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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS (CVMP)

REVISED GUIDELINE ON USER SAFETY FOR PHARMACEUTICAL VETERINARY MEDICINAL PRODUCTS

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EXECUTIVE SUMMARY

The user safety guideline has been revised to provide clearer guidance and advice on the procedure for user safety risk sassements.

1 INTRODUCTION (background)

Applications for marketing authorisations of veterinary medicinal products in the European Union are issued in accordance with Directive 2001/82/EC as amended by Directive 2008/28/EC and Directive 2009/9/EC. This legislation requires that applications for pharmaceutical veterinary medicinal products must provide safety documentation, Annex I (Directive 2009/9/EC) states that "*the safety documentation shall show 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.*"

The legislation does not give 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 provides guidance and advice on user safety and conducting user safety risk assessments.

The CVMP adopted the User Safety Guideline in July 2005, however, in November 2006, at a EMEA/IFAH-Europe Info Day, concerns were raised in a presentation on Industry's Perspective of the User Safety Guideline, that certain aspects of the guideline needed clarification. Following a focus group meeting and consultation with interested parties, the CVMP and its Safety Working Party have revised the guideline.

2 SCOPE

The objective of this guideline is:

- to provide guidance and advice on user safety risk assessments.

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

For the assessment of user safety, the user is defined as 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 or preparation), during its application, and after its application (e.g., through contact with the treated animals) .

The guideline does not cover occupational safety during the manufacture of veterinary medicinal products.

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 deliberate misuse.

Active substances categorised as "controlled drugs or scheduled substances[1]", which can be deliberately misused, may require additional consideration, such as special storage conditions so as to prevent access by unauthorised people.

3 LEGAL BASIS

Requirements for safety testing for a marketing authorisation application are laid down in Article 12 of European Parliament and Council Directive 2001/82/EC as amended by Directive 2004/28/EC, and Directive 2009/9/EC.

[1] Controlled drugs/scheduled substances: as detailed in Annex I of Council Regulation (EC) 273/2004 and the Annex to Council Regulation (EC) 111/2008

This guideline concerns the application of the requirements of Directive 2009/9/EC, Annex I, given in Part 3 of Title I. User safety shall *"…include a discussion of the effects found in the preceding sections 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."*

4 PRINCIPLES OF THE ASSESSMENT

4.1 The aspects involved in user risk assessments

An assessment of the risk presented from the VMP for those handling and administering it, should be presented by incorporating the following aspects:

- an appraisal of the inherent toxicity of the VMP
- an appraisal of how and when the user will be exposed to the VMP
- conclusions of the above two aspects proposing how the information will be communicated to the user

An appraisal of the inherent toxicity and any other harmful effects, such as flammability, of the active substance and the formulation is made. The hazards should be identified and characterised from the data from appropriate toxicity tests regarding relevant endpoints for local and systemic toxicity, taking into account the route, duration, and frequency of anticipated exposure. Studies conducted on the formulation should be relevant to the route of exposure e.g. 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 product, is made. All possible exposure scenarios should be considered; these should include route and degree of exposure, frequency of use and amount used. The users, including all people 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 the exposure levels at which no adverse effects are expected to occur. When there is a predicted risk for the user, appropriate measures for risk reduction should be proposed and evaluated.

4.2 Users

It is important to clearly identify the users of the product and to include all users some of which may not necessarily be administering the product, but may be indirectly exposed to the product.

Users are described in further detail in section 5.2.3

5 USER RISK ASSESSMENT

5.1 Hazard identification and characterisation

Generally, most of the toxicity data required to make a hazard identification are already part of a MA dossier (Part IIIA Safety Documentation). The need for any additional studies depends on the exposure and any identified gaps in data and in some cases, the nature of the substances indicate the need to focus on specific end-points of toxicity or pharmacology.

5.1.1 Toxicity data on active substance(s)

The toxicity data presented in the dossier relating to the active substance may be from published literature or from toxicity studies. These studies should be designed and selected to investigate the effects of single doses and repeated doses, and to consider endpoints for effects on reproductive performance, fertility, genotoxicity and carcinogenicity. Depending on the type of product, special studies may have been conducted, for example to investigate inhalation toxicity, sensitization potential, skin and eye irritation, or effects on immunotoxicity or neurotoxicity. In addition, if the

active substance has been used in human medicines, then data relating to observations in humans and adverse reaction data should be available and submitted in the dossier.

The results from the toxicity studies should be evaluated to determine the potential for adverse effects in humans. If the evaluation results in conclusions that the VMP may have potential to cause adverse effects in users, then further investigation is required.

Both local and systemic effects should be considered. The systemic effects are usually assessed only for the active substances, however, when there is a specific concern with regard to the systemic effects of one or more of the excipients, it may be necessary to assess the systemic toxicity of these excipients or the formulated product.

5.1.2 Toxicity data on the formulation

For toxicity studies on local effects, the test article may be the active substance, but should preferably be the formulation of the product. However, in the interest of reduced testing in animals if there are only historical data or published literature on the ingredients in the formulation, the potential effects of a product 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. Therefore no eye-irritation test has to be performed for skin irritating test articles.

5.1.3 Conduct of toxicity studies

If toxicity tests are conducted, they should be carried out in accordance with VICH guidance and current methodology (e.g., EC, OECD, or EPA) and, where advised, should follow a stepwise approach (e.g., studies to evaluate genotoxicity). Other methodology may be considered, provided that their choice is adequately justified by the applicant in terms of scientific reliability and relevance.

Whenever possible, dose-response relationships should be identified in order to derive the no observed adverse effect level (NOAEL), or, if this is not possible, the lowest observed adverse effect level (LOAEL).

It is noted that for some end-points standardised methods are currently not available, in particular for parenteral toxicity and respiratory sensitisation. However, for parenteral toxicity, target animal safety studies may provide adequate 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.

5.2 Exposure

5.2.1 Consideration of the veterinary medicinal product

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

- the pharmaceutical form
- relevant physico-chemical characteristics
- 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 The tasks and situations that lead to exposure

The next step in the exposure assessment is to identify the 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 some different tasks and situations that may be relevant for a VMP. It should be noted that these are just some examples 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-application phase	Application phase	Post-application 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	• Administration to the animal(s): • Holding/restraining animal for treatment	• Cleaning equipment & preparation areas • Disposal activities: such as disposal of packaging, equipment & surplus product • Handling treated animals • Stroking/handling the coat of treated animals

5.2.3 Exposure scenarios

Once the tasks and situations that lead to exposure are identified, the exposure for each task/situation should be further characterised. An exposure scenario should comprise the following elements:

i. Who? … the type of user,

ii. How?... the routes of exposure,

iii. What? … the components of a product to which the user is exposed,

iv. When/if? … the possibility and probability of exposure,

v. How much? How often? … the rate, extent, duration, interval, and frequency of exposure.

These five elements given above may be different for the different phases and may differ for the different users of the product. The elements are further explained below.

(i) 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 product, some of whom may not necessarily be administering the product, but may be indirectly exposed to the product.

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, a canine beautician, a miller incorporating a medicated premix into a finished feed or a sheepshearer.

(ii) the routes of exposure

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

Oral ingestion is normally considered negligible when elementary personal hygiene is maintained. However, oral exposure should be considered in the following situations:

- Oral exposure due to hand-to-mouth contact needs to be considered with certain scenarios, e.g. after stroking a pet when there are residues on the fur.
- The non-respirable fraction of an inhalation exposure is considered to be swallowed.

The observation of the warning "keep out of reach and sight of children" on the label and insert of products should normally prevent accidental ingestion by children, however, the risks of oral ingestion should always be considered and in particular for products that will be kept in the home. If the toxicity data suggest that there may be a concern, minimising exposure to children should be addressed, such as considering child resistant packaging.

(iii) 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;
- to certain components of the product (e.g., an active substance released from a collar);
- to 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.

(iv) the possibility and probability of exposure

Although all sorts of 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 will be considered as an exposure situation, but it is clear that there is a low probability that this event will actually happen when the product is used.

An estimate of the possibility of a situation occurring should be made and any available data on the incidence of events that lead to exposure related to the use of the (type of) product should be submitted.

(v) the rate, extent, duration, interval and frequency of exposure

The rate, extent, duration, interval, and frequency of exposure determine the quantitative part of an exposure scenario.

Duration, interval, and frequency of exposure are to 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 taking into account the pattern of use (variation in season or region).

The rate and extent of exposure are often determined by parameters like dose, 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 is estimated.

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

The estimation of the exposure levels may include measured data as well as model calculations. Adequately measured and representative exposure data are preferred to 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.

Examples of exposure factors include standards for bodyweights of adults and children, 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 reasonable worst case situation.

If more than one route of exposure is involved in a single situation (i.e. within one scenario), 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; several dogs in the same household), the exposure needs to be made for multiple applications.

5.3 Risk

5.3.1 Risk characterisation

Qualitative risk characterisation

For a number of toxicological end-points, the methods for testing provide qualitative, non-stochastic, results. This is in particular the case for certain local effects, e.g., sensitisation, skin irritation. For these effects no information on dose response relationship 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, the risk may be qualitatively characterised taking into account the likelihood that such effect will occur on the basis of 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 must be assumed that the effects will occur at any exposure level.

In addition, physical risks related to the physico-chemical properties should be identified.

An example to illustrate this procedure is given in the Appendix.

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 NOAEL.

Where the exposure estimate is higher than or equal to the NOAEL, the risk for the user is considered to be unacceptably high.

Where the exposure estimate is less than the NOAEL, the magnitude by which the NOAEL exceeds the estimated exposure (i.e. the margin of exposure (MOE)) needs to be considered taking account of the following parameters:

- the intra- and interspecies variation[2];
- the nature and severity of 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 database.

Where the MOE is more than needed in view of the parameters mentioned above, the risk for the user is considered acceptable. In other cases, risk management options should be proposed and evaluated.

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[2] 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.

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).

Where appropriate and justified, available toxicological limit values or exposure limit values (e.g., AOEL or other occupational limits, ADI) may be used as alternatives for the MOE approach as described above.

An example to illustrate this procedure is given in the Appendix.

5.3.2 Risk management

Users

Some users will have more experience and knowledge of handling and administering animals than others, such as veterinarians or farmers and this needs to be acknowledged in the assessment. Similarly when considering other users that do not administer veterinary medicines on a frequent basis, such as pet owners, additional information may be required in order to 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 and where it can be obtained. If this is not practical, other measures would have to be proposed; the use of a product must be acceptably safe, or have an acceptable risk with limited protection.

Risk control options

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

- restriction of the distribution, e.g. as prescription only medicine;
- excluding groups at risk, e.g., sensitised people, pregnant women;
- restriction of application methods, e.g., pour-on instead of spraying or use of closed delivery systems;
- restriction of the field of use, e.g. outdoor use only;
- modification of the formulation, e.g., ready to use rather than concentrate,
- modification of packaging, e.g., reduced pack size;
- modification of labelling;
- modification of measures for the protection of users, e.g., general controls like ventilation or PPE like protective gloves, masks or goggles. The appropriateness, i.e. the inherent efficiency, of 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).

The proposed risk reduction measures should be evaluated with the following criteria:

- the extent to which the exposure is reduced by a risk reduction 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, e.g., PPE must be readily available to the user, and measures should not hamper the use of the product too much. Impractical measures cannot be expected to be followed.

5.3.3 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.

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.

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 eyes. The warnings in the SPC and on the labels and package leaflet would be:

- This product can cause eye-irritation (A).
- Avoid contact with the eyes (B).
- Wear protective glasses (C).
- When the product comes into contact with the eyes, rinse immediately with plenty of water (D).

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

- 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)
- Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations. (B)
- Handle this product with great care to avoid exposure taking all recommended precautions. (C)
- If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention. (D)

The warnings should be written using appropriate "user friendly" terminology with specific consideration of the user who will be reading the product literature.

When warnings are extensive and can only be written in full in the package leaflet, it is important to make sure the information is communicated to the user on the label and outer packaging, and not to rely on the user reading the package leaflet in detail before using the product. In such cases an abbreviated warning cross referring to the package leaflet should be added to the labels and outer packaging. Some examples of abbreviated warnings are:

- Penicillins and cephalosporins may occasionally cause severe allergic reactions. See package leaflet for user warnings.
- Sulphonamides may occasionally cause severe allergic reactions. See package leaflet for user warnings.
- Anaesthetics [must be handled correctly/are hazardous chemicals when incorrectly handled*]. See package leaflet for user warnings. [*delete as required]
- α-2 agonists can cause severe adverse reactions. See package leaflet for user warnings.
- Prostaglandins can cause severe adverse reactions. See package leaflet for user warnings.

REFERENCES (scientific and / or legal)

- Directive 2001/82/EC of the European Parliament and of the Council as amended by Directive 2004/28/EC and Directive 2009/9/EC
- IPCS/WHO (2001). Exposure assessment: Glossary of exposure assessment-related terms: a compilation. Available at: http://www.who.int/ipcs/publications/ehc/methodology_alphabetical/en/index.html
- 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. Available at: http://www.who.int/ipcs/methods/harmonization/areas/uncertainty/en/
- Rules Governing Medicinal Products in the EU: Notice to Applicants and Note for Guidance, Volume 8 "Establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin".
- Rules Governing Medicinal Products in the EU: Notice to Applicants and Note for Guidance, Volume 6B "Presentation and content of the Dossier".
- OECD Toxicity Testing Guidelines.
- VICH Safety Guidelines

ABBREVIATIONS

ADI	Acceptable Daily Intake
AOEL	Acceptable Occupational Exposure Limit
EC	European Commission
EPA	Environmental Protection Agency
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
RfD	Reference Dose
RPE	Respiratory Protective Equipment
SPC	Summary of Product Characteristics
TGD	Technical Guidance Document
VMP	Veterinary Medicinal Product
WHO	World Health Organisation

DEFINITIONS [3]

Acceptable daily intake (ADI)	the estimate of the residue, expressed in terms of micrograms or milligrams per kilogram of bodyweight, that can be ingested daily over a lifetime without any appreciable health risk.
Application phase	The 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 application.
Controlled drugs	Active substances that are regulated for availability and access.
Exposure	Contact between an agent and a target. Contact takes place at an exposure point or exposure surface over an exposure interval. For inhalation and ingestion routes, exposure is expressed as a function of exposure concentration; for the dermal route, exposure is expressed as a function of exposure loading.
Exposure assessment	The process of estimating or measuring the intensity, frequency, and duration of exposure to an agent. Ideally, it describes the sources, pathways, routes, magnitude, duration, and pattern of exposure; the characteristics of the populations exposed; and the uncertainties in the assessment.
Exposure concentration	The amount of agent present in the contact volume divided by the contact volume. For example, the amount of agent collected in a personal air monitor divided by the volume sampled.
Exposure Interval	A period of continuous contact between an agent and a target.
Exposure loading	The amount of agent present in the contact volume divided by the exposure surface area. For example, a dermal exposure measurement based on a skin wipe sample, expressed as a mass of residue per skin surface area, is an exposure loading.
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 facts, assumptions, and inferences about how exposure takes place. Scenarios are often created to aid exposure assessors in estimating exposure.
Exposure surface	A surface on a target where an agent is present. Examples of locations of exposure surfaces include the lining of the stomach wall, the lung surface, the exterior of an eyeball, the skin surface, and a conceptual surface over the open mouth. Exposure surfaces can be absorptive or non-absorptive.
Foreseeable accidents	The use of veterinary medicinal products 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

[3] Definitions taken from Notice to Applicants Vol 8, and IPCS/WHO (2001).

	dilution of a veterinary medicinal product, common spillage scenarios, use without or with non-proper PPE).
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	The ratio of the No Observed (Adverse) Effect Level (NO(A)EL) to an estimated exposure level.
Non-respirable fraction	The part of an inhalation exposure that will settle in the nasopharyngeal region and not in the tracheobronchial or pulmonary regions. As a rough guide, particles with aerodynamic diameters below 100 µm have the potential to be inhaled. There are three main size classifications: the particles that are inhaled (inhalable); the particles that reach the thorax (thoracic) and the fine particles that penetrate the lungs (respirable). The aerodynamic diameters are: • inhalable < 50 µm > 10 µm • thoracic < 10 µm > 5 µm • respirable < 5 µm
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 includes head, eye, respiratory (RPE), body, hand, and foot protection that is designed to protect the wearer from exposure. PPE is sometimes also referred to as Individual Protective Equipment (IPE).
Scheduled substances	see Controlled Drugs above
Stochastic	Being or having a random variable.
Uncertainty factors	A numerical factor applied to a toxicological (pharmacological /microbiological) endpoint to allow for uncertainties in risk assessment such as intraspecies and intraindividual variations. These factors may be default values used in the absence of specific information on a substance and 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 or preparation), during its application, and after its application (e.g. through contact with the treated animals)

APPENDIX: WORKED EXAMPLES

Below is a worked example of a qualitative risk characterisation and a quantitative risk characterisation. The examples are not based on real VMPs and the data are not real. It should be noted that these are not full user safety assessments.

Example of a qualitative risk characterisation

An ectoparasiticide product for external parasitic infestations for topical administration in a stable/stable yard by horse owners. The product is a powder and is presented in a 500 g shaker pack.

(i) Appraisal of the toxicity and hazards

- *Skin irritation studies which showed no irritation and eye irritation studies which showed mild or no signs of irritation.*
- *Sensitisation studies show no evidence of sensitisation potential*
- *Observations in humans report mild irritation after dermal contact*

(ii) Appraisal of the exposure

- *The main routes of exposure are skin contact from handling the product and inhalation from the dust.*
- *Skin contact is minimal and the exposure is estimated to be negligible, therefore it is not considered to present a hazard when the product is used as directed.*
- *Inhalation of dust from the product when applying to the animal is considered a risk that needs to be characterised.*
- *Data on dust content: 0 – 12 mg of dust - classified as "nearly dust free"*
- *Data on particle size distribution of the product:*

  > 45% of the particles had an aerodynamic diameter of less than 10 μm (thoracic fraction);
  > 32% of particles with an aerodynamic diameter of less than 5 μm (respirable fraction);
  20% of particles had an aerodynamic diameter of less than 2 μm:
  there is therefore a considerable potential for inhalation of the dust of the product.

- *Multiple exposures from treating several horses at one time.*

(iii) Qualitative risk

- *Assuming a worst case scenario, such as a groom treating several horses at one time*
- *The product has a warning to use in well ventilated areas and it is assumed this will be followed, but if several horses are treated the amount of dust inhaled will accumulate.*
- *Referring to the data on dustiness and particle size, it can be assumed that dust will be inhaled and may be mildly irritant.*
- *The accumulation of dust is a sufficient risk to require a dust mask to be worn when treating several horses*
- *It is unlikely that stables will have dust masks available and therefore an appropriate mask should be supplied with the product.*
- *It is also considered that there is a need to supply the appropriate dust mask (such as those supplied to hospitals to avoid infection) with the 2.5 kg pack and the 500 mg pack.*

Example of a quantitative risk characterisation

An NSAID for oral administration to dogs by pet owner in the home. There are 2 strengths of tablet presented in 2 different types of packaging:

(i) in tubs of 100 tablets for the 20 mg or 50 mg tablets and in a larger tub of 500 for the 50 mg tablets only; the tub of 500 tablets will be dispensed into smaller containers to the dog owners.

(ii) in cartons containing 10 blister strips, each blister strip containing 10 tablets x 20 mg or 50mg.

(i) Appraisal of the toxicity and hazards

- *Carprofen was used in human medicines at doses of 150-600 mg/day.*

(ii) Appraisal of the exposure

- *The main routes of exposure are skin contact from handling the tablets or accidental ingestion of the tablets by a child.*
- *Skin contact is minimal and the exposure is estimated to be negligible, therefore it is not considered to present a hazard when the product is used as directed.*
- *Accidental ingestion by a child in the home is considered to be a risk that needs to be characterised.*

(iii) Quantitative risk

- *Assuming a worst case scenario, such as a young child (approximately 20 kg bw) gaining access to an open container of the higher strength tablets and ingesting 1-3 tablets*
- *Accidental ingestion of 3 x 50 mg tablets in a single exposure would give a dose of 150 mg*
- *Referring to the use of carprofen in human medicines at doses of 150-600 mg/day, the accidental dose is in the same range as the lowest dose given to humans and 4 times lower than the highest dose administered, although it is acknowledged that these data refer to adults. However adjusting for a child's weight, the accidental dose would still be lower than the upper end of the human dose.*
- *Therefore such accidental ingestion is not considered to be a hazard so the risk is low and acceptable. The tablets will be packaged in blister packs or will be dispensed into smaller containers and both of these presentations limit the amount of tablets a young child would have access to.*