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Guideline on user safety for pharmaceutical veterinary medicinal products

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Guideline on user safety for pharmaceutical veterinary medicinal products

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Executive summary

The guideline on user safety for pharmaceutical veterinary medicinal products (VMPs) provides guidance and advice on the procedure for user risk assessments. The guideline initially came into effect in 2005 and was revised in 2010. The guideline has been further revised to reference current legislation (i.e. Regulation (EU) 2019/6 and its Annex II), and to take into account updated definitions. Opportunities for the implementation of the 3Rs (replacement, reduction, refinement) and alternative testing approaches have also been included. This guideline has been updated to reflect the approaches common to all pharmaceutical veterinary medicinal products. Additional guidance on the use of uncertainty factors as they relate to the margin of exposure and consideration of the adequacy of risk mitigation measures has also been included.

1. Introduction (background)

Marketing authorisations for veterinary medicinal products in the European Union are granted in accordance with Regulation (EU) 2019/6. This legislation requires that applications for VMPs contain safety documentation. Annex II of Regulation (EU) 2019/6 states that *"the safety documentation shall be adequate for assessment of (b) the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example, during its administration to the animal."* Furthermore, it provides that, with regard to user safety *"This section shall include an assessment of the effects found in Part II.3A to II.3A4* (or Part IIIa.3a to IIIa.3A4) *and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures*."

The legislation does not provide specific guidance on data requirements and assessment methods to be used to identify the risks, or on the measures for risk reduction for users. This guideline presents guidance and advice on user safety and the conduct of user risk assessments.

2. Scope

The objective of this guideline is:

- to provide guidance and advice on user risk assessments.

While this guideline is primarily intended for pharmaceutical VMPs, it can also be applied to biologicals other than immunologicals. For applications for immunological VMPs, guidance can be found in the 'Guideline on user safety for immunological veterinary medicinal products' (EMA/CVMP/IWP/54533/2006 Rev.1).

The guideline applies to all Marketing Authorisation (MA) applications for pharmaceutical VMPs. This also includes applications to vary the MA where there is an impact on user safety.

Some types of post-authorisation changes warrant a reassessment of user safety, for example:

- Changes to the clinical use of the authorised products resulting in a significant increase in the handled dose, including the duration of use;
- The identification of new information impacting on the assessment of the risks of the VMP, such as new hazard data on the ingredients of a product including new excipients;
- A change of packaging material resulting in an increased potential for user exposure, especially taking into account the volumes that may be spilled and the child-resistant properties.

For a generic product, a full user risk assessment would not normally be expected, as the conclusion on user safety of the product and appropriate user safety warnings should reflect the user safety

evaluation undertaken for the reference product. However, in accordance with Annex II of Regulation (EU) 2019/6, section IV.1.2 (e), where there are aspects of the generic product that differ from the reference product (e.g. composition in excipients), then the impact of these differences on user safety should be addressed. For topical VMPs, for example, a difference (qualitative and quantitative) in excipients may result in different exposure of the pet owner due to a possible change in dermal absorption and/or the amount of VMP that is removed from the animal's fur when stroked. In that situation, the outcome of the risk assessment and subsequent risk mitigation measures may differ from that of the reference product. This might also be the case when salts, esters, ethers, isomers and mixtures of isomers, complexes or derivatives of the active substance of the reference VMP (i.e. differences in the active substance) significantly affect safety, as referred to in Art 18(2) of Regulation (EU) 2019/6. Also, where a difference in product packaging has been identified, the applicant must justify why the risk to users remains unchanged for the generic product or implement appropriate risk management measures (e.g., with respect to the need for a child-resistant closure).

The above is also applicable for hybrid products. In addition, in accordance with sections IV.2.2. and IV.2.5 of Annex II of Regulation (EU) 2019/6, depending on the hybrid product, new data may be required to support safety of the hybrid product.

In general, this guideline is not intended to be applied retrospectively (i.e. to products marketed prior to the adoption of this guideline). However, according to article 58(4) of Regulation (EU) 2019/6 on the responsibilities of the marketing authorisation holders, "*The marketing authorisation holder shall ensure that the summary of product characteristics, package leaflet and labelling is kept up to date with current scientific knowledge."*

For applications for Marketing Authorisation for topical products, the guideline should be used in conjunction with the 'Guideline on user safety of topically administered veterinary medicinal products' (EMA/CVMP/SWP/721059/2014).

For the assessment of user safety, the user is defined as any person that may come into contact with the VMP or its components before its application to the animal (e.g. during storage), during its application, and after its application (e.g. through contact with the treated animals).

The assessment of the user safety of a VMP should address the exposure situations resulting from the normal conditions of use and from foreseeable accidents (including accidental ingestion by children and accidental self-injection). It does not include exposure situations resulting from intentional misuse.

The guideline does not address occupational safety during the manufacture of veterinary medicinal products but covers the incorporation of premixes (VMPs) into feed. Although Regulation (EU) 2019/6 does not apply to medicated feed, the user safety requirements are relevant to both the VMP and the resulting medicated feed. Accordingly, this guideline may also be used to address the user safety aspects of the medicated feed.

3. Legal basis

Requirements for safety testing for a marketing authorisation application are laid down in Regulation (EU) 2019/6 of the European Parliament and of the Council.

This guideline concerns the application of the requirements of Annex II to Regulation (EU) 2019/6, mentioned in Part 3 of Sections II for VMP other than biological VMP, and IIIa for biological VMP other than immunological VMP, User safety shall *"…include an assessment of the effects found in Part II.3A to II.3.A4* (or Part IIIa.3a to IIIa.3A4) *and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures."* Moreover, "*User safety shall be addressed in accordance with CVMP guidelines."*

It should be noted that for an excipient used for the first time in a VMP or by a new route of administration, the same data requirements as for the active substance should apply (see II.3A (3) and IIIa.3A (3) of Regulation (EU) 2019/6).

All animal experiments should be conducted taking into account section I.1.7 of Annex II of Regulation (EU) 2019/6 and the 3Rs principles (replacement, reduction and refinement), notwithstanding the place of conduct of the experiments. Alternatives to *in vivo* test methods should be employed whenever possible.

4. Principles of the assessment

A risk analysis presented for the VMP for users handling and administering it, or who become exposed via contact with treated animals, should be provided and should address the following aspects:

- Hazard identification and characterisation. An appraisal of the inherent toxicity of the VMP and identification of the most relevant toxicological reference values (TRVs);
- Exposure assessment. An appraisal of how and when the user may be exposed to the VMP – identification of user groups, relevant exposure scenarios and estimation of the user exposure for each scenario;
- Risk characterisation. The assessment of the level of risk by establishing margins of exposure (MOEs) through comparison of the exposure levels with the toxicological reference values, and the assessment of local effects;
- Risk management and communication. The proposal of appropriate and practical risk mitigation measures, where relevant.

An appraisal of the inherent toxicity and any other harmful physico-chemical effects, such as flammability, dustiness and volatility of the active substance and the formulation, should be conducted. The hazards should be identified and characterised using appropriate data from toxicity tests or published literature regarding relevant endpoints for local and systemic toxicity, taking into account the route, duration, and frequency of anticipated exposure. The studies conducted should be relevant to the route of exposure, for example, if only dermal exposure is anticipated, no information regarding inhalation toxicity is deemed necessary.

An appraisal of the exposure of the user and any others who may come into contact with the VMP, should be conducted. All possible exposure scenarios should be considered; these should include route and level of exposure, frequency of use and amount used. The users, including all people possibly exposed to the VMP, should be identified.

The procedure for the risk characterisation consists of comparing the exposure levels to which the user is exposed or is likely to be exposed with those at which no adverse effects are expected to occur. When there is a potential risk for the user, appropriate measures for risk reduction should be proposed and evaluated.

5. User risk assessment

5.1. Hazard identification and characterisation

Generally, most of the toxicity data required to perform a hazard identification are already included in the Marketing Authorisation dossier (Part IIIA Safety Documentation). The overall assessment of the data allows a conclusion to be drawn on whether available data are sufficient for use in the risk assessment. The potential need for additional studies depends on the exposure and any identified data

gaps, and in some cases, the nature of the substances may indicate the need to focus on specific endpoints of toxicity or pharmacology. The purpose is to derive toxicological reference values (TRV) with respect to the identified exposure scenarios. If appropriate TRVs cannot be established for a particular route of exposure or by route-to-route extrapolation, new studies should be performed to generate route specific data. These new studies may be *in vivo* or based on scientifically valid alternative methods, however, a stepwise approach should be employed, with animal testing used only where absolutely necessary. The results of all provided studies should be assessed in order to identify the potential adverse health effects that can be caused by exposure to the substance(s) of concern. This applies to the active substance(s) as well as new excipients, and may also apply to other excipients which cause concern (e.g. an excipient which is known to be harmful).

5.1.1. Toxicity data on active substance(s)

The toxicity data presented in the dossier relating to the active substance may be derived from animal or non-animal toxicity studies or from published literature. These studies should ideally be designed and selected to investigate the effects of single doses and repeated doses, and to consider endpoints for effects on reproductive performance, fertility, developmental toxicity, genotoxicity and carcinogenicity. In line with the 3Rs, it is recommended to derive information on single dose toxicity from existing studies, e.g. from repeated dose or developmental toxicity studies. Depending on the type of product, special studies may have been conducted, for example to investigate inhalation toxicity, sensitisation potential, skin and eye irritation, or immunotoxicity or neurotoxicity.

Whenever possible, dose-response relationships should be identified in order to derive a TRV, i.e. the no observed adverse effect level (NOAEL), or, if this is not possible, the lowest observed adverse effect level (LOAEL). The use of the benchmark dose lower confidence limit (BMDL) is also acceptable as a point of departure. Using the BMDL as a point of departure has the advantage that it provides a quantitative dose-response assessment taking into account the variability of the data and the slope of the dose-response curve.

It is considered that the use of LD50 values as TRVs is not appropriate, as at this dose adverse effects already occur. Furthermore, LD50 studies generally provide only limited toxicological information and are therefore, not suitable for deriving NO(A)ELs.

Target animal safety studies should normally not be used for the derivation of TRVs as they are not designed for this purpose, but for observing adverse effects at the therapeutic dose (and overdoses) in the target animal. However, these studies may in exceptional cases contain the most sensitive endpoint and might then be employed for the derivation of TRVs. Similarly, pharmacovigilance data can provide additional information for a substance or product, though they cannot be used to define a NO(A)EL.

TRVs are established for all relevant toxicological endpoints (critical effects), and are specific to a substance, duration of exposure (acute, sub-chronic or chronic) and route of exposure (oral, dermal and inhalation). Pharmacological effects should also be considered, i.e. when the dose associated with pharmacological effect is below the toxicological TRV. The appropriate TRV for quantitative risk assessment is to be selected considering the route of user exposure, the duration of user exposure and the substance concerned. If more than one NOAEL is available for a given exposure scenario, the choice of the NOAEL to be used as the TRV should be fully justified.

In the context of a risk assessment, these TRVs should be compared to exposure levels of the substance(s) of concern that correspond to similar durations and routes of exposure. In the absence of a TRV for a specific route of exposure (e.g. dermal), the use of a TRV defined from an oral study should be considered using route-to-route extrapolation with appropriate adjustments to address

differences in bioavailability. Further information on route-to-route extrapolation can be found in the 'Guideline on user safety of topically administered veterinary medicinal products' (EMA/CVMP/SWP/721059/2014). Even if the TRV is based on the most sensitive critical effect, other effects may also be taken into consideration (e.g. reproductive or developmental effects) in order to focus the user safety risk assessment on specific scenarios or user groups. For instance, any possible adverse effect on the pregnant female and the development of the embryo and foetus, or on male and female fertility, should be assessed using an appropriate TRV.

In the case of developmental toxicity, Annex II to Regulation (EU) 2019/6 states that '*For the evaluation of user safety, standard developmental toxicity testing in accordance with standard tests based on established guidance (including VICH GL32 and OECD tests) shall be performed in all cases where significant user exposure may be expected.*' In this context, significant user exposure is considered to occur where systemic exposure to the substance is possible. Significant exposure is not expected to occur where it can be demonstrated that absorption following oral ingestion or from sites of local exposure (e.g. skin or eyes) will lead to negligible systemic exposure (e.g. substances that are not absorbed). In addition to the absorption properties of the substance, characteristics of the product formulation can result in negligible exposure (e.g. coated or non-divisible tablets, as it is expected that these forms leave minimal to no residues on the skin). Where standard developmental toxicity tests are not provided, based on a claim of negligible exposure, adequate justification and supporting data for the omission of such studies should be provided.

Where systemic exposure cannot be avoided following exposure to the veterinary medicinal product, significant exposure is assumed. In that case, the risk to the pregnant user should be assessed. In order to avoid unnecessary animal testing this should be done by employing first, all existing information on developmental toxicity in a weight of evidence approach that supports a quantitative risk assessment, i.e. allows for the derivation of a safe dose for the user. Such information can include, for example, studies from published literature, data derived from *in vitro* methods, observations in humans, etc. If no adequate conclusion on a safe dose or a mitigable risk for pregnant women can be drawn based on available information, standard developmental toxicity tests should be conducted.

If the active substance has been used in human medicines, then any available data, including company data as well as data in the published literature, relating to observations and adverse reactions in humans should be submitted in the dossier. If generated experimentally in humans, the applicant should confirm that the studies were conducted in accordance with recognised ethical standards[1]. Available human data can also be considered for the derivation of TRVs if these studies are relevant from a scientific point of view and can be employed for quantitative risk assessment. However, for any given substance, the accepted therapeutic dose used in human medicine does not imply an absence of risk and, therefore, is generally not acceptable as a TRV.

In the case of 'fixed combination products', containing two or more active substances, data on individual active substances should be considered as the basis. However, it may also be necessary to provide toxicological data for the combination if there are interactions between the active substances such as synergistic effects, in accordance with the EMA 'Guideline on pharmaceutical fixed combination products' (EMA/CVMP/83804/2005).

Studies reported in the scientific literature may be accepted if they contain a sufficient amount of data and sufficient details to allow an independent assessment by the competent authority (see also section II.3(2) of Regulation (EU) 2019/6). Information from EPMARs can be summarised; in that case there is

[1] If data are provided from studies conducted in humans it should be confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

no need to submit studies already evaluated as part of the MRL evaluation, only new studies should be provided.

5.1.2. Toxicity data on the formulation

The systemic effects are usually assessed only for the active substance(s). However, when there is a specific concern with regard to systemic effects due to the presence of one or more of the excipients in the VMP (e.g. an excipient which is known to be harmful), it may be necessary to assess the systemic toxicity of these excipients or of the formulated product.

For toxicity studies on local effects, Annex II to Regulation (EU) 2019/6 states that "*For products for which there may be exposure to skin and eyes, irritation and sensitisation studies shall be provided."* In the case of pharmaceutical VMPs (Section II.3A.4.1), "*those studies should be conducted with the final formulation*", whereas for biological VMPs other than immunological VMPs (Section III.3A.4.1), "*those studies should usually be conducted with the final formulation.*" New data should be generated using *in vitro* methods as described in current OECD test guidelines (see 5.1.3.), e.g. skin irritation/corrosion test methods in OECD Test Guidelines 430, 431, 435, 439; eye irritation/corrosion test methods in OECD Test Guidelines 437, 438, 460, 467, 491, 492, 492B, 494, 496; and skin sensitisation OECD Test Guidelines 442C, 442D, 442E, 497. However, many of these test methods have not been validated for mixtures. In that case, it would be acceptable to test the single substances of the VMP using these *in vitro* methods instead of the final product formulation. Nonetheless, full consideration should be given to possible interaction between active substances and/or excipients. Additionally, in the interest of reducing testing requirements in animals, if there are only historical data or published literature on the ingredients of the formulation, the potential effects of a VMP can be deduced from these data. If the test article is irritating to the skin, it is assumed that it is also irritating to the eyes.

5.1.3. Conduct of toxicity studies

If toxicity tests are conducted to address any identified gaps in the dataset, they should be carried out in accordance with VICH/OECD guidance and current methodology and, where advised, should follow a stepwise approach (e.g. studies to evaluate genotoxicity (VICH GL23)). Validated[2] or qualified[3] alternative test methods should be employed whenever possible. Information on opportunities for limiting animal use in current testing requirements is provided in the "Reflection paper on providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs" (EMA/CHMP/CVMP/3Rs/164002/2016). This document is updated regularly and the most recent version should be consulted for reference.

It is noted that for some endpoints, standardised test methods are currently not available, in particular for parenteral toxicity (e.g. from injectable VMPs) and respiratory sensitisation. However, for parenteral toxicity, target animal safety studies may provide relevant information on local and systemic effects following this route of exposure. Data on skin sensitisation may serve as a surrogate for respiratory sensitisation, in the absence of appropriate methods.

[2] Validated according to OECD guidance document 34 (https://www.oecd.org/en/publications/guidance-document-on-the-validation-and-international-acceptance-of-new-or-updated-test-methods-for-hazard-assessment_e1f1244b-en.html)
[3] Qualified according to EMA guideline EMA/CHMP/CVMP/JEG-3Rs/450091/2012 (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-principles-regulatory-acceptance-3rs-replacement-reduction-refinement-testing-approaches_en.pdf)

5.2. Exposure assessment

Exposure is the contact between an agent and a target, i.e. of a VMP with a user. Exposure assessment is the process that involves estimating the magnitude, frequency, and duration of exposure to a VMP for a specific substance, route of exposure and user.

The process includes:

- Precise identification of the product, defining the properties of the VMP (5.2.1)
- Exposure scenarios (5.2.2)
- Characterisation of the population exposed, including the type of user (5.2.3)
- Defining the routes of exposure (5.2.4)
- Defining the components of the product to which the user is exposed (5.2.5)
- Estimating the magnitude, duration and frequency of exposure (5.2.6)

The elements are further discussed below.

5.2.1. Precise identification of the product, defining the properties of the veterinary medicinal product

The first step in the exposure assessment is to consider the properties of the VMP. This should cover the following items:

- the pharmaceutical form
- relevant physico-chemical properties
- the presentation (quantity available to the user, packaging)
- the method of use, including the route of administration and any dosing equipment to be used

5.2.2. Exposure scenarios

The next step in the exposure assessment is to identify the exposure scenarios, starting with tasks and/or situations that may lead to exposure of humans. Different phases before, during and after administration of the product to the animal(s) should be considered.

Table 1 illustrates different tasks and situations that may be relevant for a VMP. It should be noted that these are examples only and that there are other situations that may be considered depending on the VMP.

Table 1. Some examples of tasks and situations that may lead to exposure

Pre-administration phase	Administration phase	Post-administration phase
Storage	Opening or accessing the product: e.g., taking product out of packaging Mixing and/or diluting of concentrates: e.g., mixing with feed & water Loading application apparatus or system: e.g., dosing gun	Cleaning equipment & preparation areas Disposal activities: e.g., disposal of packaging, equipment & surplus product Handling treated animals including stroking

	Administration to the animal(s): e.g., holding/restraining animal for treatment

For products containing particularly hazardous substances (e.g. DNA reactive/cytotoxic products), post-administration exposure to excreta (e.g. vomit, saliva) should also be considered (see the Guideline on dossier requirements for anticancer medicinal products for dogs and cats (EMA/CVMP/28510/2008) for further guidance).

Once the tasks and situations that lead to exposure are identified, the exposure for each task/situation should be further characterised. See the subsections below.

5.2.3. Characterisation of the population exposed, the type of user

It is important to clearly identify the different types of users of the product and to include all users that might come into contact with the VMP, some of whom may not necessarily be administering the VMP, but may be indirectly exposed to the VMP.

Some examples of people who are users are: a veterinarian, a veterinarian's assistant, a farmer, a bystander, a breeder, a pet-owner, a person living in the same building (e.g. child), a canine beautician or a sheep shearer. With regard to medicated premixes, the user of the VMP will be the individual incorporating the premix into a medicated feed or intermediate product. In addition, although Regulation (EU) 2019/6 does not apply to medicated feed, it is recommended that the exposure scenario for the end-user, i.e. the handler of the medicated feed, including young children who may have access to the medicated feed, be considered when assessing user safety.

When a VMP is kept in the home or in places where children may be present (e.g. horse stables), children should be identified as users.

5.2.4. Defining the routes of exposure

The routes of exposure should be specified for each exposure scenario. The routes of exposure will generally depend on the type of product, the pharmaceutical form, and the dosing equipment (if any). The routes to be considered are dermal, inhalation, ocular, and parenteral (accidental self-injection), with oral exposure often assessed.

Oral exposure should be considered for children. The inclusion of the warning "keep out of the sight and reach of children" on the label and package leaflet of products is a standard phrase for all VMPs, regardless of whether a risk is identified or not. However, the risks of oral ingestion should always be considered for products for which children have been identified as users (see section 5.3.2). If the toxicity data and subsequent risk characterisation suggest that there may be a concern after accidental ingestion, minimising exposure to children should be addressed. This might be achieved by inclusion of specific user safety warnings with respect to the storage of a VMP (e.g. storage of unused tablet parts in the blister or not to leave a filled syringe unattended), or by considering child-resistant packaging.

For adult users, oral exposure due to hand-to-mouth contact should be considered when dermal exposure is likely due to handling the product or from stroking a pet when there are residues on the fur. The non-respirable fraction of an inhalation exposure is also considered to be swallowed.

5.2.5. Defining the components of a product to which the user is exposed

Users can be exposed to:

- the whole product (e.g. a powder, a concentrate), including its active and inactive ingredients;
- certain components of the product (e.g. an active substance released from a collar);
- solutions or dilutions of a product (e.g. medicated drinking water; spray mists from dosing equipment).

For each exposure scenario, it should be specified to what (e.g. whole product, components, dilution) the user is exposed.

5.2.6. Estimating the magnitude, duration and frequency of exposure

Information on the magnitude, duration and frequency of exposure is needed in order to estimate the user exposure level to be used in the quantitative risk characterisation.

Although all situations that lead to exposure can be considered, it will not mean that each of these situations will occur every time the product is used. For example, "accidental self-injection" is an exposure situation, but there is a low probability that this event will actually happen when the product is used, i.e. it is a rare event and has a very low frequency. However, when applying a medicated shampoo to a dog, skin contact with the shampoo during application will occur almost every time it is used; dermal exposure is therefore considered to have a high frequency. Dermal and hand-to-mouth exposure from coated or non-divisible tablets is generally considered to be negligible.

The magnitude, duration and frequency of exposure determine the quantitative part of an exposure scenario.

The exposure level should be estimated by the applicant on the basis of experience with the product or comparable types of products, taking into account the use of the product by all users, and the pattern of use (single use or repeated (consecutive or interval) administration).

The magnitude of exposure is often determined by parameters like the dose or volume handled, concentration (e.g. in solutions or in air), release rate (e.g. from a collar or from a spray apparatus), vapour pressure, particle size, droplet size and spray pattern; from these data the external dose for a user is estimated.

To estimate the internal dose, the pharmacokinetic properties (in particular data on absorption and bioavailability) of the relevant compounds should be taken into account.

The estimation of the exposure levels may include measured data as well as model calculations. Any assumptions made in the exposure assessment should be clearly indicated and justification should be given, and the input data or default values used for the calculations should be documented.

When considering the exposure level per kg of bodyweight, a default bodyweight of 60 kg is used by CVMP for adults. For children, the default bodyweight is 12.5 kg, considered to represent a child aged 2 to <3 years old who is active in exploring their environment. This value is derived from a study in the Dutch population (considered to be representative for the European population) and corresponds to the 25th percentile of the Dutch population; 12.4 kg (RIVM report 090013003/2014), rounded up to 12.5 kg.

Examples of exposure parameters that can influence the magnitude of exposure, include surface areas of body parts, respiratory rates, size and volume of a room, dip tank volume, and ventilation rates of rooms.

Irrespective of the method used, the prediction of the exposure levels should describe a reasonably worst-case situation.

If more than one route of exposure is involved in a single situation (e.g. dermal and oral exposure due to hand-to-mouth contact), the total systemic exposure (sum of routes) should be calculated. In some cases, the same compound or product is to be used to treat an animal and its environment (e.g. a flea powder). When it is foreseeable that animal beddings, premises etc. will be treated as well, an assessment of aggregate exposure from both uses should be made. Similarly, if several animals are to be treated at the same time (e.g. a flock of sheep), the estimation of the exposure level should be made for multiple applications.

5.3. Risk characterisation

5.3.1. Qualitative risk characterisation

For a number of toxicological endpoints, the methods for testing provide qualitative results. This is in particular the case for certain local effects, for example, sensitisation or irritation. For these effects, no information on dose-response relationships will be available and, hence, thresholds remain unknown. Consequently, no quantitative risk assessment can be made for the anticipated exposure levels. Instead, only a hazard identification can be made.

Although a quantitative risk characterisation cannot be made for these endpoints, the risk may be qualitatively characterised, taking into account the likelihood that such an effect will occur on the basis of the concentration in the VMP and/or exposure information. Whenever possible, available information on the severity of an effect at the anticipated exposure levels should be taken into account as well. If such information is not available, it should be assumed that the effects will occur at any exposure level.

In addition, risks to the user related to the physico-chemical properties should be identified, such as pH and flammability.

An example to illustrate this procedure is given in Annex 1 (example 1).

5.3.2. Quantitative risk characterisation

The procedure for the quantitative risk assessment consists of comparing the exposure levels to which the user is exposed or is likely to be exposed with the exposure levels at which no adverse effects are expected to occur. This is generally done by comparing the estimated exposure to the relevant TRV, i.e. calculating the margin of exposure (MOE).

The duration of the study from which the TRV is derived should preferably reflect the duration of exposure of the user. The risk assessment of short-term exposure should be based on acute TRVs or, if not available, on sub-acute or sub-chronic TRVs, the latter representing, in general, a worst-case approach. In light of the 3Rs, specific acute studies should not be performed to derive an acute TRV. Instead, the acute TRV should be derived from acute effects observed in other study types, e.g. sub-chronic or developmental toxicity studies. For the risk assessment of long-term exposure, the use of a sub-chronic or chronic TRV can be considered acceptable, depending on the longest duration of user exposure, including exposure due to repeated treatment of the animal.

When comparing the estimated exposure to the relevant TRV, the following parameters should be considered:

- the intra- and interspecies variation[4];

[4] To account for uncertainty related to interspecies variation (i.e. extrapolation from animals to humans) a standard factor of x10 is used unless there is reliable data to deviate from this.

- the nature and severity of the effect;
- the human population to which the exposure information applies;
- the differences in exposure (route, duration, frequency);
- the dose-response relationship observed;
- the overall confidence in the available data.

These parameters are used to establish an uncertainty factor, which the MOE will then be compared to. It is generally recognised that the default uncertainty factor (UF) is 100, i.e. an MOE of 100 or higher would be considered acceptable. This value of 100 is the product of two factors of 10, one for interspecies extrapolation and the other for intraspecies (inter-individual) variability. The interspecies uncertainty factor is used for extrapolating the animal derived TRV to an average healthy individual, taking into account that humans may be more sensitive than laboratory animals. The intraspecies factor takes into account susceptible human subpopulations.

Where reliable data are available, there may be a case for accepting an MOE other than 100, e.g. if there is a case for accepting that the standard values for inter- and intraspecies variation do not apply. Similarly, the nature of the studies used to determine a TRV will also influence the uncertainty factor. For example, if the TRV is based on a NO(A)EL derived from a human study, then an MOE of 10 could be accepted as no interspecies extrapolation is required. Note that the accepted therapeutic dose used in human medicine does not imply an absence of risk and, therefore, it is generally not acceptable as a TRV.

The nature and severity of observed effects also influence risk assessments based on a NO(A)EL. The magnitude of the uncertainty factor can be increased for effects such as non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. Severe adverse effects such as these may require an additional factor of between 2 and 10 and may also be applied only to a specific human population, e.g. pregnant women. For example, the observation of teratogenic effects would warrant an additional uncertainty factor of 5 – 10. If the TRV is a lowest observed (adverse) effect level (LO(A)EL) then an additional factor of 2 - 5 would be required, depending on the dose-response relationship and/or the severity of effects observed.

While from a scientific point of view the exposure route of the study from which the TRV is derived should preferably reflect the route of exposure of the user, from a 3Rs point of view the use of existing data is encouraged. To this end, route-to-route extrapolation would need to be employed (see also the Guideline on user safety of topically administered VMPs for more detailed information on route-to-route extrapolation). Also, a difference in duration of the study may be a case for accepting an MOE either higher or lower than 100. With respect to the overall confidence in the available data, it should be noted that, in order to compensate for deficiencies in toxicity data, an additional factor may be required, increasing the acceptable MOE above the default factor of 100.

Where appropriate and justified, available toxicological limit values or exposure limit values (e.g. AOEL or other occupational limits, ARfD, ADI) may be used as alternatives to the MOE approach as described above. For some derived reference values (e.g. ADI and ARfD) the level of uncertainty has already been taken into account in its calculation. If sufficient uncertainty factors were applied and the same type of exposure is being assessed, exposure can be directly compared to this reference value. For

To account for uncertainty related to intraspecies variation (i.e. differences in human susceptibility) a standard factor of x10 is used unless there is reliable data to deviate from this.
When alternative factors are proposed, consideration must be given to the guidance document published by the IPCS/WHO (IPCS/WHO, 2005).

example, if the estimated oral exposure is less than the ADI, the risk for the user is considered to be acceptable.

With multiple factors influencing the magnitude of the acceptable MOE, adequate justification for each parameter should be provided. The acceptability of the MOE and, thus, the risk to the user will require expert judgement. In the case of a potential risk to the user, risk management options should be proposed and evaluated.

An example to illustrate this procedure is given in Annex 1 (example 2).

5.4. Risk management

Users

Some users will have more experience and knowledge of handling and administering VMP to animals than others, such as veterinarians or farmers, and this needs to be acknowledged in the assessment. Similarly, when considering other users who do not administer VMP on a frequent basis, such as pet owners, more detailed risk mitigation measures may be required in order to handle and administer the product safely.

Some users may have limited access to personal protective equipment (PPE) and, therefore, if required, there must be advice on what PPE is needed or the PPE has to be provided with the VMP.

In the case of users incorporating premixes into feed and users of the medicated feed, consideration should be given to the need for separate advice and warnings for the different types of users (e.g. PPE may be required when incorporating the premix, but not when administering the medicated feed).

Risk control options

In general, the following options for risk control may be used:

- restriction of the distribution, for example, as prescription-only medicine;
- specific warnings for groups at risk, for example, sensitised people, pregnant women, or where there are risks to fertility;
- restriction of application methods, for example, pour-on instead of spraying or the use of closed delivery systems;
- restriction of the field of use, for example, outdoor use only;
- modification of the formulation, for example, ready-to-use rather than a concentrate;
- modification of packaging, for example, reduced pack size or child-resistant packaging*;
- recommendation of measures for the protection of users, for example, general controls like ventilation of rooms, or use of PPE like protective gloves, masks or goggles. The appropriateness, i.e. the inherent efficiency, of these measures should be discussed. For example, the choice of materials should be justified (it is well known that certain substances are able to permeate or penetrate through certain materials, e.g. solvents through latex gloves).

*Note: Packaging can be claimed as child-resistant packaging only if it has been demonstrated to be child-resistant in accordance with the European Standard EN14375 for non-reclosable packaging or EN8317 for reclosable packaging.

The proposed risk control measures should be evaluated against the following criteria:

- the extent to which the exposure is reduced by a risk control measure, alone or in combination with other measures, must be large enough to reduce the risk to an acceptable level;
- the measure should be practicable, for example, PPE must be readily available to the user, and measures should not hamper the use of the product too much. It is considered unreasonable, for example, to expect a pet-owner to have access to personal protective equipment beyond normal household gloves. Therefore, in exceptional cases, it might be appropriate to provide adequate PPE with the VMP.

5.5. Risk communication

The warnings and safety measures are communicated via the SPC and package leaflet and should inform the user about the following aspects:

A. The concerned risk, i.e. the identified hazard

B. What exposure must be avoided to minimise the concerned risk

C. How to avoid that exposure

D. What to do in the event of exposure (if relevant)

The following illustrations explain this:

Example 1: A liquid product that is administered by the farmer using a spray gun to a flock of sheep, is irritant to the eyes. The warnings in the SPC and on the package leaflet would be:

- This veterinary medicinal product can cause eye irritation. (A)
- Avoid contact with the eyes including hand-to-eye contact. (B)
- Personal protective equipment consisting of protective glasses should be worn when handling the veterinary medicinal product. (C)
- Wash hands after use. (D)
- When the veterinary medicinal product comes into contact with the eyes, rinse immediately with plenty of water. In case irritation persists, seek medical advice immediately and show the package leaflet or the label to the physician. (D)

In the A-phrase it is recommended to specify the actual hazard, i.e. in this situation this VMP can cause eye irritation. Other examples could be 'This veterinary medicinal product can cause sedation.' or 'This veterinary medicinal product can cause neurotoxicity.', etc.

Example 2: An antibiotic tablet containing a penicillin, that is administered by the pet owner to dogs, and for which hypersensitivity reactions may be expected. The warnings in the SPC and on the package leaflet would be:

- <This veterinary medicinal product> <Penicillins and cephalosporins> may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious. (A)
- People with known hypersensitivity to penicillins or cephalosporins should avoid contact with the veterinary medicinal product. (B)
- Handle this veterinary medicinal product with great care to avoid exposure. (C)
- Wash hands after use. (D)

- If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention. (D)

The substance(s) that might cause hypersensitivity reactions should always be specified.

Example 3: An injectable that is administered by a professional user, and is assessed to be teratogenic, embryo- or foetotoxic. The warnings in the SPC and on the package leaflet would be:

- This veterinary medicinal product may be harmful to the unborn child. (A)
- Avoid contact with the skin and accidental self-injection. (B)
- Pregnant women, or women trying to conceive, should administer the veterinary medicinal product with serious caution to avoid accidental self-injection. (C)
- Personal protective equipment consisting of impervious gloves should be worn when handling the veterinary medicinal product. (C)
- In case of accidental skin exposure, wash hands/exposed skin thoroughly. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician. (D)

Note that different risk mitigation measures might be applicable for professional or non-professional users administering the same substance, depending on the formulation of the VMP, the risk characterisation, and also on the level of experience of the user.

The user safety warnings should be written and designed to be readable, clear and understandable, in terms that are comprehensible to the general public. The user safety warnings should be justified. User safety warnings should be written in full in the SPC and the package leaflet. In general, the label only contains the information '*Read the package leaflet before use'*.

For additional guidance on the presentation of user safety warnings in the product information, the reader is referred to the most recent version of the Quality Review of Documents veterinary product information template.

Two worked examples of User Risk Assessments (URAs) are presented in Annex I of this guideline to show a qualitative risk characterisation and a quantitative risk characterisation. Furthermore, a template for a URA is provided in Annex II.

Definitions

Acceptable daily intake (ADI)	The estimate of the amount of a substance, expressed in terms of micrograms or milligrams per kilogram of bodyweight, that can be ingested daily over a lifetime without posing any appreciable health risk.
Acute reference dose (ARfD)	An estimate of the exposure to a substance, expressed on a body weight basis, that can occur in a period of 24 hours or less without adverse effects or harm to the user. The route of exposure for which an ARfD applies should be specified.
Application phase	The preparation (i.e. opening or accessing the product, mixing and/or diluting of concentrates, loading application apparatus) and administration of the (prepared) veterinary medicinal product to the animal(s), including application by hand or any other dosing equipment. This phase can lead to exposure of the person administrating the product, as well as of other people who are present during the product administration.
Benchmark Dose	The Benchmark Dose (BMD) is a dose level, estimated from the fitted dose-response curve, associated with a specified change in response relative to the control group.
Exposure	Contact with a substance by oral, dermal, parenteral, ocular and/or inhalation routes. Exposure in the context of this guideline may be short-term (once or for a short time), or long-term (repeated exposure for a longer period).
Exposure assessment	The process that involves estimating the magnitude, frequency, and duration of exposure to a VMP for a specific substance, route of exposure and user.
Exposure route	The way an agent enters a human or animal after contact (e.g. by ingestion, inhalation, or dermal absorption).
Exposure scenario	A set of conditions that describe how users may accidentally come into contact with a veterinary medicinal product during each task/situation associated with its administration to target animals when the VMP is used as intended and/or when handling the treated animal.
Foreseeable accidents	The use of veterinary medicinal products that is not in line with the instructions for use or without the consideration of some or all common and specific technical, operational and personal protective measures (e.g. the over-dosing or inadequate dilution of a veterinary medicinal product, common spillage scenarios, use without or with non-proper PPE).
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. A dose-response assessment should be performed if possible.
Lowest-observed(adverse) effect-level (LO(A)EL)	The lowest administered dose in a study at which (adverse) effect(s) are observed.
Margin of exposure (MOE)	The ratio of the TRV to an estimated exposure level.
Non-respirable and respirable fractions	The non-respirable fraction of a substance refers to its airborne particles that are too large to penetrate deeply into the lungs. These particles are typically trapped in the upper respiratory tract, such as the nose, throat, and trachea, and do not reach the gas-exchange regions of the lungs. These inhalable particles can be up to 100 micrometers (μm) in diameter. In contrast, the respirable fraction refers to the portion of airborne particles small enough to penetrate deep into the lungs, reaching the alveolar region where gas exchange occurs. These particles are smaller, typically less than 10 micrometers (μm) in diameter.
No-observed-(adverse-) effect-level (NO(A)EL)	The highest administered dose in a study at which no (adverse) effect is observed.
Personal protective equipment (PPE)	PPE refers to specialized clothing or equipment to be worn by individuals to protect themselves from a health risk. Types of PPE include: eye protection (protective glasses), respiratory protection (masks), hand protection (gloves), body protection (protective clothing), foot protection (safety boots).
Risk	The probability of an adverse effect and the severity of that effect, consequential to (a) hazard(s).
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.
Risk characterisation	The qualitative and/or quantitative estimation, including associated 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.
Risk communication	The process of communicating information about risks identified during a risk assessment. It aims to inform and educate people about potential hazards, their impacts, and the measures that can be taken to mitigate the risk.
Risk management	The process of evaluating risk control options and, where necessary, implementing risk mitigation measures to reduce an identified risk to an acceptable level for the user.
Toxicological reference value (TRV)	A toxicological index that, when compared to exposure, is used to quantify a risk for human health. TRVs are established for a given critical effect and are specific to a substance, duration of exposure and route of exposure (e.g. NOEL, NOAEL, BMDL).
Uncertainty factor	A numerical factor applied to a toxicological (pharmacological /microbiological) endpoint to allow for uncertainties in risk assessment such as intraspecies (extrapolating animal data to humans) and interindividual (variation in sensitivity among humans) variations, the quality of the data, the severity of the response. The factor may be a default value used in the absence of specific information on a substance or may be modified in the light of specific information.
User	Any person that may come into contact with the veterinary medicinal product (VMP) or components of the product before its application to the animal (e.g. during storage), during its application (e.g. during preparation or administration to the animal), and after its application (e.g. through contact with the treated animals).

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References

- Guideline on dossier requirements for anticancer medicinal products for dogs and cats (EMA/CVMP/28510/2008).
- Guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014).
- Guideline on user safety for immunological veterinary medicinal products (EMA/CVMP/IWP/54533/2006 Rev.1).
- Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).
- IPCS/WHO (2005). Chemical-specific adjustment factors for interspecies differences and human variability: Guidance document for use of data in dose/concentration-response assessment. IPCS harmonization project document no. 2. World Health Organization, Geneva, Switzerland. https://www.who.int/publications/i/item/9241546786
- Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC.
- Reflection paper on providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs, (EMA/CHMP/CVMP/3Rs/164002/2016).
- VICH GL32: Studies to evaluate the safety of residues of veterinary drugs in human food: Developmental toxicity testing (CVMP/VICH/485/02).

Abbreviations

ADI	Acceptable Daily Intake
AOEL	Acceptable Occupational Exposure Limit
ARfD	Acute Reference Dose
BMD(L)	Benchmark Dose (lower confidence limit)
EU	European Union
IPCS	International Program on Chemical Safety
LOAEL	Lowest Observed Adverse Effect Level
MA	Marketing Authorisation
MOE	Margin of Exposure
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
PPE	Personal Protective Equipment
SPC	Summary of Product Characteristics
TRV	Toxicological Reference Value
VMP	Veterinary Medicinal Product

WHO World Health Organisation

Annex 1

Worked examples

Two worked examples of User Risk Assessments (URAs) are presented below to show a qualitative risk characterisation and a quantitative risk characterisation.

The examples are provided to assist in understanding how URAs are conducted and do not aim to provide comprehensive URAs addressing all aspects of these assessments. The two examples below are for guidance purposes only and should not be regarded as exhaustive. Other concerns (e.g. systemic toxicity) may need to be addressed, depending on the routes of exposure and the toxicity profiles.

The examples are presented using the template (given in Annex 2). All URAs should include the four aspects of risk assessment, namely hazard identification, hazard characterisation, exposure assessment and risk characterisation, as given in this guideline and as presented in the template. It may be noted that hazard identification and hazard characterisation are considered together in this guideline as they are intrinsically linked.

Example 1: URA based on a qualitative risk characterisation

Brief description of product: An anthelmintic for oral administration which is provided as a suspension for use in drinking water for pigs. The package size is a 4-liter plastic container, and a separate dispenser (measuring device) is provided.

Note: Only the qualitative risk characterisation is described in this example. Adverse effects which require quantitative risk assessment are not considered.

User Risk Assessment

1. Hazard Identification and Characterisation

Appraisal of the toxicity and hazards.

Pharmacology and toxicology studies, including studies on irritation and sensitisation, are presented in section 3A2-3A4, though a summary with conclusions should be provided in section 3A5 URA.

1.1 Toxicity data on active substance(s):

The following was concluded for the active substance in regard to local toxicity:

- No skin or eye irritation studies are available for the active substance.
- Observations in humans indicate skin irritation following dermal contact with the active substance.

1.2 Toxicity data on formulation:

The following was concluded for the formulation in regard to local toxicity:

- A skin irritation study with the final formulation showed mild irritation.
- An eye irritation study showed no signs of irritation.
- A skin sensitisation study showed no evidence of sensitisation.

2. Exposure

Appraisal of the exposure.

2.1 Precise identification of the product

- The product is a suspension presented in a 4-litre plastic container. A separate dispenser is provided for dosing.
- The VMP is to be administered via drinking water to pigs.

2.2 Exposure scenarios

- Exposure may occur during the application phase (when added to the drinking water and administered to the animals) or the post-application phase (during cleaning of the dispenser and disposal activities).

2.3 Type of user

- The VMP will be applied by farmers. Children are not expected to have access to the VMP as this VMP is to be used by professional users and kept in a professional environment.

2.4 Routes of exposure

- The main routes of exposure are dermal exposure from accidental spillage when handling the product and when cleaning the dispenser after dosing. Exposure of the eyes may also be possible through splashes when adding the VMP to the drinking water.

2.5 Magnitude, duration and frequency of exposure

- Under normal conditions of use, skin and eye exposure is possible every time the VMP is administered, i.e. when added to the drinking water due to accidental spillage and/or splashes. Skin exposure is very likely when cleaning the dispenser.

Note that, as only the qualitative risk assessment is described in this example, no exposure level is estimated.

3. Risk characterisation

3.1 Qualitative risk characterisation

- The risks following eye exposure are considered negligible, because adverse effects to the eyes are not expected in view of the negative eye irritation study with the formulation.
- A skin irritation study with the final formulation showed a mild irritating effect. Irritation of the skin in humans was observed after dermal contact with the active substance.
- The risk for skin sensitisation is low in view of the negative skin sensitisation study.

3.2 Quantitative risk characterisation

Quantitative risk not determined in this example.

4 Risk Management.

- Risk mitigation measures should be in place to address the possibility of irritation after accidental skin exposure when preparing the medicated drinking water and cleaning the dispenser.

5 Risk Communication.

The user warnings on the SPC and package leaflet are[5]:

- This veterinary medicinal product may be irritating to the skin. (A)
- Avoid skin contact. (B)
- Personal protective equipment consisting of impervious gloves should be worn when handling the veterinary medicinal product and cleaning the measuring device. (C)
- Wash hands after use. (D)
- In case of accidental spillage onto the skin, immediately rinse with plenty of water. Remove contaminated clothing after spillage. If irritation persists, seek medical advice and show the label or package leaflet to the physician. (D)

Example 2: URA based on a quantitative risk characterisation

Brief description of product: *A VMP for oral administration to dogs by a pet owner at home. There are two strengths of coated tablets, 20 mg and 50 mg.*

Only the quantitative risk characterisation is described in this example.

User Risk Assessment

1. Hazard Identification and Characterisation

Appraisal of the toxicity and hazards.

Pharmacology and toxicology studies are presented in section 3A2-3A4, though a summary with conclusions on the relevant (lowest) TRVs should be provided in section 3A5 URA.

1.1 Toxicity data on active substance(s).

The following was concluded for the active substance:

- NOAEL = 10 mg/kg, based on a 14-day toxicity study in dogs, where dizziness and low blood pressure were observed at higher doses.

1.2 Toxicity data on formulation.

No toxicity studies using the formulation are presented. The systemic toxicity is determined by the active substance.

2. Exposure

Appraisal of the exposure.

2.1 Precise identification of the product

- The VMP is presented in cartons containing 10 blister strips, each strip containing 10 coated tablets of 20 mg or 50 mg.
- Tablets are administered to the animals once or twice a day.

[5] The capital letters in brackets correspond to those used in section 5.5. of this guideline

2.2 Exposure scenarios.

- Exposure may occur during the pre-administration phase (storage, as the VMP is stored at home) and during the administration phase (when administered to the animal).

2.3 Type of user

- The VMP will be administered by dog owners. Children may get access to the VMP if not properly stored.

2.4 Routes of exposure

- The main routes of exposure are dermal exposure from handling the tablets or accidental ingestion of the tablets by a child.

2.5 Magnitude, duration and frequency of exposure

- When handling the tablet, skin exposure is estimated to be negligible in view of the coating on the tablet. Accidental ingestion by a child in the home needs to be addressed. A young child of approximately 12.5 kg body weight (bw) ingesting 1 tablet is considered to be a reasonable worst-case scenario, as it is assumed that a young child may be left unattended for a short time and the VMP is packed in a blister.
- Accidental ingestion of one 50 mg tablet in a single exposure would give a dose of 50 mg or 4 mg/kg bw when considering the bw of 12.5 kg.

3. Risk characterisation

3.1 Qualitative risk characterisation

- *Qualitative risk is not determined in this example.*

3.2 Quantitative risk characterisation

Based on the exposure of 4 mg/kg bw as a result of the ingestion of one 50 mg tablet by a 12.5 kg child, and considering the NOAEL of 10 mg/kg, the MOE is 10/4= 2.5. This MOE is lower than 100 (the factor needed to take account of intra- and interspecies variation), it is therefore considered that risk mitigation measures should be in place.

4 Risk Management

- Because of the risk of accidental ingestion, risk mitigation measures should be in place to prevent children from accidentally ingesting tablets.

5 Risk Communication

The user warnings on the SPC and package leaflet are:

- This veterinary medicinal product may cause dizziness or low blood pressure. (A)
- Avoid accidental ingestion. (B)
- Care should be taken to prevent accidental ingestion by children. In order to prevent children from accessing the product, do not remove tablets from the blister until ready to administer to the

761 animal. Tablets should be administered and stored (in the original packaging) out of the sight and
762 reach of children. (C)

763 • In case of accidental ingestion, seek medical advice immediately and show the package leaflet or
764 the label to the physician. (D)

765

Annex 2

Template for a user risk assessment

The following template can be used to present a user risk assessment, however it should be noted that all the headings may not be needed and can be deleted as required.

User Risk Assessment

1. Hazard Identification and Characterisation

1.1 Toxicity data on active substance(s)

1.2 Toxicity data on formulation

2. Exposure assessment

2.1 Precise identification of the product

2.2 Exposure scenarios

2.3 Type of user

2.4 Routes of exposure

2.5 Components of a product to which the user is exposed

2.6 Magnitude, duration and frequency of exposure

3. Risk characterisation

3.1 Qualitative risk characterisation

3.2 Quantitative risk characterisation

4 Risk Management

5 Risk Communication