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Veterinary Medicines and Inspections

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ONCOLOGY FOCUS GROUP MEETING

MINUTES OF THE MEETING, 25 APRIL 2007

Welcome and introduction to the guideline

Jill Ashley-Smith (EMEA) welcomed all the participants to the meeting and asked all to introduce themselves. The meeting was attended by representatives from regulatory authorities, pharmaceutical industry, university and experts in the field of veterinary oncology. A number of participants are/had been involved in research of veterinary oncology products and this was declared in the beginning of the meeting.

The chairman, Michael Holzhauser-Alberti (AFFSA, France), gave a brief overview of the draft guideline indicating that the guideline is intended to address the dossier requirements for veterinary oncology products for dogs and cats, covering areas of efficacy, target animal safety, user safety and environmental safety. Aspects of these areas would be addressed during the Focus Group meeting and feed-back from participants would be welcome, in particular on those areas highlighted by the presenters.

EFFICACY

Differention of cytotoxic and non-cytotoxic substances (TM Muhonen)

TM Muhonen (NAM, Finland) started the morning session highlighting the difficulties in dose determination for non-cytotoxic substances. While dose finding for cytotoxic substances could be based on their toxicological profile, dose finding for non-cytotoxic products is more difficult to establish due to their lack of clinically significant organ toxicity and their particular mechanism of action with a wide range of targets. Toxicity is today the most widely used surrogate end-point in dose-finding studies for non-cytotoxic agents, despite the drawbacks. For future applications of newer substances, alternatives to dose-finding through toxicity could be measuring target inhibition and PK/PD analysis.

Participants agreed to differentiate between cytotoxic and non-cytotoxic substances and acknowledged that dose determination would be difficult for non-cytotoxic substances and would also depend on the individual product/compound.

The use of toxicity as an endpoint was in principle acceptable; however, it might not be suitable for all compounds and should for non-cytotoxic agents be used in conjunction with target validation or other parameters. Sometimes it might be difficult to find a relevant tissue to identify toxicity or e.g. for substances that cause cancer itself, these effects could only be seen in long term studies.

It was discussed that biomarkers might be a good tool; however, biomarkers are difficult to establish on the human side and there are no really validated biomarkers. It would be even more difficult to establish biomarkers for veterinary products. Target validation is necessary and if a new product is developed, the target marker needs to be identified. However, in some cases, there might not be a change in the clinical signs but only in the target marker. Another problem might be the use of a biomarker in cases when the test substance is used in combination.

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It was recommended not to restrict the guideline too much on the dose determination requirements.

Dose finding - use of healthy versus diseased animals

G. Hahn (BVL, Germany) gave a presentation highlighting the different studies that could be used for dose determination for cytotoxic or non-cytotoxic substances. Assuming that many veterinary products will probably be based on existing human products, data from those studies (usually in healthy dogs) could be provided. Alternatively, (veterinary) products might be developed in diseased animals. Both ways could be acceptable, if appropriately justified.

Problems when using data from healthy dogs, is that in human medicines development, usually the maximum tolerated dose is established and these data might not be suitable for a veterinary dose setting. However, the use of animal patients for dose finding studies might not be acceptable from an animal welfare point even for patients for whom no alternative treatment is available.

Participants agreed that the use of patients for whom other, effective alternatives exist would be unethical. Only in exceptional cases and depending on the sort of cancer, such patients could be treated with a test substance; however, if that would not work, treatment should be continued with the standard treatment. For fast developing cancers, this option would be unacceptable. Also, getting animal owner compliance to include their pets in such studies might be difficult to obtain. For products used in combination with other medicines, the test substance might be used, followed by treatment with the other drugs, however, effects of an individual product might be difficult to establish in this combination. It was noted that dose adjustment is made in practice; i.e. treatment starts with the recommended protocol but might need to be adjusted based on parameters measured. Some protocols already give guidance as to what to do in case of toxicity.

Another difficulty in accurate dosing for animals is the great variability in animal size and weight. For use of administration and user safety concerns, oral formulations (coated tablets) which would not require breaking to obtain a smaller dose would be the preferred pharmaceutical form. Oncologists working in practice confirmed this indicating that new veterinary product wishing to be successful on the market would require different strength. However, representatives from the pharmaceutical industry argued that oncology products would only cover a limited market. In order to develop medicines for animals (in particular those based on new, expensive substances) the guideline should not rule out other formulations.

It was discussed that the most accurate dosing would be given when addressed in relation to body surface area and not - as for most other products - the bodyweight of the animal. However, the clinicians pointed out that veterinarians in practice might not know how to apply this type of dosing regime.

Reference therapy – positive control versus placebo

H. Jukes (VMD, UK) gave an overview of the four different options for reference therapy and highlighted their advantages and disadvantages. All options could be acceptable, if appropriately justified.

Positive control group:

In the absence of authorised veterinary medicinal oncology products, a positive control would be the "best available evidence based treatment", i.e. usually a (combination of) human medicine(s).

For certain types of tumours, sufficient protocols are available which are well described and used in large number of patients. Although there might not be a single, harmonised "gold standard" protocol, animals of similar stages of disease which are treated with such well described protocols could be considered suitable for a positive control group; however, other types of cancer are less common in animals and only individual reports are available e.g. for colon cancer. Most common cancers in dogs and cats are lymphoma, osteosarcoma, melanoma and mast cell tumours and acceptable protocols are available; these indications would also be the ones most likely to be applied for in a marketing authorisation application.

However, it was stressed that only a limited number of anti-cancer therapies require monotherapy, including those mentioned above; the majority of products are used in combination with (human) medicines and/or in combination with other measures such as surgery or radiotherapy. If a combination is to be used for a new product, non-inferiority of the test substance in combination with the standard therapy should be demonstrated (superiority would be difficult and not realistic). Cancers for treatment with a single substance only are rare; however, in case of a relapse of a tumour, single drugs might be used.

Concern was expressed that it should remain possible to use a substance authorised as a veterinary oncology product in combination with human medicines, if the treatment would require this. Appropriate reference to the combination therapy with the relevant (human) medicines should be made in the product literature. It was acknowledged that these issues could not be dealt with at the focus group meeting and would be raised at CVMP.

Placebo / Best supportive care
For certain types of tumour (e.g. slowly progressing tumour, no known treatment) or situations, the use of a placebo group could be considered. Such animals would nevertheless still receive the best supportive care, i.e. painkillers, antibiotics, diet, as required. However, it will be more difficult to find owners willing to participate as compared to positive control. If an animal requires rescue treatment, it needs to be withdrawn from the trial and in this case, withdrawal is used as an endpoint for the study.

Single arm studies
Only for certain types of cancer (e.g. if number of patients is very small), a treated animal could act as its own control. Literature data could provide a useful source of information to support such studies; however, reliable information is usually only available for more common types of cancer, e.g. lymphoma, and historical data may not be acceptable.

Non-medical treatment
Comparing the treatment of a group with an investigational veterinary medicinal product with the results of non-medical treatment e.g. radiotherapy, surgery might be an option in certain cases. However, it was discussed that under practical conditions, this might be difficult to achieve, since indications for these treatments would differ, usually chemotherapy would not be an alternative to surgery or radiotherapy. Also, comparison of the results of these groups might be difficult. Possible areas might be in the treatment of metastatic disease, e.g. mast cell tumours where the results of surgery & radiotherapy with surgery & chemotherapy could be compared or adjuvant radiotherapy (i.e. surgery followed by radiotherapy or chemotherapy). Accurate staging and grading of the disease would be important.

Endpoints – parameters for therapeutic response

Introduction / Problem Statement

F. Hulten (MPA, Sweden), introduced the different parameters that had been identified for the choice of study endpoints, i.e. quality of life of the treated animal, survival and tumour development. It was highlighted that different to human medicines, where endpoints in relation to overall survival are considered primary parameters for efficacy assessment, the first aim with anticancer treatment in dogs and cats is palliative (i.e. endpoints in relation to quality of life). However, the animal owner expects that treatment would also prolong life to a meaningful time (endpoints in relation to survival) and an effect on the neoplastic disease (endpoint tumour development).

Proposed parameters in relation to survival were survival free from tumour progression/death, survival free from disease recurrence/death or survival free from any event in relation to the cancer. Possible endpoints in relation to tumour development in order to demonstrate the antineoplastic effect could include objective response rate (partial or complete), time to tumour progression, treatment failure, remission or tumour stabilisation and PD-markers.

The participants agreed that the quality of life of the animal should be the primary endpoint. Cure of the disease would be a preferable endpoint, but is not always possible; therefore, survival was considered a secondary endpoint.

Regarding the survival parameters, event free survival was the preferred option. There was some discussion in relation to "death" as a parameter. In veterinary medicine, euthanasia is an option for animals; however, the reason for this would need to be clarified. Differences in countries are known with regard to the "cultural acceptance" or legal requirements for euthanasia and this should be taken into consideration. Autopsy of animals should only be recommended in the guideline, but not mandatory, otherwise it would be more difficult to get owner compliance.

View from research/industry

R. Narbe, (Boehringer Ingelheim, Germany) provided a presentation reflecting on the expectations from industry on the proposed guideline. The definition of endpoints should be accepted by all the European authorities and should take into account the diversity of types of cancer, the particularities in veterinary oncology, both, treatment and prophylaxis as well as the impact of the requirements on the speed and costs of development and also ethical considerations.

Acceptable primary endpoints and alternative endpoints have already been defined for human products and described in a guideline (CPMP/EWP/205/95/Rev.3/Corr.2); these should be equally eligible in animals, except for survival parameters. However, for veterinary products, overall survival, progression free survival and disease free survival should not be overestimated; in particular overall survival should not be mandatory as primary or secondary parameter. Euthanasia may be driven by other parameters than efficacy of anticancer veterinary products, e.g. due to other disease of the animal or the owner's decision and that should be taken into consideration.

Considerations should be given to establish response evaluation criteria similar to the "Response Evaluation Criteria in Solid Tumours" (RECIST) i.e. standard parameters used when documenting responses to solid tumours in human medicines. However, such criteria should allow sufficient flexibility for veterinary medicines. The statistical data analysis, should take into account rare tumours and more than one primary parameter.

View from practitioner

E. Teske (University Utrecht, Netherlands), explained that endpoints for efficacy measurement of chemotherapeutics would depend on whether the product is to be used for curative, potentially curative or palliative effects and also if it is used for adjuvant or primary therapy.

According to Dr Teske *palliative treatment* is not often done with chemotherapy. Cancer types for palliative treatment could be e.g. primary metastatic lung carcinoma or malignant histiocytosis. In case of palliative treatment, quality of life parameters should be used as endpoint, not tumour response. It was noted that anticancer treatment of dogs and cats would not imply aggressive treatment strategies and thus, quality of life should be considered the most important parameter.

Adjuvant therapy, i.e. chemotherapy after primary tumour therapy is aimed to control occult micrometastatic disease, e.g. osteosarcoma, hemangiosarcoma or mast cell tumour. Endpoints for adjuvant therapy would be parameters in connection with prolongation of the disease free period / survival.

Chemotherapy used for *primary therapy* is done in macroscopically measurable tumours. Examples for sensitive tumour types are lymphoma, multiple myeloma or transmissible venereal tumours. Endpoints here would be the tumour response rates (tumour progression, partial or complete) and as secondary endpoints, response duration and survival.

In order to monitor the efficacy, regular check-ups are essential. Frequency of the checks dependant on the tumour type, and should always include local control, lymph node, X-Rays, ultrasound and - depending on tumour type - other parameter. For tolerance, special parameters should be monitored. Representatives from industry noted that check-ups in some of the studies had been up to 1600 days and expressed some concern about the duration of the studies. Dr Teske explained that it is not too difficult to achieve complete remission in some cancers i.e. lymphoma. However, relapses are frequent and follow-up is important and should be done at least for 1 year following treatment.

Representatives from industry stated that some parameters might be statistically significant but not necessarily primary endpoint parameter and the guideline should allow the use of other parameters as well. However, reference was made to the statistical guideline and also to the study protocols in which the primary endpoints have to be specified before the trial starts.

Some concern was expressed to conduct studies with medicines not approved for use in animals. In addition, different national requirements apply for the conduct of clinical studies for veterinary products. This was an issue that would need to be resolved.

For most types of tumours, survival was considered the least important parameters of all endpoints. Consideration should be given to tumours that are breed-related.

Quality of life

Introduction/problem statement

A. Golombiewski (BVL, Germany) introduced the session on Quality of life and the problematic on how quality of life could be measured. For any application for a veterinary medicinal product, the benefit-risk balance should be positive. Different to a human cancer patient, where prolongation of life is the key parameter, the key parameter to evaluate the benefit for the animal patient would be the "Quality of life". However, treatment with anticancer medicines may have side effects and the assessment of the impact of the „bad days" on the expected „good days" can be difficult to establish. Parameters to measure Quality of Life in animals could include be clinical signs (pain, discomfort, nausea, depression, changes in appetite) or changes in the behaviour (grooming, attitude to owner, play). Scoring systems could be a useful tool to measure quality of life, to be completed by the animal owner and/or veterinarian.

View from research

D. Argyle (University Edinburgh, UK) presented the view on Quality of Life from a veterinary oncologist in research. Judging the quality of life is very subjective, depending on owners, veterinarians, (oncology) specialist's or observer's perception. (Anticancer) animal research is strictly regulated and a number of established models in rodents are available with defined endpoints. However, expanding these principles to animals involved in clinical trials might be difficult. Assessing the quality of life during therapy is usually performed using clinical parameters; however, in view of future research and new product development, biological endpoints might need to be applied.

When undergoing treatment, quality of life is of the highest importance and therapy should be considered in terms of prognosis; taking into account if the therapy is justified on the basis of scientific evidence. Euthanasia could be a result of unacceptable quality of life. In general, conventional anti-cancer therapies (Chemotherapy and Radiation) are well tolerated in dogs and cats. Newer therapies offer greater opportunity to reduce off target effects, and improve outcome.

Scoring systems for quality of life have been applied in research, but less so in clinical practice and include metric (e.g. bodyweight) and parametric (e.g. appearance) signs which should be applied in relation to the individual animal.

View from practitioner

J. Dobson (University Cambridge, UK), gave a presentation in relation to the quality of life from the perspective of a veterinary practitioner. While there are forms of cancer, which cannot be cured or where successful treatment would nevertheless impact on the quality of life of the treated animal, the same would apply for other chronic diseases, e.g. chronic arthritis or congestive heart disease.

There is no general measure for the quality of life. A large number of dogs with tumours nevertheless enjoy a good quality of life. Some primary tumours might be treatable, but animals might die due to metastasis. "Traditional" clinical endpoints might not be possible to be applied to newer substances.

There are some scoring systems available based on human medicines: Skin toxicity scoring following radiotherapy (RTOG scoring scheme; Radiation Therapy Oncology Group); adverse reactions using the VCOG-CTCAE scoring (Veterinary Co-operative Oncology Group - Common Terminology Criteria for Adverse Events); Quality of life scoring (Karnofsky performance status) and EORTC - QOL- C30 (European Organisation for Research and Treatment of Cancer).

As a veterinary example, a survey at Cambridge University was shown based on owners feed-back following anticancer (nasal) treatment in dogs. Although scoring system confused some owners, overall an improvement in attitude, level of activity and "improvement of Quality of life" was noted in treated animals. Problems in using scoring systems might arise from the person who is assessing (Owner / nurse / veterinarian) and can be subjective/biased. However, veterinary scoring systems could be revised / developed, but would need to be adapted for the species (e.g. different grooming behaviour in dogs and cats).

Some aspects were noted which might impact on quality of life but are difficult to judge, e.g. a treated dog without side effects due to treatment but kept for weeks in hospital for user safety concerns.

Regulators were asked if there is any experience or recommendations available from scoring systems used for assessment in other types of products, e.g. for NSAIDs. However, these scoring systems often only use selected parameters, e.g. pain and might not be suitable for oncology. It was noted that if the scoring would be done by owners, the studies should be blinded studies.

Scoring systems or questionnaires were in general considered good tools to measure the quality of life. Such questionnaires should include more objectively measurable performance questions ("Does the dog eat / runs well?") rather subjective questions ("does the dog feel better?") and be possible to be completed in a reasonable quick time to achieve owner compliance. Visual analogue scales are less frequently used and provide accurate results but the logistics still need sorting. However, this option should be kept in the guideline.

USER SAFETY

S. Jones, (VMD, UK) introduced the requirements asked in relation to the user safety. The safety dossier for veterinary medicinal products not intended to be used in food-producing animals, requires pharmacological data, toxicological data and user safety studies. Some substances are likely to be already authorised for human use and data are probably available and could be submitted to support a veterinary application. Applicants are also encouraged to seek scientific advice on particular issues. In order to justify a reduced data package, requirements as outlined in relevant MUMS guidelines could be applied.

Guidance on user safety assessment is provided in the CVMP user safety guideline and the principles of this guideline will be referred to or included in the oncology guideline. In addition, the oncology guideline will provide guidance on the hazard and exposure evaluations that are specific to cytotoxic and DNA reactive substances/products and how to address the user safety assessment. The purpose of the guidance will be to provide information on how to use the data available and to minimise the need for additional data. Given the particular nature of anticancer product, a detailed hazard assessment has to be provided. Exposure assessment will be significantly different to other types of products in relation to pre-administration and preparation of the product to be applied, administration of the medicine and the post-administration and handling of waste and excreta. Examples of various scenarios that would need to be investigated were given.

Participants were encouraged to provide their expectations from an oncology guideline in relation to (user) safety. Suggestions were made to differentiate between cytotoxic and non-cytotoxic substances and also, that data should be provided based on the individual pharmaceutical form.

Some concern was expressed that extrapolation of data obtained from humans to dogs and cats might be difficult, in particular in relation to the (handling of) waste and excreta. Some data might not be available, others might not be applicable. Also, requirements for human products seem to be less stringent than for veterinary products. It was clarified that animal behaviour would be different to human use (e.g. a treated dog might lick the face of children) and more detailed guidance would probably be needed for people in contact with a treated animal as compared to a treated human. However, guidance for data requirements for human products will be taken into consideration when drafting the guideline.

Clinicians confirmed that one of the main problems in relation to user safety is the lack of (animal relevant) data in relation to the handling of excreta. User safety issues are a main concern in oncology practice and animal owner compliance would probably be more difficult to achieve than handling of excreta and waste in hospitals. However, prolonged hospitalisation of dogs should be avoided for animal welfare reasons. Reference was made to the *guidelines for preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine*, developed by the European College of Veterinary Internal Medicine (ECVIM).

Representatives from industry expressed concern about the required user safety data and that too tight restrictions might have negative impact on future development of new medicines. However, some of these data might already be included in other parts of the dossier, e.g. for pharmacokinetic or environmental studies.

It was discussed that oncology products are often used in combination with other (human) products and further clarification should be provided if data would also need to be provided for other (not veterinary) products to be used in such a combination.

Great concern was expressed by both, representatives from industry and oncology practice that the authorisation of veterinary oncology products might result in a loss of treatment options. Currently, dogs and cats can be treated with human products via the cascade; however, clarification is needed as to which extent human products could still be used once veterinary products are available. It was stated that veterinary products might be less efficient and/or more expensive than their human

equivalents. Also, it is unlikely that many veterinary products will be authorised and some standard protocols require the use of a number of products, some of them probably only authorised for humans. It was stated that authorisation of veterinary medicinal products was welcome and would greatly facilitate the safe use of product by veterinarians; however, if there would be a loss of treatment options using human products, it would be better not to have new veterinary products.

ENVIRONMENTAL IMPACT ASSESSMENT

C. Carlsson (MPA, Sweden), summarised the legal requirements and guidance documents for the data to be submitted for the environmental risk assessment. In general, assessment of veterinary products for non-food producing animals stops at Phase I; however, some veterinary products might be identified that require a more extensive, Phase II, assessment in order to address particular concerns associated with their activity and use. Oncology products containing direct DNA-reacting compounds are likely to be such products. The main question for environmental safety would be the handling of waste material and excreta. Safe handling of waste material would be assured by classifying and regulate it as hazardous waste. An integrated risk analysis of user and environmental safety might be necessary to balance risk mitigation measures concerning the excreta, i.e. direct exposure (owners handling excreta), contra indirect exposure (children on playground getting in contact with dog excreta) and exposure to sensitive organisms in the environment.

Oncologists try to inform owners about potential hazards in connection with the treatment of their dogs. However, it was stated that most data currently available for veterinarians are based on human authorisations, and these data are not necessarily relevant for dogs. Also, until recently not much information on environmental impact were requested for human products and data are incomplete and/or old. Urine is probably more problematic than faeces, but practically not possible to collect. Animal specific data would be welcome. Such owner warnings are currently provided in detailed verbal advice by the oncologist, but also in writing. Detailed information e.g. in a package leaflet would be welcome.

Final Discussions / conclusions

In general, proposals addressed in relation to efficacy issues could more or less be agreed by all participants.

Differentiation should be made between cytotoxic and non-cytotoxic substances and classical dose determination studies would be difficult to be used for non-cytotoxic substances.

Use of healthy dogs for purposes of dose finding was in general not considered ethical; however, scenarios might apply where this could be considered. Clinicians stressed the need for more accurate dosing taking into account user safety problems; however, in view of the limited market of these substances, this might not be feasible.

Four different options were given for the choice of control groups / reference therapy; although single arm studies might only be acceptable in very exceptional cases.

The choice of endpoints was discussed from various points of view and “quality of life” was considered by all participants as the main primary parameter. However, the diversity of types of cancer should be taken into account and the guideline should allow the use of other parameters as well.

The problem on how to assess “Quality of life” was also addressed and reference was made to several scoring systems, all useful but not (yet) sufficiently adapted to be used in veterinary oncology, taking into account different target animals.

The main problematic areas of concern in relation to user safety and environmental safety were linked and concerned mainly the handling of excreta and waste. The general user safety guideline would apply and only particular issues in relation to oncology products would be highlighted in the guideline.

Likewise, the general VICH guidelines 6 and 36 would be applied to veterinary oncology products. While clinicians welcomed more detailed user warnings and veterinary specific data; representatives from industry expressed concern about the increased requirements, which might limit the development of veterinary oncology products.

Concern was expressed in relation to some regulatory aspects in relation to the particular use of combined treatment protocols using human products, which would need to be addressed / resolved before finalisation of the guideline:

1) It should be possible to use a substance authorised as a veterinary oncology product in combination with human medicines, if the treatment protocol would require this and appropriate reference to the combination therapy should be made in the product literature.

2) Different national requirements apply for the conduct of clinical studies for veterinary products and it might be difficult to conduct studies with products not authorised for veterinary use.

3) It should still be possible to use a substance authorised in human medicine for a certain type of cancer, even if another substance is authorised for the treatment of this disease in veterinary medicine.

4) Use of oncology product might be restricted in Member States to certain specialists. However, the term “veterinary oncologist” is not a registered term and reference to this should be avoided (e.g. to be used in certain/specialist environment).

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