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Guideline on dossier requirements for anticancer medicinal products for dogs and cats

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This guideline replaces the guideline on dossier requirements for anticancer medicinal products for dogs and cats (EMA/CVMP/28510/2008).

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*The current revision consists of administrative changes made in order to align the guideline to the new definitions and terminology provided by Article 4 of Regulation (EU) 2019/6. The references to the legislation applicable and other scientific guidelines have also been updated. As no changes were made to the scientific content, no concept paper and no public consultation were deemed necessary.



Guideline on dossier requirements for anticancer medicinal products for dogs and cats

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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 (background)

Anticancer medicinal therapy is an established part of small animal clinical practice offered to dogs and cats. In the past, anticancer therapy in these species was primarily based upon products registered for use in humans, however in recent years, several products for dogs as a target species were developed. In accordance with Article 112 of Regulation (EU) 2019/6, veterinarians are also allowed to use medicinal products outside the terms of the marketing authorisation in dogs and cats where there is no authorised veterinary medicinal product available.

Authorisation of anticancer medicinal products for veterinary use is generally to be encouraged, as this would ensure that the use of such compounds is based on sufficient information regarding efficacy and safety for the target species and furthermore that appropriate precautions for humans is implemented. 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 in most situations the objective would be palliation or to postpone disease progression and the development of clinical signs. 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 or the veterinary surgeon 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 should be considered as important as 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 4), 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. Relevant activity 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. Regarding user safety issues the Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03) is fully applicable for cytotoxic as well as non-cytotoxic products except for those substances which are DNA-reactive. For DNA reactive substances special precautions may be needed and guidance on how to ensure safe use of such products is detailed in section 5 of 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 2 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 3 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 clinical trials 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 Regulation (EU) 2019/6. 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. Quality documentation (Part 2)

4.1. Chemical, Pharmaceutical and Biological Data

The requirements for Marketing Authorisations are given in Regulation (EU) 2019/6, 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 parenteral products. On the other hand, changes such as the use of syringes designed to measure very low volumes of an injection, or reconstitution of a powder for oral solution to a lower concentration than prescribed for human use, 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 1 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.
7. A brief paper considering how the correct dose will be measured and administered in practice for the proposed target species/indication, together with a justification for the proposed SPC statements designed to help ensure accuracy of dosing.
8. Supplementary in-use studies as appropriate.

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

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

Items 7 and 8 will be assessed.

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

4.1.2 Development of an entirely new medicine for veterinary use

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

Active substance batch analysis data¹

- Data required for 2 pilot batches only.

Active substance stability²

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

Final product process validation data

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

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

Final product batch analysis data

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

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, coated tablets are the preferred pharmaceutical form. Whilst whole capsules prevent the user from direct contact with the formulation, hard capsule shells may sometimes be damaged during administration and therefore the type of capsule to be used needs to be considered carefully. The strength of tablets should be formulated to allow precise dosing for different animal sizes/weights, 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

To minimize the risk for accidental intake of the drug product by children, oral dosage forms should be packed in child resistant containers/closures. This should be demonstrated e.g. by compliance with the International Standard (EN ISO 8317) Child-resistant packaging – Requirements and testing procedures for recloseable packages and/or the International Standard (EN 14375) Child-resistant non-recloseable packaging for pharmaceutical products – Requirements and testing.

To ensure the user does not come into direct contact with a cytotoxic formulation, the use of suitable, integral dosing devices should be considered, where appropriate, for example an integrated dropper device for oral solutions.

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.*

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 3)

The requirements for Marketing Authorisations are given in Regulation (EU) 2019/6, 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 4 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. Generally, most of the toxicity data required are already part of a product dossier (Part 3A Safety Documentation). The need for any additional studies depends on any identified gaps in the data. 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 (EMA/CVMP/543/03) 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 exists (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 (EMA/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 (EMA/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 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 (EMA/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 proposals should provide suitable advice which should be both for in-clinic and home situations/environment settings.

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 Hazard identification and characterisation

This assessment should discuss the effects found in the pharmacological and toxicological data (presented in Part 3 and Part 4 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.

5.3.4 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-authorized personnel, pets and children.
- Preparation areas: requirements of preparation in biological safety cabinets, 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: it is important to clearly identify the users who will be administering the product: veterinarian, animal nurse, kennel/cattery staff, pet owner. It is likely that medicines administered by users other than veterinarians will only be administered by the oral route; if users other than veterinarian or veterinarian assistants 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 2 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 of specialised delivery devices (e.g. needles and syringes).
- Handling of treated animal, including handling of waste and excreta.

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-authorized 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 user who will be preparing these products. This may include recommendations related to possible requirements of preparation in biological safety cabinets 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.

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 2). According to the risk assessment, the administration of substances that have a direct action on DNA (no threshold value) should be limited to veterinarians;

Stage 3 Post administration and handling of waste and excreta

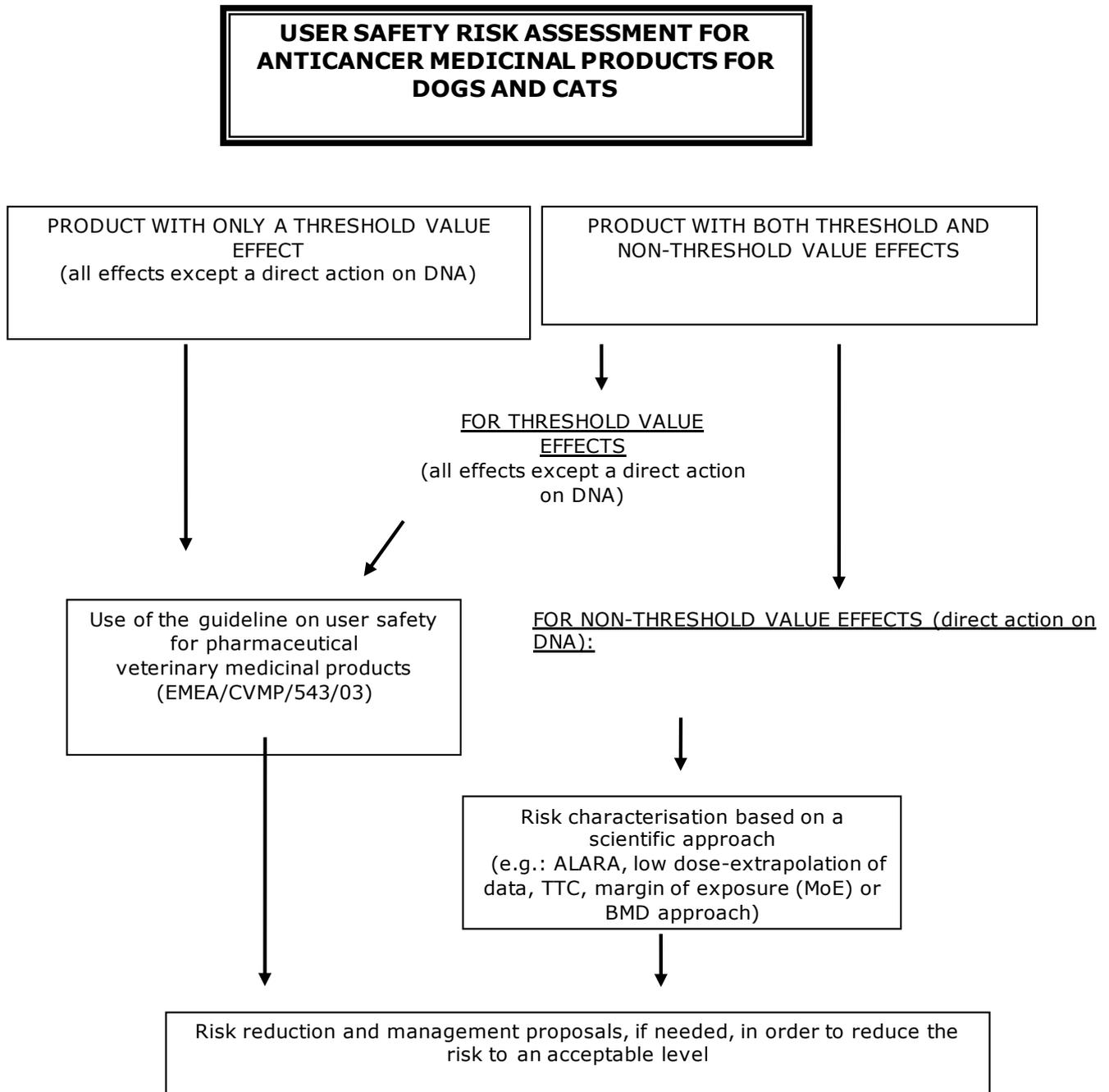
Handling of the product post administration and specifically the storage of tablets or unused product should be considered. Advice on disposal of unused product and packaging is considered as part of the Environmental Risk Assessment (see below)

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 may 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 spat out or stuck to hair around the mouth.
- Observing the dog or cat during administration and for an appropriate period afterwards for potential acute effects.
- Ensuring safe disposal of faeces or vomit (e.g. pet owners: put into a plastic bag and dispose of in household waste; veterinarians: in veterinary surgery put into 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 (e.g. children's playground).
- 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 children or pregnant women will not be licked by the dog or cat for a suitable time period following the last treatment, because substances present in the blood might be excreted in the saliva.

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

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



5.4 Environmental Impact Assessment

All new applications should be accompanied by an Environmental Risk Assessment (ERA), aiming at protection of the environment, and performed in accordance with VICH GL6 (Ecotoxicity Phase I) - Guideline on environmental impact assessment (EIAS) for veterinary medicinal products - Phase I (CVMP/VICH/592/98), VICH GL38 (Ecotoxicity Phase II) - Guideline on environmental impact assessment for veterinary medicinal products - Phase II (CVMP/VICH/790/03), and the CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMA/CVMP/ERA/418282/2005).

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 ERA.

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 Directive 2008/98/EC.

6. Efficacy documentation (Part 4)

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.

6.1 Pre-clinical studies

6.1.1 Pharmacological data

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 on conduct of pharmacokinetic studies in target animal species (EMA/CVMP/EWP/133/1999). 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.

6.1.2 Target animal tolerance

6.1.2.1 Cytotoxic substances

For cytotoxic compounds, the VICH GL43 on target animal safety for veterinary pharmaceutical products 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.

6.1.2.2 Non-cytotoxic substances

Tolerance data should be presented in accordance with the requirements presented in existing guidelines (VICH GL43 on target animal safety for veterinary pharmaceutical products, EMEA/CVMP/VICH/393388/2006).

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.

6.1.3 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.

6.1.3.1 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 pre-clinical studies and clinical 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.

Evaluation of toxicity

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

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

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

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

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

6.1.3.2 Non-cytotoxic substances

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

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

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

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

6.1.4 Dose confirmation studies

The aim of these studies is to investigate single-agent activity in a variety of tumour types or in a selected tumour type, or to investigate activity and feasibility of a combination or multimodality

regimens. This section is focused on studies where the primary objective is to estimate single-agent anti-tumour activity in animals with a defined tumour type in order to identify substances to bring forward to clinical trials.

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

Objectives and design

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

If dose confirmation studies and clinical trials are performed in a combined design, an appropriate comparator should be included, as further detailed under 6.2 (Clinical trials).

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

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

Selection of animals

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

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

The target population could be cancer patients with no available established treatment option or patients where an anticancer treatment not approved for veterinary use is potentially available. Treatment naïve animals may be used in the context of “window of opportunity” studies.

Other concomitant treatment

All chemopotentiator/chemoprotector/resistance-modifying agents also to be used as part of the protocol must be clearly detailed. Ancillary treatments may be given as medically indicated, but must be recorded. Treatments which are contraindicated during the study period should be specified. Any other antineoplastic therapy as well as any steroid treatment should be not permitted, unless

specifically described in the treatment protocol during the study period. If another antineoplastic therapy is needed, the animal should be removed from the study. Should concomitant surgery or radiotherapy be used, the treated area may only be used for response assessment if the purpose is to explore a multimodality treatment protocol.

Treatment protocol

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

Termination and conclusions

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

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

6.1.4.1 Cytotoxic substances

Dose and schedule

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

Evaluation of toxicity

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

Evaluation of activity

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

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

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

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

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

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

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

6.1.4.2 Non-cytotoxic substances

Study design and measures of activity

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

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

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

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

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

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

- Randomised dose comparative study – comparing the lowest dose likely to be pharmacologically active, with a higher dose.
- Randomised withdrawal of therapy – patients with non-progressive disease are withdrawn from therapy after a set time.

- Within patient comparison of TTP - compare TTP of the last prior therapy with TTP of the test substance.
- Randomised study including a substance known to be active in the selected population, or placebo/BSC, if justified.
- TTP without an internal reference – last option, in combination with a systematic literature review. Assessment of the percentage of progression-free patients after a set time point may be a relevant end point in this situation.

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

Evaluation of toxicity

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

6.1.5 Dose finding /dose confirmation for combination therapies

Different cytotoxic medicinal products could be used in combination, in order to increase the anti-tumour activity at an acceptable level of toxicity, by combining products with incompletely overlapping toxicity and partly non-overlapping pre-requisites for activity/resistance. This approach is acceptable and may also include combinations with non-cytotoxic products. Such combination therapies are almost exclusively based on treatment protocols combining single-agent medicinal products, and fixed combination products are very uncommon in human oncology. Nevertheless, if approval is sought for fixed combination product, the CVMP Guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005) may provide additional useful information.

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

6.2 Clinical trials

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

6.2.1 Clinical safety

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

6.2.2 Design

Randomisation and blinding

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

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

Study endpoints

The overall aim is to postpone disease progression to a clinically meaningful extent and to maintain or to improve quality of life during the remaining lifetime (palliative approach), and the owner is likely to expect a prolongation of the expected life time. Endpoints should be selected to properly reflect to what extent the medicinal product fulfils these expectations.

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

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

A) Endpoints relating to tumour development

This category includes e.g. TTP, time of remission, tumour stabilisation, and the assessment of different tumour markers.

ORR is normally not accepted as a primary endpoint for confirmatory trials. To potentially accept response assessments for this purpose a clinically relevant proportion of complete responders (CR) should be demonstrated and additional efficacy data to support the benefit of treatment in relation to the natural course of the disease or in comparison to other treatments is expected.

Each of the parameters has to be properly defined, preferably by use of generally accepted criteria where such are available. To reduce the need for 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. Endpoints should be selected to accurately reflect the influence of treatment on the specific cancer disease.

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 clinical trial. However, a positive outcome based solely on parameters from this category – which are often 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 some of 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 evidence demonstrating 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 radiation 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 whenever relevant.

Other concomitant treatment

In accordance with the guidance given for dose confirmation studies (section 7.4) concomitant treatments are allowed but must be documented in the protocol and their potential effect on efficacy should be evaluated.

6.2.3 Methodological considerations

Assessment of life quality

It is crucial to identify or develop appropriate 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. Post mortem examination should be encouraged in all

cases after euthanasia or death, regardless of the cause of death, whenever possible and allowed by the owner..

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.

Definitions

BSC

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

Chemosensitizer (or drug resistance modifier)

A compound without own anti-tumour activity which increases the activity through pharmacodynamic interaction with anti-tumour compound(s).

Chemoprotectant

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

CR

Complete response.

CRF

Case report form.

Cytotoxic

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

DFS

Disease-free survival (time from randomisation to tumour recurrence; metastasis or death from any cause).

DLT

Dose limiting toxicities.

DNA reactive

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

EFS

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

HRQoL

Health Related Quality of Life.

MTD

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

Non-cytotoxic

Anticancer compounds not belonging to the class of cytotoxic compounds (e.g. antisense compounds, signal transduction, angiogenesis or cell cycle inhibitors, and immune modulators).

Non DNA reactive

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

ORR

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

OS

Overall survival (time from randomisation to death from any cause).

PD

Pharmacodynamics

PFS

Progression-free survival (time from randomisation to objective tumour progression or death from any cause).

PK

Pharmacokinetics.

PR

Partial response.

Toxicological threshold value

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

Treatment Protocol

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

TTF

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

TTP

Time to tumour progression (time from randomisation to observed tumour progression, censoring for death without progression).

References (scientific and/or legal)

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes

Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives

[CVMP](#) and [CVMP/CHMP](#) quality guidelines

[VICH quality guidelines](#)

VICH GL6 (Ecotoxicity Phase I) - Guideline on environmental impact assessment (EIAS) for veterinary medicinal products - Phase I (CVMP/VICH/592/98)

VICH GL38 (Ecotoxicity Phase II) - Guideline on environmental impact assessment for veterinary medicinal products - Phase II (CVMP/VICH/790/03)

CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMA/CVMP/ERA/418282/2005)

CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03)

VICH GL9 - Guideline on good clinical practices (CVMP/VICH/595/98)

OECD Principles on Good Laboratory Practice

VICH GL43 - Guideline on target animal safety for veterinary pharmaceutical products (EMA/CVMP/VICH/393388/2006)

CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)

CVMP Guideline on conduct of pharmacokinetic studies in target animal species (EMA/CVMP/EWP/133/1999)

CVMP guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005)

Additional documentation which might be of use for the applicant:

Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95)

Note for guidance on evaluation of anticancer medicinal products in man - *Addendum* on paediatric oncology (EMA/CPMP/EWP/569/02)

ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals (EMA/CHMP/ICH/646107/2008).

Guideline on clinical trials in small populations (CHMP/EWP/83561/05)

Guideline on the choice of the non-inferiority margin (EMA/CPMP/EWP/2158/99)

CVMP Guideline on safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 (EMA/CVMP/345237/2020)

CVMP Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 (EMA/CVMP/52665/2020)

ECVIM-CA. Guidelines for preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine (ECVIM-CA 28/0907)