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**COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
(CVMP)**

**GUIDELINE ON DOSSIER REQUIREMENTS FOR ANTICANCER MEDICINAL
PRODUCTS FOR DOGS AND CATS**

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In April 2007, a Focus Group Meeting on oncology products for veterinary use was held with interested parties at the EMEA (see minutes of the meeting [EMEA/CVMP/EWP/180579/2007](#)). Discussions at this meeting were taken into account when drafting this guideline.

KEYWORDS	<i>Veterinary medicinal product, medicine, dog, cat, oncology, anti-cancer drug</i>
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EXECUTIVE SUMMARY

This guideline outlines the conditions and data requirements for the demonstration of quality, safety (user, target animal), efficacy and environmental impact of anticancer veterinary medicinal product used in dogs and cats and should be read in conjunction with current EU/VICH guidelines.

1. INTRODUCTION

Anticancer medicinal therapy is an established part of small animal clinical practice offered to dogs and cats. Therapy has hitherto been based only upon products registered for use in humans, thus treatment protocols have mainly been established by extrapolation. In accordance with Directive 2001/82/EEC as amended by Art. 10 No 1b) in Directive 2004/28/EC (the so called cascade principle), a wide panorama of these products may be prescribed by veterinarians, including compounds with cytotoxic as well as those with non-cytotoxic properties.

Authorisation of anticancer medicinal products for veterinary use is generally to be encouraged, as this would provide a basis for the use of such compounds under sufficient regulatory control. To successfully apply for registration of anticancer products aimed for use in animals, the applicant should comply with general requirements set in the EU legislation and in appropriate European and VICH guidelines. However, many anticancer products are unique in the sense that their therapeutic effect is strongly associated with their high toxicity. A comprehensive benefit-risk balance should, therefore, be provided by the applicant taking into account recommendations for the handling and administration of the product, as well as the management of the treated animal and waste products or excreta, that would be acceptable with respect to user and environmental safety. In addition, the toxic properties of many anticancer compounds imply that there are requirements outlined in general guidelines that may not be relevant or may be too extensive.

Veterinary anticancer medicinal therapy could in certain cases have a curative aim, but would in most situations be considered palliative. The aggressive medication strategies used in human oncology, which are commonly associated with serious adverse reactions, can be justified by the fact that humans can communicate their desires and perceptions and this gives the doctor guidance for necessary ethical considerations. However, animals cannot reflect on the future benefits of treatment e.g. a longer life, and thereby be motivated to endure a high degree of discomfort; and this fact will have implications on the choice of endpoints for efficacy assessment as well as on the recommendations for ethically acceptable treatment strategies. In human oncology, the presence of adverse effects may be correlated to a more favourable prognosis. The opposite is usually the case in veterinary oncology, since an animal owner can decide to stop treatment rather than to compromise the animal's quality of life. For a palliative aim, adverse events during treatment would have to be low, and any changes with regard to symptom relief and quality of life may be considered relatively more important than endpoints related to longevity. In addition, the fact that endpoints related to perception are subjective in nature puts special demands on study design (blinding). Despite the importance of subjective endpoints, the need to also include accurate objective endpoints relating to tumour burden should not be neglected.

The scientific community regularly performs efficacy and safety assessments in dogs and cats with different treatment protocols for single or combinations of antineoplastic substances, applied to several kinds of neoplasia. Results are presented in numerous scientific reports. Although these reports may well provide useful information for clinical applications, variation between the study protocols and in the selection of endpoints may hamper an accurate benefit risk analysis for the use of a specific substance in a specific neoplastic disease. Nevertheless, such bibliographic data may act as supportive information in an application for approval of an anticancer product for veterinary use and depending on the quality of the data may, from an ethical point of view, exclude the need to perform e.g. placebo controlled studies. In this context, the guideline aims to provide information on the appropriate use of previously compiled efficacy and safety data from the target species, which could reduce the need for new studies for a specific application. Likewise, preclinical data included in dossiers, or compiled post approval, for anticancer products intended for use in humans could provide support for approval of the

same active substance for veterinary use. The specific role this kind of information could play in a veterinary application is further detailed in this document.

This document is mainly focussed on the situation where a previously known active substance, for which data on the mode of action and target of toxicity are already available and documented according to CHMP guidelines, is developed for veterinary use. If the intention is to develop a veterinary medicinal product including a new active substance not previously studied, certain issues that are beyond the scope of this document may have to be examined in more detail. In these situations it is recommended to seek scientific advice from regulatory authorities.

In this document, for guidance regarding preclinical and clinical issues (Part IV), the substances are classified as either cytotoxic or non-cytotoxic since such a categorisation is relevant with regard to the design of exploratory studies and efficacy and safety assessments in the target animal as well as environmental impact. From a user safety perspective, categorisation into DNA-reactive and non-DNA reactive substances may be more relevant as this is further detailed in section 5 of this document (Safety documentation). Regarding safety issues for non-DNA-reactive substances, the Guideline on User Safety for Pharmaceutical Veterinary Medicinal Products (CVMP/SWP/543/03) is fully applicable, whereas for DNA-reactive compounds additional guidance is given in this document on how to appropriately address this field. Relevant efficacy assessments may vary between cytotoxic and non-cytotoxic substances. Cytotoxic substances act by causing cell death and thereby tumour shrinkage suggesting that apart from toxicity, objective response rate (ORR) is an accurate marker for activity. In contrast, the main effect of non-cytotoxic substances is tumour growth inhibition, but in some situations there is also tumour shrinkage and for these substances a prolonged exposure time is often needed. These properties put special demands on study design, and ORR and/or toxicity may not be the best markers for activity. Relevant design options for efficacy assessment for the two different categories are further detailed in this document.

The current rapid development with regard to understanding of tumour biology, targets for anti-cancer therapy, imaging techniques, etc. makes the field of veterinary oncology highly dynamic. When established approaches to drug exploration are considered suboptimal and in need of revision, it is advisable to seek regulatory scientific advice, especially prior to the conduct of pivotal studies.

2. SCOPE

The aim is to provide guidance regarding cytotoxic/DNA-reactive as well as non-cytotoxic anticancer medicinal products intended for use in dogs and cats. The following specific points are addressed:

- Chemical, pharmaceutical and biological data submitted in Part II of the dossier, and the aspects of the pharmaceutical form and packaging, in terms of user safety and accurate dosing.
- Pharmacological and toxicological data submitted in Part III of the dossier and the appropriate use of such data originally produced for other purposes (e.g. product development of the same active substance for human use, and possibly post authorisation experience from human use).
- Documentation of user safety and environmental risk assessment.
- Target animal safety depending on type of active substance, and recommendations on when to deviate from general guidelines where appropriate taking into account animal welfare considerations.
- Appropriate design of dose finding and dose confirmation studies dependent on the type of active substance and any possible combination therapy.
- Appropriate design of field studies with regard to the selection of primary and secondary safety and efficacy endpoints and the selection of comparators (placebo/positive controls).

3. LEGAL BASIS

This document is intended to provide guidance on the dossier requirements for veterinary anticancer products for dogs and cats and should be read in conjunction with Directive 2001/82/EC, as amended. Applicants should also refer to other relevant European and VICH guidelines, listed in the reference list of this document. In addition, applicants should be aware that national and EU legislation regarding the handling of hazardous material may have to be taken into account in the development of recommendations for the handling of cytotoxic substances.

4. ANALYTICAL DOCUMENTATION (PART II)

4.1 *Chemical, Pharmaceutical and Biological Data*

The requirements for Marketing Authorisations are given in Annex I, Directive 2001/82/EC as amended by Directive 2004/28/EC, and apply to all veterinary medicinal products. However in the interest of animal welfare and medicines availability, it is considered appropriate to define the acceptable data requirements for these specialised veterinary medicinal products.

The main categories for these products are considered to be 1) adaptation of an existing human medicinal product or 2) development of an entirely new medicine for veterinary use.

4.1.1 *Adaptation of an existing human medicinal product*

In the EU, through the cascade system, human medicines may be used to treat animals where no alternative authorised veterinary medicinal product is available. Notwithstanding, in many cases they would not be able to be used as such, since the strength and dosage forms may not be appropriate for their use in animals. Besides, there would be some handling operations of the human medicines that cannot be condoned for their adaptation to the veterinary use. That is the case of crushing and dilution of tablets/capsules, as well as the use of half tablets and dilution of injections. On the other hand, changes such as the use of syringes designed to measure very low volumes of an injection can be acceptable (see also sections 4.2 and 4.3). Furthermore, issues such as user safety and accurate dosing must be taken into account when considering use of such products in animals.

If a human medicine is already authorised in the EU and has been assessed for conformance with the current legislation, an acceptable quality dossier already exists for the product. If it is confirmed that the proposed veterinary medicinal product is identical to an EU authorised human medicine with the exception of the labelling of the product and any administration devices supplied with the product, then the assessment of the core quality data will **not** be repeated by the Veterinary Regulatory Authority. The supporting quality data which would be routinely assessed would be those dealing with the use of the product in the animal i.e. dosing accuracy and in-use studies.

In order to progress such an application, the administrative data required in addition to that in Part I of the dossier, and the quality data required would be as follows:

1. The Marketing Authorisation number of the human medicine.
2. The name of the member state in which the human medicine is authorised and the date this authorisation was issued.
3. The current agreed SPC for the authorised human medicine.
4. The complete formula of the human medicine.
5. A letter from the Marketing Authorisation holder of the human medicine confirming that they have either, supplied the Applicant with all of the necessary data and know-how to allow them to manufacture a product identical to the human medicine, or, that they will be supplying product directly to the Applicant that is of identical quality to the authorised human medicine.
6. A full copy of the quality part of the dossier as submitted to the relevant human Regulatory Authority with the initial application, taking account of any responses to questions and subsequent changes.

- 146 7. A brief paper considering how the correct dose will be measured and administered in practise
147 for the proposed target species/indication, together with a justification for the proposed SPC
148 statements designed to help ensure accuracy of dosing.
149 8. Supplementary in-use studies as appropriate.

150 Items 1 to 5 are required to check that the proposed product is indeed identical to the EU authorised
151 human medicine.

152 Item 6 will not be assessed, unless review of points 1 to 5 reveal that the proposed veterinary
153 medicinal product differs from the human authorised product.

154 Items 7 and 8 will be assessed.

155 In the case of variations to the veterinary medicinal product once authorised, systematic variation
156 applications with supporting data will be required. However, evidence of approval of a variation by a
157 Human Regulatory Authority will mean that no additional assessment will be undertaken on core
158 quality issues by the Veterinary Regulatory Authority unless directly relevant to points 7 and 8 above.

159 4.1.2 *Development of an entirely new medicine for veterinary use*

160 The following are examples of the areas in which the data requirements might be reduced, depending
161 upon the active substance and the dosage form:

162 *Active substance batch analysis data*¹

- 163 • Data required for 2 pilot batches only.

164 *Active substance stability*²

- 165 • For all active substances (i.e. pharmacopoeial and non-pharmacopoeial) formal stability
166 studies according to CVMP guidelines are not required if testing to full specification
167 immediately before manufacture of the final product is proposed.

168 *Final product process validation data*

- 169 • Provision of a process validation scheme for full scale batches is acceptable. Thus
170 permitting process validation studies to be conducted on full scale batches post
171 authorisation³. Final reports from such process validation studies are to be available for
172 scrutiny during GMP inspections. However, the Licensing Authority must be informed if
173 problems are encountered on validation of the process at the full scale, together with the
174 proposed action.

175 *Final product batch analysis data*

- 176 • Data required for 2 pilot batches only.
- 177 • Commitment to be given to inform the Regulatory Authorities immediately if any of the
178 first three production batches fail to meet the agreed Finished Product Specification and to
179 submit these batch analyses data together with the proposed action.

¹ If the active substance is already used in human medicinal product, a full data package should be provided where available

² If the active substance is already used in human medicinal product, a full data package should be provided where available

³ Process development and validation data should be included in the dossier pre-authorisation as necessary in accordance with the normal requirements set out in the guideline on process validation.

Final product stability

- Data required in application for two pilot batches only.
- First 2 production batches (usually post authorisation) to be subjected to stability testing.
- Concept of bracketing/matrixing to be applied.
- Photostability data not required as long as the product is provided in a carton (or other suitable protective packaging) and is labelled “protect from light”.

In the case of variations to the veterinary medicinal product once authorised, systematic variation applications with supporting data will be required. However, changes in supporting data requirements should be applied in line with those detailed above.

4.2 Pharmaceutical form

The applicant should be able to justify the chosen pharmaceutical form in terms of user safety and accurate dosing.

For oral administration of cytotoxic or DNA-reactive substances, tablets are the preferred pharmaceutical form. Whilst whole capsules prevent the user from direct contact with the formulation, capsule shells are frequently damaged during administration and, therefore, their use should be avoided. The strength of tablets should be formulated to allow precise dosing for different animal sizes/weight, by use of whole tablets. A tablet that allows division should be avoided. In general, a tablet should be designed with the aim of minimising the risk for user exposure. This could include the development of an appropriate coating.

4.3 Packaging

The tablets should be packed in containers, which have been proven to be child resistant and which are designed to avoid physical damage to the tablets. Blister packs rather than bottles are preferred. Where an alternative dosage form is proposed for oral administration, e.g. oral solution, it is necessary to demonstrate that the packaging, including the dosing device, ensures that the user does not come into direct contact with the cytotoxic formulation. The use of suitable, integral dosing devices may be appropriate.

For parenteral formulations of cytotoxic or DNA-reactive substances, containers should be designed to reduce risk for user exposure and the accumulation of hazardous waste material. This would include e.g. the use of vials with rubber caps rather than glass ampoules, the use of pre-filled syringes, the design of appropriate sizes/doses for any size of animal, and the development of a concept that requires a minimum of preparation steps. If it's technically possible, a marker can be added in the solution in order to follow a potential contamination.

5. SAFETY DOCUMENTATION (PART III)

The requirements for Marketing Authorisations are given in Annex I, Directive 2001/82/EC as amended by Directive 2004/28/EC, and apply to all veterinary medicinal products. However it is considered appropriate to define the acceptable data requirements for anticancer products for dogs and cats.

5.1 Pharmacological data

It is necessary to provide pharmacological data for the product in order to demonstrate the mode of action, however it is possible to cross refer to existing data and data from target species studies.

Pharmacological studies in laboratory animals and the target species can be replaced by cross reference to the target species studies submitted in Part IV of the dossier by means of a summary of any observed effects in the pharmacodynamic studies and a summary of the pharmacokinetics to

include absorption, distribution, metabolism and excretion (ADME). Absence of studies in laboratory animals must be satisfactorily justified. Additional information regarding target animal tolerance and kinetics is presented in sections 6.1 and 6.2 of this Guideline.

Applications involving active substances used in existing human medicinal products are expected to have (or permitted access to) the necessary pharmacological data which is expected to be in accordance with the guidance for Human Medicinal products (Ref Note for Guidance on pre-clinical evaluation of anticancer medicinal products CPMP/SWP/997/96). In the case of applications involving a new active substance, not previously used in human or veterinary medicine and not intended for human use, it is recommended that specific scientific advice is applied for.

5.2 Toxicological Data

Toxicological data are required for the establishment of user safety and the assessment of adverse effects in the target animal and in humans. The data must be adequate for the evaluation of potential adverse effects associated with pre-administration (preparation...), administration and post-administration (handling of waste and excreta...), such as exposure by inhalation, dermal or oral contact and accidental self injection or administration. For example, it must be sufficient to assess the potential to cause sensitisation, as well as effects on fertility or reproduction. The omission of studies should be adequately justified.

5.3 User safety

A full user safety risk assessment must be performed in order to quantify the risk. According to the results obtained, risk management proposals must be submitted for all applications: an assessment must be provided in order to prove that these risk management proposals are sufficient to reduce the risk to an acceptable level. The requirements of the user safety guideline (EMEA/CVMP/543/03-FINAL) should be applied and this assessment should include a discussion of the effects found in the pharmacological and toxicological data and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings.

5.3.1 Substances with or without a toxicological threshold value

For the user safety, the risk must be assessed and quantified whatever the type of substance and the type of effect. Nevertheless, the approach should be different according to whether a threshold value can be defined or not.

When a threshold value exist (non-DNA reactive and indirect DNA reactive anticancer products such as topoisomerase inhibitors), the general guidance given in the guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03) is applicable. Anticancer products that have a direct action on DNA may produce for example alkylation, DNA single or double strand breaks, DNA-DNA cross link, DNA adducts. Since a genotoxic effect is presented, a threshold value cannot be defined and a safety assessment based on NOEL is inappropriate. This implies that parts of the guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03) may not be applicable. Nevertheless, a whole risk assessment should be performed in order to quantify the risk. Methods are now available (e.g. benchmark doses...) to calculate a margin of exposure. In the post-application phase the potential for exposure of the non-professional user may be expected to be more prolonged, as it is likely to include disposal activities and the handling of waste and excreta, and the handling of treated animals.

In fact, substances that have a genotoxic effect (without a threshold value) have generally other effects with threshold value, such as reprotoxicity. In these cases, both approaches should be followed: the general guidance given in the guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03) should be followed in order to assess and quantify the risk related to effects with a threshold value and a specific risk assessment should be performed (benchmark dose

approach for example) in order to assess and quantify the risk related to effects without a threshold value.

According to the level of risk, risk reduction and risk management, proposals must be submitted, and an assessment must be provided in order to prove that these risk management proposals are sufficient to reduce the risk to an acceptable level. Risk management in the case of both professional and non-professional user should emphasise risk minimisation activities such as restrictions for certain groups of potential users (professional users only via hospitalisation, not during pregnancy etc...) to handle hazardous material(s).

5.3.2 Handling waste and excreta

The assessment of handling of waste products and excreta are specific to the DNA reactive/cytotoxic products and this assessment should be included as part of the user risk assessment when considering the exposure and risk management proposals.

For anticancer products that are DNA reactive, there are, in addition to considerations addressed in the guideline on user safety, particular issues that require specific discussion. National and EU guidelines and legislation on the safe handling and disposal of cytotoxic/hazardous drugs should also be considered in the assessment. The discussion below details issues that should be addressed, either by conducting necessary studies to generate data required, referring to data available and proposing appropriate restrictions, advice, and warnings during the different stages of handling of cytotoxic/hazardous products.

5.3.3 Exposure Assessment

This is the part of the user risk assessment which requires more detailed consideration than for a usual pharmaceutical application. This assessment should consider the different exposures for the use of the product and this exposure can be divided into three stages as follows: stage 1 which considers the pre-administration of the product; stage 2 which considers the administration to the animal and stage 3 which considers the post administration (handling of the product and animal as well as the handling of waste and excreta).

Some key exposure criteria to include in the assessment are given below:

Stage 1 Pre-administration

- Storage areas and storage of chemotherapeutic agents: usually these would require special storage and be kept out of reach of non-authorised personnel, pets and children.
- Preparation areas: requirements of preparation in fume hoods, ventilation,
- Preparation procedures: availability of instructions and procedures and necessary equipment and materials to carry out procedures and personal protection equipment (PPE e.g. goggles, gloves).
- Activities of users during preparation (e.g. to avoid eating, drinking, chewing gum, smoking etc).
- Users who may be pregnant, attempting to become pregnant, breast-feeding, immunosuppressed or medically compromised.
- Users who may have other medical conditions that should be considered (e.g. skin conditions such as eczema).
- Storage of prepared product, if prepared in advance of administration

Stage 2 Administration

- Identification of user: professional/non-professional e.g. veterinarian, animal nurse, kennel/cattery staff, pet owner. It is likely that medicines administered by non-professional users will only be administered by the oral route; if non-professional users are expected to handle and administer other types of products a detailed and justified risk assessment should be provided.

- Frequency of exposure: posology and administration procedures including opening packaging, preparation of dose e.g. breaking of tablets and inhalation of dust.
- Pharmaceutical form and any specialised delivery devices.
- Route of administration, method and instructions for administration.
- Restraint of animals and possible accidental self injection.
- Potential accidental contact e.g. skin and eye contact or accidental self injection.

Stage 3 Post administration and handling of waste and excreta

- Returning unused product to storage (Note: storage conditions and requirements are assessed in Part II of the dossier).
- Disposal of unused product and packaging; specific disposal advice is considered as part of the Environmental Risk Assessment (see below) but some cross reference may be required.
- Disposal or specialised delivery devices (e.g. needles and syringes).
- Handling of treated animal, including handling of waste and excreta.

5.3.4 Hazard identification and characterisation

This assessment should discuss the effects found in the pharmacological and toxicological data (presented in Part III and Part IV of the dossier) and discuss the inherent toxicity and any other harmful effects of the product and summarise the hazards for the user. Generally most of the data required to make a hazard assessment are already in the dossier and additional toxicity studies on the active substance are not necessary. Information on local effects of the product, such as skin and eye irritation, sensitisation and inhalation toxicity may be required depending on the extent of exposure. However, it is possible that a scientific review and assessment considering the overall hazards may remove the necessity to conduct such studies.

Antineoplastic substances may be classified according to the fact that they have effects with or without a threshold value. Substances that have a direct action on DNA (no threshold value) can be expected to have carcinogenic, mutagenic and/or teratogenic potential.

5.3.5 Risk assessment and risk management

Similarly to the approach for discussion of exposure, the assessment of the risks to the user and the recommended user warnings can be considered in three stages followed by an overall summary of the risk management recommendations presenting the advice and warnings for the user. It may also be necessary to present separate advice and warnings for different users (e.g. for the veterinarian and the pet owner) and this should be clearly presented in an understandable style in the product literature.

Some key issues to consider are given below:

Stage 1 Pre-administration and Preparation

Advice on special storage conditions for storage areas and storage of chemotherapeutic agents is required with warnings to be kept out of reach of non-authorised personnel, pets and children. In addition, advice is required on the storage of pre-prepared product, if relevant.

Advice aimed to minimise exposure during preparation of intravenous formulations as well as oral formulations should be given to the professional user who will be preparing these products. This may include recommendations related to possible requirements of preparation in fume hoods and satisfactorily ventilated areas as well as wearing of personal protection equipment such as goggles and gloves. Further risk reduction measures may also include recommendations as to what activities to avoid (e.g. eating, drinking, chewing gum, smoking etc) during preparation and what materials should be available to follow the procedure instructions before starting work (e.g. alcohol to wipe exposed vial tops, re-sealable bags for waste).

According to the risk assessment, users who are pregnant, attempting to become pregnant, breast-feeding, immunosuppressed or medically compromised should not be involved in the preparation of cytotoxic substances and appropriate warnings should be included. In addition, users who may have other medical conditions such as skin conditions (e.g. eczema) will require consideration and, if necessary, appropriate warnings and advice should be included.

Stage 2 Administration

Specific user warnings, precautions and advice on protective clothing and equipment should be given for the administration procedures taking into account the exposure assessment. Clear guidance on how to administer the product should be given including precautionary measures for the user when accidental contact occurs and advice on what to do in these instances. Breaking, cutting or crushing pills may result in dustiness and it is recommended to develop appropriate tablet sizes to minimise the necessity to divide tablets (see also Part II). According to the risk assessment, the administration of substances that have a direct action on DNA (no threshold value) should be limited to professional users;

Stage 3 Post administration and handling of waste and excreta

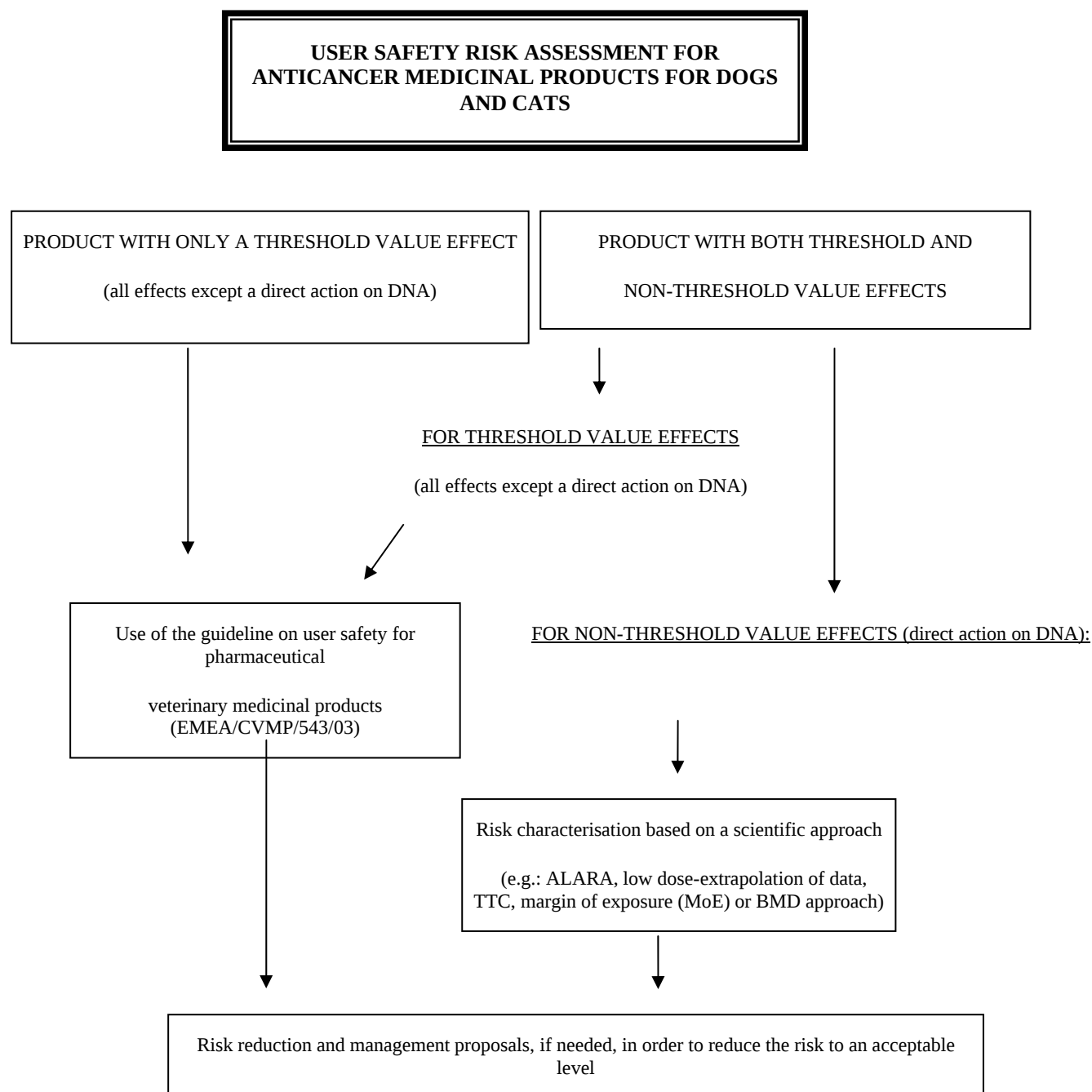
Handling of the product post administration and specifically the storage of tablets or unused product should be considered. Advice on disposal of unused product and packaging is considered as part of the Environmental Risk Assessment (see below)

Handling of waste and excreta from the animal needs to be discussed and recommendations given on instructions, specific warnings and/or precautions related to handling of this waste and excreta. According to the risk assessment for substances that have a direct action on DNA (no threshold value), and in these cases where the recommendations were not able to limit the risk to an acceptable level, a hospitalisation period must be considered and specified in relation to pharmacokinetic data. These recommendations should be based on relevant critical time points that are defined by product specific pharmacokinetics and species-dependency and during which it is important to follow specific safety routines with respect to both, social interactions with the dog or cat as well as in handling of waste and excreta. Parameters that may influence these assessments include clearing time from tissues (tissue half-lives may range from minutes to several days), main excretory routes and whether the substance is excreted in the active form or as inactive metabolites. Examples of issues to consider include:

- Observing the dog or cat to ensure that the medicine is completely taken up by the animal and not spit out or stuck to hair around the mouth.
- Observing the dog or cat during administration and for a short period afterwards for potential acute effects.
- Ensuring safe disposal of faeces or vomit (e.g. flushed down a toilet or put into a plastic bag and placed in a chemotherapeutic hazardous waste container).
- Specific recommendations on disposal/storage of gloves, plastic bags and cat litter should be given, when treatment is performed by the owner(s).
- Walking the dog on a lead to reduce the likelihood that it will defecate or urinate in an inappropriate location.
- Consideration that the area where the patient has urinated may need to be hosed down.
- Recommendations that the dog or cat should only be allowed to defecate and urinate outside children play areas, because most chemotherapeutics are eliminated via faeces and/or urine.
- Precautions may need to be taken so that the dog or cat does not lick e.g. children or pregnant women for a suitable time period following their last treatment, because substances present in the blood might be excreted in the saliva.
- The efficacy of decontamination of the excreta must be shown.

Finally, an overall summary of the risk management proposals should be presented with the recommended warnings and advice to the users.

408 The diagram below presents a Decision Tree showing the decisions required in the user risk
409 assessment.



410

6. ENVIRONMENTAL IMPACT ASSESSMENT

All new applications should be accompanied by an Environmental Impact Assessment (EIA), aiming at protection of ecosystems, and performed in accordance with CVMP/VICH/592/98 VICH Topic GL6 (Ecotoxicity Phase I) Step 7 Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products - Phase I, and CVMP/VICH/790/03 Guideline on Environmental Impact Assessments for Veterinary Medicinal Products (VMPs) Phase II.

In general, products intended for use only in non-food species are qualified for a Phase I assessment and exempted for further testing due to the anticipated low environmental exposure. However, the cytotoxic properties of many anticancer medicinal products would implicate potential ecotoxic properties. The Applicant should discuss if potential ecotoxic effects are anticipated from the mechanism of action and the extent of excretion of active substance. A more detailed exposure assessment should be provided on a case-by-case basis. The prevalence, frequency, duration, and location (at the animal hospital or at home) of treatment and the likelihood that excrements containing active compounds are concentrated locally (at the animal hospital exercise yard) should be discussed. Suitable risk mitigation measures to reduce environmental exposure may be warranted on a case-by-case basis. Secondary human exposure from contact with excreta or other waste material containing active compounds should be dealt with in the User safety assessment (see above) and is not considered in the EIA.

Waste material arising from the use of cytotoxic compounds might be classified as hazardous waste. Thus, the applicant should provide appropriate information in the package leaflet to ensure that the use of the product will be in accordance with the Hazardous Waste Directive 91/689 amended by 94/31.

7. PRECLINICAL AND CLINICAL DOCUMENTATION (PART IV)

As mentioned in the introduction, guidance is given according to the classification of active substances into cytotoxic and non-cytotoxic categories for those cases where such a distinction is considered relevant. Otherwise the recommendations given should be considered valid for all kind of substances. This general information is put first under each main heading.

7.1 *Pharmacological documentation*

The mode of action of the active substance should be presented. Whenever justified, relevant data collected during the development process for authorisation for a medicine for human use could be referred to, irrespectively of the animal species investigated (including the target animal species).

The kinetic profile should be presented as outlined in the guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/EWP/133/99). It is recommended to collect pharmacokinetic data in dose finding/tolerance studies when possible. The studies should be designed to address issues relating to target animal pharmacokinetics and, in addition, user safety i.e. the excretion phase should be well characterised. If feasible, pharmacokinetic studies could be performed in patients; however, collection of rich data might be problematic for ethical reasons. A justification for the selection of either patients or healthy animals should be provided. The use of population kinetics is encouraged.

If the active substance is intended for use in combination with other substances, pharmacodynamic and/or pharmacokinetic interactions should be considered.

The possible capacity for the development of resistance should be discussed and, if possible, the underlying mechanisms presented.

7.2 Target animal tolerance

7.2.1 Cytotoxic substances

For cytotoxic compounds, the draft VICH-TAS guideline is not applicable in all aspects as the “margin of safety”-concept is presumed not to be relevant. Overdose studies are not requested as toxicity is dose limiting. If dose finding is based on the dose-limiting toxicities and the target of toxicity is established and presented in Part III no further target animal tolerance studies are requested. If patients are used in dose finding studies, relevant data on local and systemic tolerance should be collected. For further details on dose determination aspects see below.

7.2.2 Non-cytotoxic substances

Tolerance data should be presented in accordance with the requirements presented in existing guidelines (draft VICH Topic GL 43 on Target Animal Safety, EMEA/CVMP/VICH/393388/06).

If patients are used in dose finding studies, relevant data on local and systemic tolerance should be collected. For further details on dose determination aspects see below.

The applicant should comment on the potential for toxicity resulting from long term use in chronic neoplastic disease. Where this is relevant, provisions should be made for post-marketing surveillance.

7.3 Dose determination studies

Dose determination studies could be performed either in patients or in healthy animals, but applicants should thoroughly justify their choice. If patients previously treated with chemotherapy are included, a listing of those animals who have had prior chemotherapy and their treatment received, must be provided to allow for an examination of the effect of previous therapy on toxicity. The use of treatment naïve patients for dose determination purposes is attractive from a resistance development perspective. If ethical concerns can be appropriately addressed, this could be accepted.

The proposed route of administration, dosage and frequency of administration of the test substance should be described and justified using appropriate data. In the case of a previously explored substance intended for use in humans, data (including DLT/MTD and PK/PD) obtained in the target species for which the present application is intended, may be available and could constitute sufficient support for an appropriate dose.

The method used for dose calculation (e.g. per body surface area, per kg body weight) should be justified, and be performed in a manner that most accurately reduces variability in exposure.

7.3.1 Cytotoxic substances

Dose finding for cytotoxic substances should be based on their toxicological profile. The objective is to define DLT and MTD for defined schedules and modes of administration, and to determine on the basis of this the accurate dose (usually one step below the MTD) to bring forward in further trials. The use of healthy or diseased animals should be justified.

Starting dose and dose increments should be justified with regard to toxicity. If there is no prior experience in the target species, an appropriate starting dose could be the one without severe toxicity in any other species explored. The methodology and scheme used for dose escalation should be described (e.g. modified Fibonacci scheme, accelerated titration, Bayesian designs etc) and the number of animals in each cohort stipulated. If dose finding studies are performed in patients, care should be taken to minimise the number of animals exposed to non-efficacious doses. Within-animal dose escalation may be appropriate where toxicity is clinically insignificant, provided pre-clinical data do not indicate the occurrence of cumulative toxicity.

495 *Evaluation of toxicity*

496 Adverse reactions and target organs for toxicity should be recorded for severity and reversibility, by
497 monitoring clinical signs and general condition, ECG, echocardiography, haematology (e.g. WBC and
498 differential cell count), clinical pathology and urine constituents. These assessments should also
499 include accurate monitoring and quantification of pain/discomfort signs by use of properly validated
500 methods e.g. questionnaires and scores or visual analogue scales (VAS).

501 Furthermore, local reactions at the administration site should be recorded.

502 The toxicity should be graded according to a generally recognised system (e.g. criteria suggested by
503 the Veterinary Co-operative Oncology Group, VCOG), suitably modified or extended in advance if
504 necessary, to include an anticipated toxicity.

505 If death occurs during the study, the cause of death and its possible relationship to the medicinal
506 product under study, must be assessed. Autopsy is strongly recommended. All appropriate, blood and
507 tissue material should be collected for pathology.

508 If cancer patients are included, tumour measurement and response evaluation should be performed by
509 use of relevant and validated markers and imaging techniques as further detailed below.

510 **7.3.2 Non-cytotoxic substances**

511 The aim is to identify a dose/exposure range that shows pharmacological activity/target occupancy,
512 with or without dose limiting toxicity.

513 If the substance has been evaluated previously in the target species in support of development of a
514 medicine for human use, this prior generated data may provide a sufficient base for dose
515 determination.

516 A pre-requisite for performing dose determination studies in healthy animals is that appropriate
517 experimental models or PD-markers are available. The choice of using only either DLT or
518 pharmacological endpoints for dose finding should be justified. If there are no PD measures of activity
519 available in experimental models, dose finding may be performed in patients. Biopsies from tumours
520 (primaries and/or metastatic lesions), and/or in some cases normal tissues, might be needed to obtain
521 data on target saturation or to verify any effect through secondary markers (down stream events).
522 Multiple, serial biopsies are feasible in animals with accessible tumours.

523 The choice of endpoints will depend on the mode of action of the active substance. Tolerance, safety
524 and, if possible, PD measures of activity are appropriate objectives.

525 **7.4 Dose confirmation studies**

526 The aim of these trials is to investigate single-agent activity in a variety of tumour types or in a
527 selected tumour type, or to investigate activity and feasibility of a combination or multimodality
528 regimens. This section is focused on trials where the primary objective is to estimate single-agent anti-
529 tumour activity in animals with a defined tumour type in order to identify substances to bring forward
530 to field trials.

531 If the dose level has been established in patients (not in healthy animals) in a dose determination
532 study, further confirmatory studies may not be considered necessary before proceeding to field studies.
533 If additional support for the appropriate dose is considered necessary in this situation, it might be
534 justified to combine dose confirmation and field studies.

535 *Objectives and design*

536 Dose confirmation trials may be conducted with or without a randomised reference group. If ethical
537 concerns can be overcome, a randomised placebo/BSC controlled design is likely to be preferred,
538 especially if a non-cytotoxic substance is under study (see 6.4.2), as this requires a smaller number of
539 patients. Open label (i.e. non-blinded) studies could be accepted if properly justified, but the
540 limitations for statistical inference should be considered.

541 If dose confirmation studies and field trials are performed in a combined design, an appropriate
542 comparator should be included, as further detailed under 6.6 (Field trials).

543 The dose confirmation studies could be used to fulfil the following objectives:

- 544 • To assess the probability of response in the target tumour type and determine the need for
545 further studies (investigate earlier stages of the disease, combination of substances compare
546 with standard therapy);
- 547 • To further characterise the dose and schedule dependency, with respect to safety and activity;
- 548 • To further characterise the adverse effects of the veterinary medicinal product;
- 549 • Where applicable, to further characterise the best route of administration;
- 550 • If the neoplastic condition in question typically encompasses paraneoplastic syndromes, to
551 evaluate the effect of treatment on these, and vice versa;
- 552 • To identify biomarkers for response, which can be used to better define the target population
553 in field studies.

554 *Selection of animals*

555 The exact definition of the target disease, previous therapy (if any), tumour grade and clinical stage
556 should be recorded.

557 Each eligible animal should have at least one objectively measurable or evaluable indicator of disease
558 for which validated diagnostic methods are available.

559 The target population could be cancer patients with no available established treatment option or
560 patients where an anticancer treatment not approved for veterinary use is potentially available.
561 Treatment naïve animals may be used in the context of “window of opportunity” studies, as long as
562 owner’s informed consent is obtained.

563 *Other concomitant treatment*

564 All chemopotentiator/chemoprotector/resistance-modifying agents also to be used as part of the
565 protocol must be clearly detailed. Ancillary treatments may be given as medically indicated, but must
566 be recorded. Treatments which are contraindicated during the study period should be specified. Any
567 other antineoplastic therapy should be not permitted, unless specifically described in the treatment
568 protocol during the study period. If another antineoplastic therapy is needed, the animal should be
569 removed from the study. Should concomitant surgery or radiotherapy be used, the treated area may
570 only be used for response assessment if the purpose is to explore a multimodality treatment protocol.

571 *Treatment protocol*

572 A clearly defined treatment protocol should be provided (for further details, refer to glossary). The
573 dose and schedule and the potential adjustments and the criteria for these adjustments should be
574 clearly defined. In addition, relevant information in regard to ancillary treatment (e.g. diuresis)
575 required to obtain the anticipated effect or to avoid toxicity should be given.

576 *Termination and conclusions*

577 The duration of the study should be adequate to obtain data for an accurate report on:

- 578 • Adequacy of the studied dose and/or schedule;
- 579 • Adequacy of rules for dose reduction and dose escalation;
- 580 • Toxicity, including cumulative toxicity and if feasible also long term effect;
- 581 • The effects on disease related signs of pain/discomfort.

582 **7.4.1 Cytotoxic substances**

583 *Dose and schedule*

584 Frequently, pre-defined rules will be applied to cease treatment if the efficacy of the treatment is
585 deemed too low or toxicity deemed too high. Information should be provided outlining dose
586 modifications relating to the severity of the observed toxicity. Rules for dose escalation in case of low
587 toxicity should be considered. Rules for dose reduction in case of high toxicity should be considered.

588 *Evaluation of toxicity*

589 The evaluation of adverse reactions should be conducted at predetermined intervals. Any evidence of
590 cumulative toxicity should be recorded and estimated as a function of total dose. This should be
591 specifically studied according to target organ or function. Standardised toxicity criteria should used,
592 e.g. VCOG (Veterinary Co-operative Oncology Group), suitably modified or extended in advance, if
593 necessary, to include an anticipated toxicity.

594 *Evaluation of activity*

595 The method(s) to be used to measure and evaluate activity should be stated and justified in the study
596 protocol.

597 An objective response is defined as a measurable reduction in the tumour burden, assessed by
598 reduction of the target lesion/other indicator using justified procedures.

599 The effect on symptoms related to a paraneoplastic syndrome could also be used to assess response.

600 When multiple lesions are present, representative lesions may be selected and defined for the
601 measurement and assessment of objective response at the start of the study, but progression of other
602 lesions and the development of new lesions should be assessed during the study period.

603 It is recognised that imaging techniques may be inappropriate for the assessment of certain tumours,
604 e.g. superficial lesions where photo documentation or callipers may be used.

605 The ORR (CR and/or PR) should be documented according to international standards (e.g. RECIST,
606 or WHO criteria). Modifications of these criteria may be appropriate in certain situations but should be
607 justified and defined *a priori* in the study protocol. The study protocol should provide details as
608 regards to criteria for response/progression and timing of response assessments. External independent
609 review of tumour response is encouraged, according to the objectives of the trial. In evaluating ORR,
610 data for all patients entered into the trial should be reported. Where ORR in the per-protocol analysis
611 set is considered to be of primary interest, then data for all patients included in the trial should also be
612 reported. Data on TTP should be reported, if feasible. The use of tumour markers and other dynamic
613 measures of activity is encouraged, especially in molecularly targeted therapies.

614 In animals with symptomatic disease at base line, the assessment of clinical sign control (signs of
615 pain/discomfort) is considered important, provided a randomised trial is undertaken. If a combined
616 dose confirmation-field trial design is applied, endpoints reflecting quality of life should always be
617 included.

618 7.4.2 *Non-cytotoxic substances*

619 *Study design and measures of activity*

620 The aim is to explore the effects on a specific tumour type or in tumour types with a common
621 target/molecular lesion, using a pre-defined treatment protocol.

622 These substances may act through growth inhibition or by eliciting early tumour shrinkage, and the
623 same substance may act differently in this respect, in different subgroups of patients. This has impact
624 on whether TTP or ORR is the most appropriate endpoint for anti-tumour activity assessment. TTP is
625 often the best choice. Where ORR is used, modification of the response criteria may be required if the
626 product causes e.g. tumour necrosis or oedema. Any modification of the response criteria should be
627 described and defined *a priori* in the protocol.

628 To enable accurate assessment of activity studies should preferably include patients with a
629 documented progressive disease.

630 Since spontaneous regression fulfilling the criteria for at least partial response is highly unlikely, ORR
631 is considered an interpretable measure even if a control group is not used.

632 Time to tumour progression (TTP) is a function of “underlying tumour growth rate” and of the activity
633 of the anti-cancer substance. The underlying growth rate is hard to define, thus a randomised control
634 group using a reference product or placebo, is likely to be required for the proper assessment of effect.
635 To enable comparison of tumour development, the same assessment time-points must be used for all
636 animals.

637 No ideal design exists for exploratory studies for substances assumed to mainly elicit tumour growth
638 control. Possible options are listed below (note that some of these may also be suitable for cytotoxic
639 substances):

- 640 • Randomised dose comparative trial – comparing the lowest dose likely to be
641 pharmacologically active, with a higher dose.
- 642 • Randomised withdrawal of therapy – patients with non-progressive disease are withdrawn
643 from therapy after a set time.
- 644 • Within patient comparison of TTP - compare TTP of the last prior therapy with TTP of the
645 test substance.
- 646 • Randomised study including a substance known to be active in the selected population, or
647 placebo/BSC, if justified.
- 648 • TTP without an internal reference – last option, in combination with a systematic literature
649 review. Assessment of the percentage of progression-free patients after a set time point may
650 be a relevant end point in this situation

651 If a randomised blinded design is used, quality of life assessments and assessment of control of
652 clinical signs are encouraged.

653 *Evaluation of toxicity*

654 The same assessment principles as those stated for cytotoxic compounds should be applied.

655 7.5 *Dose finding/dose confirmation for combination therapies*

656 Different cytotoxic medicinal products could be used in combination, in order to increase the anti-
657 tumour activity at an acceptable level of toxicity, by combining products with incompletely
658 overlapping toxicity and partly non-overlapping pre-requisites for activity/resistance. This approach is
659 acceptable and may also include combinations with non-cytotoxic products. Such combination
660 therapies are almost exclusively based on treatment protocols combining single-agent medicinal
661 products, and fixed combination products are very uncommon in human oncology. Nevertheless, if

662 approval is sought for fixed combination product, the Guideline on Pharmaceutical Fixed Combination
663 Products (EMA/CVMP/83804/2005) may provide additional useful information

664 If the mono-therapy is registered for veterinary use, or sufficient bibliographic support exists
665 regarding the effect of the mono-therapy, a randomised trial comparing the combination therapy with
666 one of the components as a mono-therapy could be performed for dose confirmation purposes,
667 including, for example, toxicity, ORR, TTP, HRQoL, and control of clinical signs as appropriate
668 endpoints.

669 **7.6 Field trials**

670 Field trials should be designed with the aim to establish the benefit-risk profile of the experimental
671 medicinal product, including supportive measures, in a well-characterised target population of
672 relevance for clinical practice. These studies should preferably be randomised and reference or
673 placebo controlled. The target population as well as the reference regimen should be defined by
674 disease, stage and, if applicable, prior lines of anticancer therapy.

675 **7.6.1 Field safety**

676 Safety assessment should be performed using established and well defined criteria e.g. those suggested
677 by VCOG. Since quality of life is an essential issue in anticancer therapy for dogs and cats, adverse
678 events should be carefully monitored and reported. Similarly, the presentation of withdrawals from a
679 study should include a detailed report on safety related reasons for discontinuation.

680 **7.6.2 Design**

681 *Randomisation and blinding*

682 Randomisation and blinding is preferred. However, in some cases blinding may not be an option due
683 to differences in toxicity between study regimens or due to safety concerns. Randomised open label
684 studies could be accepted if properly justified, although it must be acknowledged that this design
685 influences the availability of accurate endpoints. Single armed field studies (i.e. studies without
686 control group) are generally not accepted. However, in case the applicant can convincingly justify the
687 omission of a control arm, which would include the demonstration of exceptional results regarding
688 tolerance and efficacy, a single armed design may in rare cases be considered sufficient. In such a
689 situation additional bibliographic support is expected.

690 A period of follow up should be included which is relevant to the disease in question.

691 *Study endpoints*

692 The overall aim is to improve quality of life during the remaining lifetime (palliative approach), but
693 the owner is also likely to expect a prolongation of the expected life time. Endpoints should be
694 selected to properly reflect to what extent the medicinal product fulfils these expectations.

695 Endpoints should provide a valid and reliable measure of clinical benefit in the patient population
696 described by the inclusion criteria. This assumption regarding the selected endpoints should be
697 justified.

698 Endpoints could be categorised into those relating to A) tumour development B) survival, and
699 C) health related quality of life, acknowledging an overlap between these categories for several
700 endpoints.

701 *A) Endpoints relating to tumour development*

702 This category includes e.g. ORR (complete or partial), TTP, time of remission, tumour stabilisation,
703 and the assessment of different tumour markers. Each of these parameters has to be properly defined,
704 preferably by use of generally accepted criteria where such are available. To reduce the need for
705 frequent monitoring some of these parameters could be used in a fixed-time point comparison design.

In this situation prior knowledge regarding expected distribution of events is required. Appropriate endpoints from this category should normally be reported. However, a conclusion on treatment benefit cannot be based solely on the outcome of any of these endpoints, but the effects on life quality must also be reported.

B) Endpoints relating to survival

In human medicines, endpoints relating to survival (OS, PFS, DFS, EFS) are considered primary parameters for efficacy assessment. Although a prolonged survival time may not be considered equally important for veterinary applications, survival endpoints are robust from a methodological perspective and should normally be reported. However, any possible bias occurring due to the use of euthanasia has to be considered (see below). Treatment benefit cannot be judged solely on survival outcome; the effects on life quality must also be explored.

C) Endpoints relating to quality of life

In patients with tumour-related symptoms at baseline, or symptoms related to paraneoplastic syndrome, this category could include: control of clinical signs, time to symptomatic tumour progression, and pain/discomfort/vitality assessments. In addition, this category could also include performance parameters such as food intake and weight or body condition score changes.

These endpoints are considered to be of particular importance and an appropriate combination of these endpoints, aimed at demonstrating the overall effect of treatment on life quality, should always be included in a field study. However, a positive outcome based solely on parameters from this category - all being subjective in nature - could not be considered sufficient to demonstrate treatment benefit. A positive outcome in any endpoint from either of the other two categories is also required.

The fact that these endpoints are subjective in nature has to be considered in the study design. This would suggest that trials should be performed blinded, and deviation from such a design has to be justified. Each parameter has to be defined and use of scales is encouraged as it enables a proper statistical evaluation.

Impaired quality of life is not acceptable unless there is convincing historical data suggesting that treatment is connected to a restricted period of discomfort followed by a dramatic beneficial effect regarding longevity and life quality.

Primary and secondary endpoints

A primary endpoint should be selected from categories A or B, which contain those with the best potential of being objectively measurable. However, a positive outcome in a single primary endpoint from either of these categories is not considered sufficient for a positive benefit conclusion; additional support from relevant secondary endpoints, of which a sufficient number of parameters should be from group C, is also required.

Reference therapy

The choice of reference regimen should be justified and normally this regimen should be selected from best available, evidence-based therapeutic options (i.e. a widely used regimen with a favourable benefit-risk convincingly documented through randomised trials). Reference products could be, but are not limited to, veterinary medicinal products approved for the indication in the target species. If an approved product exists, this product should be the first choice. If no sufficient bibliographic evidence exists to support the use of a reference regimen for a specific target population, a regimen used in clinical practice with a well-documented and positive safety profile is acceptable.

However, a placebo controlled design should also be considered, since this would allow an accurate assessment of efficacy presumably by use of a smaller number of animals as compared to the previously mentioned alternatives. In this design option, ethical concerns could be met by e.g. a fixed treatment time design followed by a shift to best available treatment, or by increasing the allocation ratio between experimental product and control. However, in the latter alternative, the loss of statistical power should be considered. Independent of design, BSC should always be available for all patients included, although the potential effect on study outcome must be considered and reported.

A non-inferiority design is also considered acceptable in situations where the best available reference therapy consists of a well documented treatment strategy including a substance/a combination of substances not approved for veterinary use for this indication.

Single substance and combination therapies

The experimental regimen should be compared with the “best available” comparator. If the experimental agent (A) is added to an established regimen (B), superiority of AB vs. B alone should be demonstrated and the benefit-risk balance should be shown to be favourable.

In case of substitution studies, i.e. studies where a component (C) of an established regimen (BC) is replaced with an experimental agent (A) and if non-inferiority (BC vs. BA) is the aim, the contribution of C to the activity of BC has to be well-defined.

Regarding drug resistance modifiers, radio/chemo sensitisers and chemoprotective agents, the design should be straight forward: The combination of the tested agent (A) and the established regimen (B) should be demonstrated to be more active and beneficial than the established regimen (B) on its own.

(Neo)adjuvant therapy

For the combination of pharmaceutical anticancer therapy and/or radiological and/or surgical therapy, the objective may be to improve overall outcome and/or to preserve organs. The effect of treatment should be explored by use of appropriate endpoints as mentioned above, and at least non-inferiority to the comparator (surgery/radiation minus chemotherapy) should be documented. The selection of endpoints should be justified.

Interactions

Since for some compounds the anti-tumoural activity may be influenced by feed constituents, the potential interactions with food and concurrent use of nutraceuticals should be addressed.

7.6.3 Methodological considerations

Assessment of life quality

It is crucial to identify or develop properly validated tools for the assessment of treatment-related effects on life quality and for the occurrence (and magnitude) of pain and discomfort. Recording bias/variation is likely to occur due to the fact that the owners, who presumably will provide some of this information, may show variation in tolerance/perceptiveness with regard to clinical signs. The quality of this information may be improved by ensuring that assessments are always performed by the same person or blinding of the owner to treatment etc.

Euthanasia

Variation in the assessment of survival related endpoints will partly be due to owner/veterinary-dependent criteria for the proper time for euthanasia. This will decrease the possibility of showing a significant effect of treatment (given such an effect exists). In addition, bias may occur due to a systematic variation in these criteria between e.g. clinics and countries. Thus, survival estimates have to be justified in the context of these concerns. Necropsy should be encouraged in all cases after euthanasia or death, regardless of the cause of death.

Fixed-time endpoints

In open labelled studies and instead of PFS/DFS being repeatedly assessed, a fixed-time point comparison of the proportion of patients that are event-free has some merits. From a statistical perspective, this reduces to some extent the sensitivity of the trial to detect differences in the distribution of the times to events between treatment groups but this procedure is less likely to cause detection bias and reduces the need for resource consuming and frequent imaging.

798 8. GLOSSARY

799 **BSC:** Best supportive care – include antibiotics, nutritional support, correction of metabolic disorders,
800 optimal symptom control and pain management (including radiotherapy), etc. and does not include
801 tumour specific therapy

802 **Chemosensitizer (or drug resistance modifier):** A compound without own anti-tumour activity
803 which increases the activity through pharmacodynamic interaction with anti-tumour compound(s).

804 **Chemoprotectant:** A compound which counteracts the activity of anti-tumour compounds on normal
805 tissue without (or clearly less) affecting the anti-tumour activity.

806 **CR:** Complete response

807 **CRF:** Case report form

808 **Cytotoxic:** Anticancer compounds inducing irreversible lethal lesions through interference with DNA
809 replication, mitosis, etc. following short term exposure in non-clinical studies.

810 **DFS:** Disease-free survival (time from randomisation to recurrence or death from any cause)

811 **DLT:** Dose limiting toxicities

812 **DNA reactive:** A DNA reactive substance is one that interacts directly with DNA and so produces a
813 direct genotoxic effect. Such substances can be considered to have the potential to damage DNA at
814 any level of exposure and such damage may lead/contribute to tumour development

815 **EFS:** Event-free survival (variable protocol specific definitions, e.g. time from randomisation to
816 objective tumour progression, secondary malignancy, or cancer-related death.

817 **HRQoL:** Health Related Quality of Life

818 **MTD:** Maximum tolerated dose, often defined by dose-limiting toxicity occurring in at least 2 of 6
819 patients so that further dose-escalation is not undertaken.

820 **Non-cytotoxic:** Anticancer compounds not belonging to the class of cytotoxic compounds (e.g.
821 antisense compounds, signal transduction, angiogenesis or cell cycle inhibitors, and immune
822 modulators).

823 **Non DNA reactive:** A non DNA-reactive substance is one that does not interact directly with DNA.
824 Such a substance may nevertheless exert indirect genotoxic effects. For such a substance it may be
825 possible to define a toxicological threshold value below which there is no appreciable increase in the
826 risk of tumour development

827 **ORR:** objective response rate (ORR) is the proportion of patients with tumour shrinkage of a pre-
828 defined amount for a predefined minimum amount of time. Response duration is usually measured
829 from the time of initial response until documented tumour progression. ORR is usually defined as the
830 sum of complete (CR) and partial responses (PR).

831 **OS:** Overall survival (time from randomisation to death from any cause)

832 **PD:** Pharmacodynamics

833 **PFS:** Progression-free survival (time from randomisation to objective tumour progression or death
834 from any cause)

835 **PK:** Pharmacokinetics

836 **PR:** Partial response

837 **Toxicological threshold value:** the threshold value below which effects injurious to health do not
838 occur, even with life long exposure. In the context of this guideline the term toxicological threshold
839 value is used with reference to non-DNA reactive genotoxic substances (see above).

840 **Treatment Protocol:** A treatment protocol is a plan for a course of medical or multimodality
841 treatment of a patient with a certain diagnosis. The protocol contains dose rate, dose frequency and
842 administration instructions for one or several medicines and schedule for possible other treatment
843 modalities (radiation therapy for example). The treatment protocol may preferably also contain
844 information on nadir of each active ingredient and on timing of subsequent whole blood samples for
845 differential count.

846 **TTF:** Time to treatment failure (time from randomisation to discontinuation of therapy or add-on of
847 new anti-cancer therapy for any reason including death, progression, toxicity)

848 **TTP:** Time to tumour progression (time from randomisation to observed tumour progression,
849 censoring for death without progression)

850 **REFERENCES (SCIENTIFIC AND / OR LEGAL)**

- 851 • Guideline on the Summary of Product Characteristics for Pharmaceutical Veterinary
852 medicinal products ([DG ENTR/F/2/KK D\(2006\)](#))
- 853 • [CVMP](#) and [CVMP/CHMP](#) quality guidelines
- 854 • [VICH quality guidelines](#)
- 855 • [VICH Topic GL 6](#) (Environmental Impact Assessment (EIAS) for Veterinary Medicinal
856 Products - Phase I - CVMP/VICH/592/98)
- 857 • [VICH Topic GL 38](#) (Environmental Impact Assessments for Veterinary Medicinal Products
858 (VMPs) - Phase II - CVMP/VICH/790/03)
- 859 • CVMP Guideline on user safety for pharmaceutical veterinary medicinal products
860 ([EMEA/CVMP/543/03](#))
- 861 • [VICH Topic GL9](#) (Good Clinical Practice - CVMP/VICH/595/98)
- 862 • Guideline on the evaluation of the safety of veterinary medicinal products for the target
863 animal ([7AE2a Volume 7](#))
- 864 • CVMP Guideline on statistical principles for veterinary clinical trials ([EMEA/CVMP/816/00](#))
- 865 • CVMP Guideline for the conduct of pharmacokinetic studies in target animal species
866 ([EMEA/CVMP/133/99](#))

867 **Additional documentation which might be of use for the applicant:**

- 868 • Guideline on the Evaluation of Anticancer Medicinal Products in Man ([CPMP/EWP/205/95](#))
- 869 • Guideline on the Evaluation of Anticancer Medicinal Products in Man *Addendum* on
870 Paediatric Oncology ([CPMP/EWP/569/02](#))
- 871 • Note for guidance on the pre-clinical evaluation of anticancer medicinal products
872 ([CPMP/SWP/997/96](#)).
- 873 • Guideline on Clinical Trials in Small Populations ([CHMP/EWP/83561/05](#))
- 874 • Guideline on the Choice of the Non-Inferiority Margin ([CPMP/EWP/2158/99](#))
- 875 • Guideline on Quality Data Requirements for Veterinary Medicinal Products intended for
876 Minor Uses or Minor Species ([EMEA/CVMP/QWP/128710/2004](#))
- 877 • Guideline on Safety and Residue Data Requirements for Veterinary Medicinal Products
878 intended for Minor Uses or Minor Species ([EMEA/CVMP/SWP/66781/2005](#))
- 879 • Guideline on Efficacy and target animal safety data requirements for veterinary medicinal
880 products intended for minor uses or minor species ([EMEA/CVMP/EWP/117899/2004](#))
- 881 • Draft [VICH Topic GL43](#) at Step 4 Guideline on target animal safety for pharmaceuticals
882 (EMEA/CVMP/VICH /393388/06)