional benefits are benefits not directly linked to the claim of the product. These can be general benefits for the veterinarian, the farmer, the user, or relate to particular properties of the product such as ease of administration (palatability, long lasting effect) resulting in improved compliance. These benefits are important but might not be easily assessed in the majority of cases and may be very subjective.

These benefits should be reported separately, but would generally only be considered central to the overall assessment of the benefit-risk balance where the direct benefits are adequately established first i.e. the product must have shown a positive benefit-risk balance based on the direct therapeutic benefits before additional benefits (e.g. palatability or unmet medical need) would be taken into account.

Some benefits will not be taken into account as they are considered out of the scope of the evaluation process, for example, comparative cost-effectiveness of a veterinary medicinal product.

5.5 Risk assessment

Risks relating to use of the product are defined in Directive 2001/82/EC as any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health and any risk of undesirable effects on the environment. 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, efficacy, antimicrobial resistance development) in line with the existing guidelines. A guideline for assessors on how to prepare an assessment report exists.

For the quality part, the risk assessment should consider whether the product is of appropriate quality and that conclusions made on safety and efficacy remain valid throughout the life cycle of the product. The hazards that may be assessed include, for example, degradation products or non-compatibility with other products, which may have consequences in terms of safety or efficacy.

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

In the case of consumer safety, the risk assessment has largely already been considered by the establishment of maximum residues limits (MRLs). In the marketing authorisation procedure, the assessment is limited to the establishment of the withdrawal period.

In general, lack of efficacy should not be considered as an inherent risk as it is assessed already in the benefit analysis, except in specific situations e.g. zoonotic risk, lack of efficacy in certain categories of animals, farming conditions etc. During efficacy trials, secondary effects including adverse events in the target species may be reported which may contribute to the risk assessment for the target animals.

Each relevant risk should be assessed taking into account all the elements present in the different parts of the dossier.

Main risks:
- For the target animals
- For the user
- For the environment
- For the consumer of an animal derived foodstuff

Specific risks, according to the nature of the product (examples):
- Antimicrobial resistance development
- Unintended spread of the vaccine strain
- Reversion to virulence

5.6 Risk management or mitigation measures

For each relevant risk an assessment should be provided which should be accompanied, if appropriate, by proposals for risk management or risk mitigation measures. The Summary of Product Characteristics (SPC) and the product literature 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. When risk management/risk mitigation measures are proposed, care should be taken to ensure that they are practicable. In appropriate cases, and in line with guidance currently under development by the EMEA, reference can be made to a specific risk management plan where such a plan is proposed by the applicant or required by the competent authority.

5.7 Evaluation of the overall benefit-risk balance

After the analysis of benefits and risks a clear discussion and conclusion should be drafted. The evaluation of the benefit-risk balance should follow the benefit-risk evaluation principles (see 5.3). It should not be the intention of this section to detail again every benefit and risk. The aim is to discuss the benefits and risks and to explain the reasoning leading to the conclusion. If applicable, additional or indirect benefits should be mentioned at this stage. Particular attention should be paid to the applicability of the risk mitigation and risk management measures proposed. When the marketing authorisation is recommended under exceptional circumstances the specific condition for authorisation should be stated.

The authorisation should be granted when the benefits of the product have been sufficiently substantiated and when the risks are considered as acceptable, taking into account the proposed management measures to mitigate the risk. See Annex IV for an example structure and sentences that may be included in a benefit-risk evaluation by regulators and which may also be useful for benefit-risk evaluations made by applicants or marketing authorisation holders.

6. Where to include the benefit-risk evaluation

6.1 Presentation of the benefit-risk evaluation in applications and PSURs

When applicable, the benefit-risk evaluation should be presented in the marketing authorisation application in Part 1 of the dossier after the detailed and critical summaries (Part 1C) on quality, safety and efficacy.

The applicant's benefit-risk evaluation should draw on the conclusions of the preceding detailed and critical summaries for each of the relevant disciplines. The benefit-risk evaluation should be a concise summary and preferably no more than two to four pages.

For post-authorisation applications requiring an update to the benefit-risk evaluation the same location would apply i.e. in Part 1C of the dossier. For PSURs, the benefit-risk evaluation should be presented

as part of the overall safety evaluation, as described in Volume 9 of The Rules Governing Medicinal Products in the European Union.

6.2 Presentation of the benefit-risk evaluation in the assessment report

The assessment report and Public Assessment Reports currently include a scientific overview. The benefit-risk evaluation should form part of this scientific overview and should be regularly updated during the various milestones of assessment to reflect the status of the benefit-risk evaluation at that point in time. When updates of the benefit-risk evaluation are required after the marketing authorisation has been granted, it could be included in the scientific overview or as a separate addendum.

7. Future steps

The evaluation of the benefit-risk balance is a complex process that is fundamental to the decision to grant a marketing authorisation of any veterinary medicinal product as well as of any re-evaluation of the product during its life cycle. The CVMP has developed this recommendation with the aim of improving the methodology for benefit-risk analyses and facilitating a more systematic approach, hence improving the consistency and transparency of decisions taken. This recommendation reflects the status of the current thinking of the CVMP on the matter and takes into account comments received from interested parties during the public consultation. It is envisaged that the CVMP will review the recommendation within a few years in light of experience gained.

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12. European Pharmacopoeia: http://www.pheur.org.

[3] OJ L 311, 28.11.2001, p. 1-66.

[4] Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82 on the Community code relating to veterinary medicinal products; OJ L 136, 30.4.2004, p. 58-84.

[5] Commission Directive 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to veterinary medicinal products; OJ L 44, 14.2.2009, p. 10-61.

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Annex I: Principles and definitions for benefit-risk analysis for veterinary medicinal products

Introduction

A number of risk analysis principles used by international bodies (Codex Alimentarius, OIE, IPCS) have been taken into account and adapted by CVMP in developing the benefit-risk analysis methodology.

Benefit: Veterinary medicinal products are defined in Directive 2001/82/EC 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 either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis. The direct benefits are, therefore, the positive or intended effects triggered by the use of the product and linked to the therapeutic potential or zootechnical properties in a broad sense and to the claim of the product. Indirect benefits are additional benefits, which cannot be directly linked to the claim of the product.

Summary and definitions of risk analysis principles

The risk analysis principles and definitions given in this recommendation are based on definitions agreed by Codex Alimentarius and those agreed by the WHO International Programme on Chemical Safety (IPCS) and OIE and have been adapted accordingly .

Risk analysis: A process consisting of three components: risk assessment, risk management and risk communication. These steps follow each other.

Risk assessment: A process intended to calculate or estimate the risk to target animals, users, consumers of animal derived food and to the environment, including attendant uncertainties, following exposure to a particular agent.

Risk assessment is a science-based process consisting of the following four steps:

(i) Hazard identification,
(ii) Hazard characterisation,
(iii) Exposure assessment,
(iv) Risk characterisation.

The following definitions apply:

Hazard: A biological, chemical or physical agent or situation having the potential to cause an adverse effect.

Hazard identification: The identification of biological, chemical, and physical agents or situations capable of causing adverse effects.

Hazard characterisation: The qualitative and/or quantitative evaluation of the type and nature of the inherent property of biological, chemical or physical agents or situations having the potential to cause adverse effects. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are available.

Exposure: The concentration or amount of biological, chemical, or physical agent that reaches target animals, users, consumers of animal derived food or the environment in a specific frequency for a defined duration.

Exposure assessment: The qualitative and/or quantitative evaluation of the likely concentration or amount of biological, chemical, or physical agents (and their derivatives) to which target animals, users, consumers of animal-derived food or the environment are exposed.

Risk: The probability of an adverse effect and the severity of that effect, consequential to (a) hazard(s).

Risk characterisation: The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse effects in target animals, users, consumers of animal derived food or on the environment based on hazard identification, hazard characterisation and exposure assessment. The assessment of the 'probability' or 'likelihood' of a hazard occurring is an essential part of 'risk assessment'.

Risk management: The process, distinct from risk assessment, of weighing policy alternatives, considering risk assessment and other factors relevant to ensure quality, safety (including environmental safety) and efficacy of the veterinary medicinal product. Risk management should include, if needed, risk mitigation measures.

Risk communication: The exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, including the explanation of risk assessment findings and the basis of risk management decisions.

Benefit-risk analysis definitions

Based on the processes and definition for risk analysis the processes for the benefit-risk analysis are defined by CVMP as follows:

Benefit-risk analysis: Benefit-risk analysis comprises three distinct but interdependent components: benefit-risk assessment, benefit-risk management and benefit-risk communication.

Benefit-risk assessment: 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.

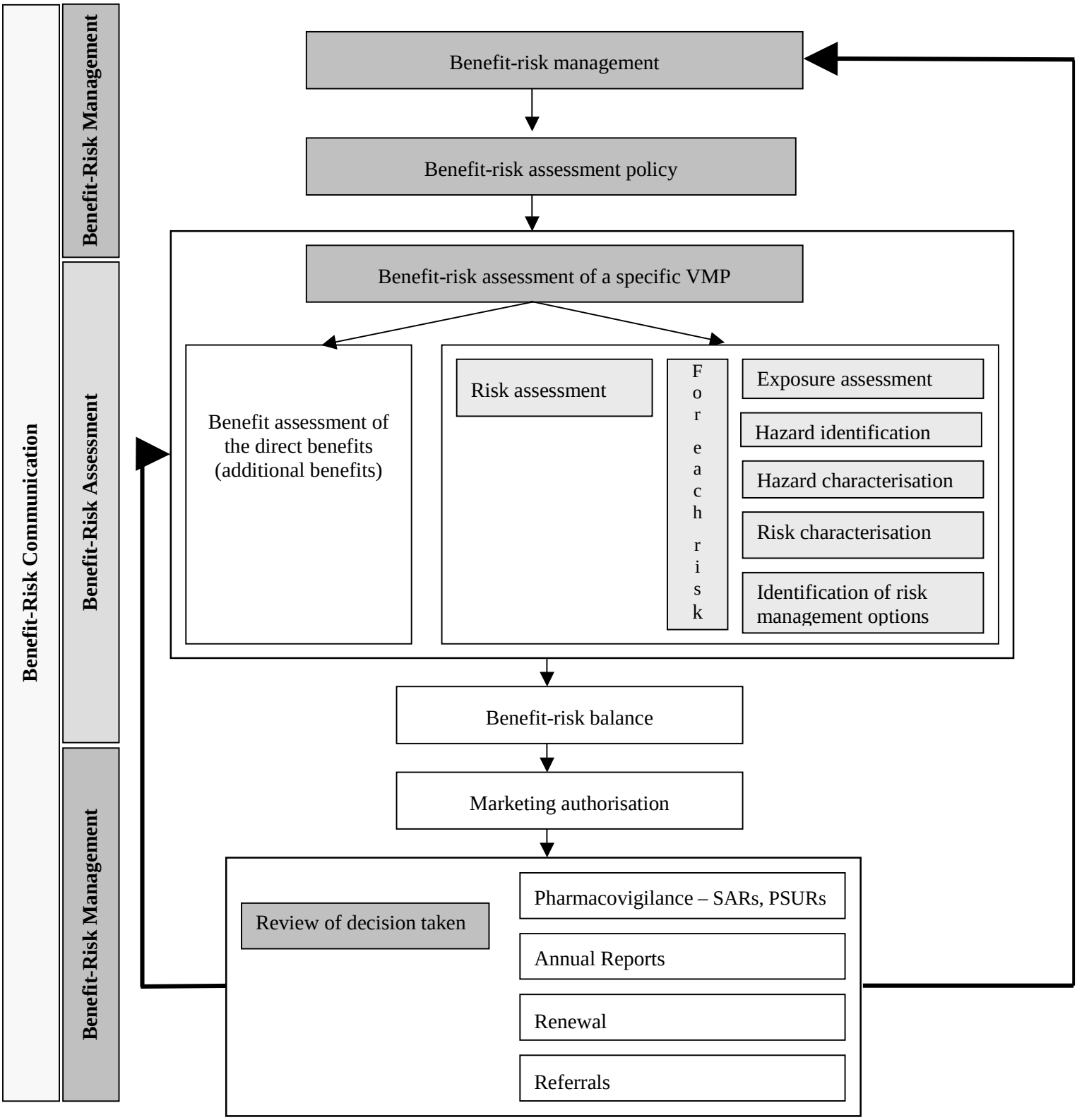
Benefit-risk management: Benefit-risk management is the process, distinct from benefit-risk assessment of weighing policy alternatives. It includes the establishment of a benefit-risk assessment policy, the evaluation of benefit-risk management options and the monitoring and review of decisions taken.

Benefit-risk communication: 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. This includes the exchange of information and opinions throughout the benefit-risk analysis process and the explanation of benefit-risk assessment findings and the basis of benefit-risk management decisions.

Benefit-risk balance: In Article 1 of Directive 2001/82/EC definitions of risks relating to the use of the product and of the benefit-risk balance are given.

> 19. *Risks relating to use of the product:*
> - any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health;
> - any risk of undesirable effects on the environment.
>
> 20. *Risk/benefit balance:*
> An evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks as defined above.

Benefit-risk assessment policy: Benefit-risk assessment policy is defined by the legislative and regulatory framework for the authorisation of veterinary medicinal products and in guidelines on data requirements and assessment of dossiers published by the EMEA and the European Commission. It is part of benefit-risk management and should be established in advance of the benefit-risk assessment.



Annex II: Figure 1 General scheme of benefit-risk analysis for a veterinary medicinal product (VMP)

This scheme is intended to summarise the text and intended to give a clearer picture of the benefit-risk (B/R) analysis process. This is very similar to other schemes that are used in the risk analysis framework in international bodies. On the left, the aim is to highlight that risk communication is important throughout the whole process; B/R management comes before and after the B/R assessment phase. The first B/R management phase deals with the establishment of the B/R policy, this means that the 'rules' should be defined first. Then, when a specific dossier is assessed, the B/R assessment phase would comprise the different steps as indicated in the recommendation. The identification of risk management options and the evaluation of the B/R balance are the last steps of the B/R assessment phase. This is followed by the opinion and the marketing authorisation decision making process which is part of B/R management. At the end, the decision(s) taken (B/R management) are reviewed, which may involve some revision of the assessment of the B/R balance (a new B/R assessment), for example in the case of new adverse events.

Annex III: Table 1 Summary of the benefit-risk evaluation approaches in relation to the basis for marketing authorisation applications

All the Articles (Art.) numbers referred to are those from Directive 2001/82/EC.

Type of the application	Legal basis	Basis for benefit-risk evaluation in the dossier	
		MA dossier specifics	**Consequence for benefit-risk evaluation**[7]
• **Standard authorisation**			
Pharmaceuticals (incl. combination where at least one active is new)	Art. 12	Standard data requirements as per Art. 12.3	Standard
Immunological VMPs	Art. 12	Standard data requirements as per Art. 12.3	Standard
Homeopathics following a standard authorisation	Art 19	Standard data requirements as per Art. 12.3 Special provisions possible depending of Member States	Standard or tailored depending on specific MS' rules
• **Abridged application**			
Generic product	Defined as in Art. 13.2(b)	Bioequivalence to reference product	Tailored benefit-risk evaluation
Well-established use	Art. 13a(1)	Bibliography	Standard
Hybrid	Art. 13a(3)	Bioequivalence + newly generated data as per Art. 12.3 for new species	Standard
Combination of known substances	Art. 13b	Standard data requirements as per Art. 12.3 for the combination	Standard
Informed consent	Art. 13c	None	Not required

[7] This column details whether the particular nature of the application impacts on the B/R assessment. The latter can be either standard for classical applications, tailored (i.e. can skip some items for instance) or not required

Type of the application	Legal basis	Basis for benefit-risk evaluation in the dossier	
		MA dossier specifics	**Consequence for benefit-risk evaluation**[7]
Similar Biological VMPs (not generic)	Art. 13.4	Supplementary data as per Annex I and relevant guidelines	Tailored benefit-risk evaluation
• **Other specific MA applications**			
Immunological products authorized under exceptional circumstances	Art. 13d	Exemption from certain data on a case-by-case basis or Art. 26 (3)	Specific benefit-risk evaluation based on specific circumstances
Minor market/MUMS	-	Standard data requirements as per Art. 12.3 amended by specific guidelines **and/or** exemption from certain data on a case-by-case basis as per Art. 13d or 26 (3)	Tailored benefit-risk evaluation based on relevant guidelines
Homeopathics following a simplified registration procedure	Art. 17.2	Proof of therapeutic effect not required	Risk assessment only

Annex IV: Example of structure and sentences that may be included in a benefit-risk evaluation

This example has been included to demonstrate that the benefit-risk evaluation should be a concise document summarising the key considerations for each individual product. The sentences suggested below are included as examples for benefit-risk evaluations conducted by competent authorities, although they may also be useful for applicants or marketing authorisation holders. The example presented here should not be considered as a check-list; neither should it prevent regulators or applicants or marketing authorisation holders from using another appropriate approach.

Introduction

- product name, active ingredients
- benefit-risk basis, i.e. new active component/ full application/ licensed under exceptional circumstances/ generic/…

Benefit assessment

Direct therapeutic benefits
<product> is a fixed combination/generic product/new treatment principle ….
The active substances are innovative/well-known/valuable supportive treatment
The mode of actions is…
<product> is of value in the treatment of <disease>, which causes….
The cure rate is… /therapeutic benefit for the animal … / the alteration of the physiological function…
Well-conducted controlled clinical trials demonstrated that the product is efficacious in …
Control of a zoonotic agent can be obtained…
Reliable diagnostic tool…

Lack of data relating to direct therapeutic benefits (efficacy) should be identified e.g.

- dose finding studies do not provide clear data.
- no data are provided for young or pregnant animals

Uncertainties related to direct therapeutic benefits should be addressed e.g.

- repeated treatment often necessary but not investigated.

Additional benefits
<product> is easy to apply by the owner …/increased compliance.
<product> has a long lasting effect…/ reduces the need for antimicrobial treatment…/ reduces the field contamination…
<product> increases the range of available treatment possibilities…/ provides a new treatment possibility for a minor species…

Risk assessment
(when a risk is identified, explain risk mitigation options (e.g. that appropriate text has been included in the SPC or the product has been contraindicated for …), and potential residual risk. The specific risk mitigation measures for a product may also be listed separately)

Main potential risks:

- for the target animal e.g.
  - adverse event - seriousness and frequency
- for the user
- for the environment
- for the consumer

Specific potential risks, according to product type and application:

- emergence of antimicrobial resistance
- unintended spread of vaccine strain
- reversion to virulence

- unknown issues related to the product e.g.
    - expected additional risks in old animals
- storage conditions or very short in-use shelf-life constitutes a problem in practical use

Any lack of data or uncertainty about the data related to a risk should be addressed under the discussion of the assessment of the specific risk, e.g.

- target animal safety studies do not provide clear data

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall. The product has been shown to be efficacious for the indication …
The formulation and manufacture of <product> is well-described and the specifications set will ensure that a product of consistent quality will be produced.
It is well-tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings has been included in the SPC. A sufficient withdrawal period has been set.

Conclusion

The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the original and complementary data presented, it is concluded that the quality, safety and efficacy of <product> were considered to be in accordance with the requirements of Directive 2001/82/EC.