European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON

DRAFT GUIDELINE ON DOSSIER REQUIREMENTS FOR ANTICANCER MEDICINAL PRODUCTS FOR DOGS AND CATS (EMEA/CVMP/28510/2008-CONSULTATION)

Interested party (Organisations or individual stakeholders) that commented on the draft Guideline as released for consultation:

Name of Organisation or individual	Country
Association of Veterinary Consultants (AVC)	Belgium
Danish Society of Veterinary Oncology	Denmark
European College of Veterinary Internal Medicine - Companion animals (ECVIM - CA)	The Netherlands
Dr C. Hugnet; Clinique Vétérinaire des Lavandes	France
IFAH Europe	Belgium
Dr M.J. Brearley; The Queen's Veterinary School Hospital, Cambridge	United Kingdom
Dr J. Dobson; University of Cambridge	United Kingdom

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1. GENERAL COMMENTS – OVERVIEW:

Stakeholder *see coverpage*	**General Comment (if any)**	**Outcome (if applicable)**
AVC	The Association of Veterinary Consultants (AVC) regards the current draft guideline as a key document which will help the development of much needed anticancer medical products for dogs and cats. We believe the guideline is particularly helpful in a therapeutic area were major gaps exist and were the type of molecules used make drug development very challenging. We agree that the development of compounds in this are requires extensive data to be presented by applicants (particularly on safety and toxicity aspects), as detailed in the draft guideline. However, we also believe that the availability of these compounds should be promoted by facilitating their development and registration. Therefore, as an interested party in the development and rational use of anticancer drugs in dogs and cats we would encourage the inclusion in the guideline of any facilitating measures which will promote the development of these compounds in a much needed therapeutic field.	The aim of this guideline is to provide clear and relevant recommendations regarding the quality and quantity of data that could be regarded acceptable for obtaining market authorization for a veterinary anticancer medicinal product. Several options forward to gain sufficient support regarding efficacy and safety is presented. Regarding user and environmental safety issues see answer to comment from IFAH Europe below.
ECVIM - CA	In general the ECVIM-CA is pleased by the effort EMEA has made to compose this document. Many important items regarding the safe use of cytotoxic drugs and the design of clinical trials for these products in the dog and cat are being proposed. Some general remarks may include that regulation of the use of these compounds should never be so strict that in practice these compounds cannot be used. In addition, registration of one compound for one type of tumour does not exclude the right to use other non registered products, if they have proven less toxicity, or in combination protocols for this tumour type or for other types of tumours according to the cascade principle.	See comment to AVC and IFAH Europe. Furthermore, the cascade principle is not affected by this guideline. Anti-cancer products registered for use in humans can still be used for dogs and cats if no relevant veterinary product is available.
IFAH Europe	In response to the concept paper for this guideline, IFAH-Europe recommended that a guideline should not be developed until more experience had been gained with this group of products. Although IFAH-Europe recognised the value of providing guidance in an area where there is currently none, it also recognised that this advantage was overshadowed by the risk that the development of a guideline would lead to over-regulation and loss of flexibility. This flexibility was seen as critical to the development of a new class of veterinary products, and to avoid innovation being stifled in birth. In principle, the need for this guideline could be supported by IFAH-Europe as it would give guidance to industry for product development decisions and subsequent project evolution. But unfortunately prediction that a guideline would lead to over-regulation appears to have been correct. This guideline, as	See comment to AVC and ECVIM-CA. The requirements on the environmental safety aspects do not differ from any other veterinary medicinal product. An EIA in accordance with current guidelines should be provided. It is further clarified in the text that some oncology products may have

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	currently drafted, will be detrimental to the development of these products. It will be counter-productive to the aim of encouraging research in this area. Although the safety element of the use of an anticancer medicinal product is clearly of great importance, we feel that there is over-emphasis of this area. Thereby, we can foresee a potential over-reaction and regulation with regards to user safety and particularly environmental safety aspects of these products. The guideline requires evidence that all the concerned persons can use such a product safely and with minimal effects on the target animal and the environment. Nevertheless the complexity and depth of data requirements outlined in this guideline will prove a large hurdle to the effective development and future use of such products. For example, human patients are not hospitalised for long periods when on anticancer drugs, and such a proposal for companion animals would in many cases push the quality of life decision for an individual animal towards euthanasia. Today no related registered substances exist for this kind of treatment in veterinary medicine, that is why current compounds / products from the human side are used "off-label". Of course these products do not carry any warnings regarding the above-mentioned issues. It is our concern that, with an over-regulation and/or over-interpretation of the user safety and/or environmental requirements, many potential candidates will not come on the veterinary market as licensed drugs. We would urge more pragmatism in all the safety areas but particularly in the user and environmental risk assessments where the requirements seem particularly extensive and burdensome. Companies could be very reluctant to develop products with the current form of this guideline due to the high risk and costs associated, especially as a registered (single) veterinary product would block the use and research of current more efficacious multi drug combination therapies and would thus be not beneficial to both patients and veterinarians. This guideline also suggests that EMEA anticipates seeing existing substances, already used by Veterinary oncologists, submitted for MA in preference to new substances. Although possible, it is unlikely to be financially attractive enough to pharmaceutical companies to develop such older compounds.	properties implying potential ecotoxicity and this should be discussed and if necessary a more detailed exposure assessment should be provided. It is also pointed out that the Hazardous Waste Directive needs to be taken into account. These measures are considered necessary and are required by EU legislation. Following review of comments received during the public consultation changes have been made to the guideline that will hopefully lessen these concerns

2. SPECIFIC COMMENTS ON TEXT

Stakeholder *see coverpage*	**Line No.**	**Comment and Rationale; proposed changes**	**Outcome**
IFAH Europe	**Introduction** **007 - 8**	This statement contradicts that in lines 39 to 42. There are many published studies on the treatment of animals with anti-neoplastic substances. Although the quality of such studies is of some debate, it is not true that treatment protocols have been mainly established by extrapolation. **Proposed change:** Delete as follow: "*Therapy has hitherto been based only upon products registered for use in humans, ~~thus treatment protocols have mainly been established by extrapolation~~.*"	**Accepted.** The proposed change is supported
J. Dobson	**012 - 13**	What is meant by "sufficient regulatory control"? At present the products used are licensed human pharmaceuticals and are used under the "cascade" i.e. already are under regulatory control. If the authorities feel the existing control is insufficient for this group of products, an alternative would be to license Veterinary Oncology Specialists to use these drugs.	**Partly accepted** It is agreed that this concept is unclear. **A clarification has been made:** *"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 forhandling and administering the products are implemented".*
IFAH Europe	**032**	Although the owner does have an important input into a "quality of life" decision, it is still primarily the Veterinary Surgeon decision. In addition, the word "The opposite" is too strong here. **Proposed change:** Delete: ~~"The opposite is usually the case…than to compromise the animal's quality of life~~", and replace it with: *"In veterinary oncology, both the veterinarian and the animal owner have an important input to establish a balance between the medical treatment and quality of life."*	**Partly accepted** It is agreed that the decision regarding discontinuation of treatment is a mutual decision between the owner and the veterinary surgeon. **The text has been slightly amended to clarify this.**
IFAH Europe	**035 - 36**	**Comment:** This perhaps over emphasises the importance of quality of life measures. Tumour response and survival remain very important end points.	**First proposed change is partly accepted** although it must be emphasised that quality of life should be regarded as important as endpoints related to

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		Proposed change: Line 35-36: replace "~~relatively more important than~~" with "<u>as important as</u>". Line 35-36: Delete the following sentence: ~~*"In addition, the fact… on study design (blinding)".*~~	longevity. **The text has been amended in line with the proposal** **Second proposes change is not accepted**. In case subjective endpoints are used study design must be appropriate to allow a conclusion based on the results. It is considered appropriate to emphasise on this fact. **No change to the text suggested**
ECVIM - CA	**035 - 38**	It is suggested that most endpoints in veterinary medicine are related to a palliative aim and therefore subjective in nature. This is not true. Objective endpoints as response rates, DFP, and toxicity scores are frequently reported endpoints in veterinary articles on clinical trials. Quality of life can also be scored (e.g. Karnofsky index)	**Partly accepted.** The text has been slightly revised to clarify that apart from palliation the aim of treatment could also be to postpone disease progression and the development of clinical signs.
J. Dobson	**037 - 38**	Tumour response and patient survival remain very important endpoints.	**Agreed**. In section 7.6.2 (primary and secondary endpoints) of the current guideline draft it is made clear that primary endpoints should be selected to reflect effect on tumour development and/or effect on life expectancy. **No change to the text is proposed.**
J. Dobson	**053 - 58**	Interesting – this implies EMEA would like to see existing products licensed for veterinary use as opposed to new products?	**Not accepted.** The paragraph is inserted only to clarify that in case product development concerns a new chemical entity additional information/advice may have to be sought from regulatory authorities, since a guideline can not cover all critical issues in such a situation. We have no preconceived notion regarding what kind of application could be more or less likely to be submitted. **No change to the text proposed**.
IFAH Europe	**059 - 81**	**Comment:** As toxicity is per definition dose dependent it is not a good classification.	**Partly accepted**. From a user safety/environmental safety perspective

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		For DNA reactivity the irreversibility is highly important and correlated with the absence of threshold levels, therefore 'mutagenic vs non-mutagenic' would be good terms to discriminate irreversible changes from reversible DNA changes/toxicity. However, it would be preferable to have one classification and we suggest "cytotoxic and non-cytotoxic" because everybody understands these terms. **Proposed change:** We would suggest the use of the term "cytotoxic".	the critical issue is to clarify whether the substance have potential to induce changes in the DNA implying no threshold level can be determined. However, from an efficacy point of view this is not the critical issue, but rather if the substance is cytotoxic or not since this influences what effect on the tumour could be expected and thus which endpoint should be selected. This classification is in line with the guideline on anticancer medicinal products in man in which this categorization was introduced in connection to the most recent guideline revision. The text has been slightly amended to make the rational behind this distinction more clear**.**
J. Dobson	**060**	The use of two categorisations ["cytotoxic or non-cytotoxic and DNA reactive or nonDNA reactive"] confuses and overcomplicates the issue – please select one categorisation throughout.	See above (comment from IFAH Europe)
J. Dobson	**Quality** **116 - 124**	Accuracy of dosing is not usually a problem with the formulations of cytotoxics drugs available in the UK. Crushing of tablets / capsules is not acceptable practice but dilution of solutions should not pose a problem if performed under controlled conditions. Many of the cytotoxic drugs we use are available as powders that require reconstitution with water or saline which is no different to dilution.	**Partially accepted.** The text of the guideline refers to dilution of sterile injections (wording now clarified to state "Dilution of parenteral products") whilst the comment appears to relate to non-sterile solutions / powders for re-constitution. Therefore an additional section has been added to the following sentence to clarify regarding reconstitution of a powder for oral solution to a lower concentration than prescribed for human use, can be acceptable. "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)."

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ECVIM - CA	**116-124**	We agree that crushing of tablets or breaking of tablets should not be done by owners, however, reconstitution of powders and diluting of solutions can be done by trained staff under controlled circumstances, e.g. negative pressure pharmaceutical isolator. Therefore, the statement that these human medicines cannot be condoned for their adaptation to the veterinary use should be adapted.	**Partially accepted.** The text of the guideline refers to dilution of sterile injections (wording now clarified to state "Dilution of parenteral products") whilst the comment appears to relate to non-sterile solutions / powders for re-constitution. Therefore an additional section has been added to the following sentence to clarify regarding reconstitution of a powder for oral solution to a lower concentration than prescribed for human use, can be acceptable. "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)." Note: Negative pressure isolators are designed to protect the user and are not suitable for the dilution of sterile injections as when the integrity of the vial is broken, sterility cannot be assured.
M.J. Brearley	**116-124 (para 4.1.1)**	Of course tablets should not be broken or crushed but reformulation of capsules by a professional pharmacy into more appropriate doses is possible. However agree with point made in para 4.2 Where drugs are available as injectable solutions accurate dosing is feasible.	**Not accepted.** Reformulation of capsules not condoned.
IFAH Europe	**116-124**	This is not really an accurate reflection of the current situation where in fact few cytotoxic products are used in Veterinary medicine by the oral route. There are virtually no situations where solutions currently have to be further diluted for accuracy of dosage. **Proposed change:** Delete the sentence: "~~*That is the case…dilution of injections.*~~"	**Not accepted.** Whilst it may not be widespread practice, it is still valid to state that dilution of injections should not be carried out.

Stakeholder *see coverpage*	**Line No.**	**Comment and Rationale; proposed changes**	**Outcome**
IFAH Europe	**143 - 145**	It is unclear why this is needed if (as in line 129) it is stated that the assessment of the core quality data will **not** be repeated. **Proposed change:** Delete the following wording: ~~*"6. A full copy of the quality part of the dossier.*~~*"* and replace it by: *"6. An abbreviated quality part of the dossier."*	**Not accepted.** The dossier will not be re-assessed, however, the Competent Authority must have on file all relevant data supporting every application for a marketing authorisation. These data might also be required by the Competent Authority to refer to in relation to future variations to the product.
IFAH Europe	**152 - 153**	See comment above. It is preferable to not include this in the application, but provide it only if requested by the assessors. If the product is being sourced from a 3rd party (e.g. an animal health company is sourcing the product from an unrelated human pharmaceutical company), many pharmaceutical companies are naturally reluctant to pass their manufacturing and quality details on to an applicant. Replace: ~~*"Item 6 will not be assessed…from the human authorised product*~~*"* with: *"Item 6 will not be included in the application, unless it is requested by the assessors."*	**Not accepted.** See comment above (143-145).
J. Dobson	**192**	Specify: "coated" tablets	**Accepted.**
IFAH Europe	**193-194**	The statement that capsule shells are frequently damaged and the use should be avoided is exaggerated. Many Veterinary products can also be made available as soft gelatine capsules, which are not considered as critical for compliance and safety. Issues related to the capsules, if any, will be addressed in the safety evaluation of the product. **Proposed change:** Delete the sentence: "~~*Whilst whole capsules…..should be avoided*~~".	**Partially accepted.** This section has been reworded: "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."
IFAH Europe	**192,206,204**	See earlier comment – one classification if possible. In line 204, the term "cytotoxic" is used, whereas Lines 192 and 206 uses the wording "cytotoxic or DNA-reactive substances". **Proposed change:** A choice between the two wordings has to be made.	**Not accepted.** See comment to IFAH Europe line 059-081
AVC	**195-197 (P. 4.2)**	We believe that availability of tables that allow division should be permitted so long as the user safety precautions are clearly stated and	**Not accepted.** When developing an entirely new product, subdivision

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		followed.	of tablets should be avoided as stated.
M.J. Brearley	**200-205 (para 4.3)**	Blister packs in cardboard containers (e.g. cyclophosphamide BP) are NOT child-proof and I am amazed that they are allowed under human regulations! When I dispense these I put the tablets into a plastic pill bottle that has child-proof twist lid. **Proposed change :** Blister packs where used must be packaged in secondary child-proof containers	**Accepted (principle of, not the wording).** The section has been reworded: "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."
J. Dobson	**201**	In the case of cytotoxic drugs, all tablets / capsules should be provided in child proof containers, whether blister packed or not.	**Accepted.** See comment above.
IFAH Europe	**204**	It would be helpful if an example of a "suitable, integral dosing device" could be given. **Proposed change:** Please add an example	**Accepted.** An example has now been included.
IFAH Europe	**Safety** **238 -239**	For cytotoxic compounds the product will be certainly contraindicated for use in breeding animals. As such, companies would prefer not to carry out expensive reproductive studies for no point (particularly as they consume large numbers of experimental animals). Would it not be acceptable to assume the worst-case scenario here without providing specific studies? **Proposed change:** Line 238, amend as follows:*" as well a effects on fertility or reproduction if justified by the toxicity profile of the compound and the risk of exposure."*	**Not accepted.** However, the point is noted and revised text has been developed.

Stakeholder *see coverpage*	Line No.	Comment and Rationale; proposed changes	Outcome
ECVIM - CA	**252-263**	We have some concern related to the distinction between drugs which have a direct and those with an indirect effect on DNA. We believe these are a bit oversimplified. For example, Topoisomerase inhibitors, which you give as an example of indirect DNA drugs, do in fact cause single and double strand breaks, which you list as effects of direct DNA affecting drugs. Lines 338-340 imply that indirect DNA acting drugs are not carcinogenic, but Topoisomerase inhibitors may be carcinogenic and etoposide induced leukaemia is well known. Therefore these drugs should be classed along with direct DNA affecting drugs.	See comment to IFAH Europe line 059-081
AVC	**261-263 (P. 5.3.1)**	Under exposure of the non-professional user and disposal activities it would be useful to provide some guidance on disposal of dead animals. This comment also applies to subsequent sections (Ln 277- 287 and Ln 374) where no comment is made on disposal of dead animals.	**Not accepted** The appropriate way to dispose dead animals would be controlled by national regulations which must be taken into consideration by the responsible veterinarian. No specific guidance in this regard is considered to be needed for animals that have been treated with anti-cancer medicinal products. No change to the text proposed
IFAH Europe	**261-263**	Needs a definition of a "non-professional user". Does this mean "owner"? What is the risk of exposure mentioned in this sentence? If owners are expected to collect urine and faeces of their pets, they would wear gloves! Finally, what can be the risk of exposure by handling the animals? Is any drug expected to be excreted transdermally? **Proposed change:** Delete the sentence: ~~*"In the post application phase…and the handling of treated animals"*~~.	**Partly accepted**. Revised text has been provided.
IFAH Europe	**264 - 270**	It is unclear why effects with a threshold value should be assessed when it is already established that the product has some effects without a threshold value. Surely the product will be assessed and warnings/precautions established based on the worst case scenario in which case the assessment on threshold value effects are irrelevant. **Proposed change:**	**Not accepted**. Non-threshold endpoints do not always represent the worst case.

Stakeholder *see coverpage*	**Line No.**	**Comment and Rationale; proposed changes**	**Outcome**
		Delete Lines 264 to 270: ~~*"In fact, substances that have a genotoxic effect…to effects without a threshold value."*~~	
IFAH Europe	**273**	A definition or some guidance/example of what is an "acceptable level" is required. **Proposed change:** Add a definition	**Not accepted**. The acceptable level is always subject to the benefit-risk evaluation and therefore an absolute level cannot be given.
J. Dobson	**273**	What is an "acceptable" level of risk?	See above
IFAH Europe	**273 - 276**	Do the current Veterinary Medicine regulations allow for such restrictions on who can use a product? **Proposed change:** Delete the sentence "~~*Risk management… the handle hazardous material*~~" and replace it with *"Appropriate measures should be recommended to minimise exposure"*	**Partly accepted** The relevant section has been clarified.
IFAH Europe	**278 -281**	Clarity of terminology needed again – use of "DNA reactive/cytotoxic" and "DNA reactive" (see comments to lines 59-81). **Proposed change:** See proposal for lines 59-81.	See comment to IFAH Europe line 059-081
M.J. Brearley	**288 (para 5.3.3)**	Worthy of mention is the ECVIM Guidelines http://www.ecvim-ca.org/guide_lines.htm **Proposed change:** Include in References	**Accepted**. Guidelines for Preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine (ECVIM-CA 28/0907) has been inserted into the list of additional useful documents
ECVIM - CA	**297-309**	We think that the requirements for pre-administration are incomplete or inadequately. We refer to our document "Preventing Occupational and Environmental Exposure to Cytotoxic Drugs in Veterinary Medicine" [www.ecvim-ca.org/guide_lines.htm]. Negative pressure pharmaceutical isolators or a Class 2B Biological Safety cabinet should be used in stead of a fume hood.	**Accepted** The relevant section has been modified
IFAH	**299**	Incorrect equipment	**Accepted**

Stakeholder *see coverpage*	**Line No.**	**Comment and Rationale; proposed changes**	**Outcome**
Europe		**Proposed change :** *…"requirements of preparation in ~~fume hoods~~ biological safety cabinets, ventilation,…"*	See above
AVC	**303-304**	Activities of users during preparation: this is absolute normal routine practice in any labor environment and does not need to be incorporated here. EU legislation currently covers this anyway. **Proposed change :** Delete these two lines.	**Not accepted** This is a normal part of the user safety risk assessment.
IFAH Europe	**354**	Incorrect equipment **Proposed change :** *This may include recommendations related to possible requirements of preparation ~~in fume hoods~~ biological safety cabinets and …*	**Accepted**
AVC	**356-359; 360-364**	See comments on Ln 303-304 **Proposed change :** Delete this sentence or replace by "use precautionary principles and material dependent on product handled") Pregnant etc. ladies are not allowed in labs anyway!!	**Not accepted** See comment in response to comment on line 303-304.
J. Dobson	**358 - 359**	Alcohol can affect the permeability of latex gloves.	**Accepted** The text has been deleted
IFAH Europe	**358**	Alcohol may affect the protectiveness of latex gloves. **Proposed change :** Delete the following wording: *~~"e.g. alcohol to wipe exposed vial top~~*"	**Accepted** The text has been deleted
AVC	**369-371**	Breaking, cutting or crushing …… This hints purely at tablets, but other formulations have different risks at administration. As mentioned, this is a Part II issue, should be crossed out here. **Proposed change :** Delete sentence.	**Not accepted** As this could influence exposure it is considered to be a user safety issue as well as a quality issue

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J. Dobson	**372 - 373**	Define "professional users" does this refer to Vets and Nurses, or could it be used to refer to Specialist veterinarians?	**Accepted** The text has been revised.
IFAH Europe	**373**	The term "Professional users" again requires a clear definition. **Proposed change :** add a definition.	See above
AVC	**374**	**Proposed change :** Add: change header by including treated animals	**Not accepted** The header is considered to be sufficiently clear.
IFAH Europe	**374-405**	If all precautions listed in this section have to be followed, the animal will be rather euthanized. Too many constraints, most of then inapplicable on a routine basis. Products with such warnings can not be marketed. **Proposed change :** No proposal can be made here. This is a fundamental issue. If these kinds of precautions are to be required, then these drugs are clearly not marketable (see additional comments below). A more pragmatic approach is required.	Revised text has been provided.
ECVIM - CA	**378-388**	In general, regular (frequent) hospitalisation periods will be unacceptable for most owners, meaning that too strict regulation will result in non-treatment of many veterinary cancer patients. The division into active form or inactive metabolites is less interesting than the division into still carcinogenic or no longer carcinogenic.	Revised text has been provided.
Danish Society of Veterinary Oncology	**381**	What is considered an acceptable level for dogs and cats and the environment – i.e. do we have documentation, will that be sought or asked to be provided? How will this be approached?	See response to IFAH-Europe comment on line 273
M.J. Brearley	**382**	Hospitalisation of animals post administration of drugs is likely to lead to greater potential for contamination of local hospital environment and exposure of staff. Treatment given on out-patient basis with owners practicing strict hygiene, collection/appropriate disposal of faeces, avoiding children's play areas etc is arguably a better, safer and least likely	**Partly accepted** The wording has been changed to 'hospitalisation may be considered' (rather than 'must be considered').

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		to contaminate attending persons.	
IFAH Europe	**382**	Although hospitalisation appears to be a sensible way of minimising/removing such risks, it will in effect stop the routine use of many cytotoxic products due to the severe reduction in the quality of life associated with such a prolonged stay in a veterinary hospital. This will not only sway the quality of life decision for an owner and /or a Vet, in many cases the associated high costs of such a stay will be prohibitive. The need for hospitalisation needs further debate on animal welfare grounds alone. **Proposed change :** "*…a hospitalisation period ~~must~~ may be considered*"	See above
J. Dobson	**381 - 388**	A requirement that once treated with a cytotoxic drug an animal must be hospitalised for probably 3 – 5 days, to reduce the risk to owner of handling waste and excreta, would severely curtail the use of cytotoxic drugs in Veterinary Medicine for reasons of quality of life and expense.	See above
AVC	**391-392**	Observation period: it is questionable, if "short" period is sufficient **Proposed change :** Put "appropriate" instead of "short"	**Accepted**
AVC	**393**	Flushing down toilets appears unacceptable according to EU legislation and precautionary principles. In LN 429-431, waste is correctly categorized as "harzardous" **Proposed change :** Delete "flushed down a toilet or"	**Accepted** Revised text has been provided.
IFAH Europe	**393**	The example of faeces / vomit being flushed down the toilet requires much more clarification. Clearly in the human field it is acceptable. The regulators need to justify why it should be different for Veterinary medicines and companion animal faeces. If it is acceptable many of the points on environmental safety are much simpler to address. **Proposed change :**	See above.

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		Clarifications on this point are needed.	
M.J. Brearley	**393**	Flushing faeces down a toilet may not be the best means of disposal – what is the evidence that sewage treatment and water purification removes all the cytotoxic / DNA-reactive chemicals? Disposal as General Household Waste is arguably less dangerous to environment and human exposure.	See above
IFAH Europe	**394**	Is there a standard "chemotherapeutic hazardous waste container" across the whole of Europe?	**Accepted**: Revised text has been provided.
AVC	**398 (P 5.3.5)**	We are not clear what is regarded as an "inappropriate location" **Proposed change :** Inclusion of example(s) may help. Alternatively, animals may need hospitalisation for 24 to 48 hours post treatment.	**Accepted**: An example has been provided
IFAH Europe	**403**	How is it possible to practically prevent a dog from licking a person? Can an occasional licking be considered risky? **Proposed change :** Clarifications are needed.	**Accepted**: Revised text has been provided
ECVIM - CA	**405**	How will you demonstrate the efficacy of decontamination of the excreta?	**Accepted**: This bullet point has been deleted.
IFAH Europe	**409 table**	As with comment 264, it is totally unclear why one would want to assess threshold value effects for a product, which has also non-threshold value effects. All precautions and warnings will surely be based on the non-threshold hazards. Finally, not all direct DNA actions are without a threshold, this is where the irreversibility is important. **Proposed change :** Please delete the double analysis and the faulty definition The threshold values effects link should be removed from the non-threshold values tree.	See response to IFAH Europe comments on line 264 - 270
IFAH Europe	**417 to 431**	It is unclear why an EIA should be carried out (because of user risk) if excreta have to be treated as hazardous waste and disposed of in an	**Not accepted.** An EIA is required for all VMPs. If it is concluded in

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		appropriately controlled manner. **Proposed change :** It should be specified	the User safety assessment that excreta (urine and feces) should be collected and safely disposed this will have the consequence that there will be no environmental exposure. This should be reflected in the EIA report.
AVC	**422-424**	See our comment to LN 397-398: recommend to hospitalize animals within the first 24 to 48 hours post treatment, where relevant. **Proposed change :** Add such statement into the bracket (at the animal hospital exercise yard, as long as the animals are hospitalised, generally the first 24-48 hours post treatment, risk seems to be limited, as controlled!)	**Not accepted.** The possible environmental impact from local concentrations at the hospital exercise yard should be discussed on a case-by-case basis taking into account the mechanism of action and applicable risk mitigation measures where necessary.
IFAH Europe	**432**	Reference to the MUMS guideline should be made in section 7 on Preclinical and Clinical documentation. For certain types of tumour (low incidence), the quantity of data required is simply much too expensive to justify any development. **Proposed change:** Add as follow*: PRECLINICAL AND CLINICAL DOCUMENTATION "(Doc. Ref. EMEA/CVMP/EWP/43872/2006.)"*	**Not accepted.** Whether reference to MUMS can be justified or not is not a specific issue for these types of products. The aim of the guideline is to provide sufficient information for any type of application and thus a reference to the mentioned guideline in section 7 is not considered appropriate. It should be noted that the guideline is currently mentioned in the reference list **No change to the text proposed**
IFAH Europe	**449-452**	These two areas, although interesting, could be extremely difficult and expensive to investigate. **Proposed change:** Proposal: *"…should be considered whenever relevant."* *"…the underlying mechanisms presented whenever relevant."*	**Not accepted**. It would be relevant to consider potential interactions in case combination therapy is recommended. Thus the clarification proposed by IFAH is considered superfluous. **No change to the text proposed** **Not accepted** In the current text it is said that the possible capacity for resistance development should be discussed. If through this discussion it is made clear that the risk of

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			resistance development is of clinical importance it would be relevance to clarify the underlying mechanisms. In the current text it is said that underlying mechanisms for resistance development should be explored only if possible. Thus, through the current text it is implied that underlying mechanisms should be presented only when relevant. **No change to the text proposed.**
IFAH Europe	**Efficacy** **467**	The "Provisions for post-marketing surveillance" need further clarification. Surely Pharmacovigilance should be the mechanism for such investigations. It is also unclear how such post-marketing surveillance can be incorporated in the current Market Authorisations. **Proposed change:** Delete the sentence: ~~"Where this is relevant, provisions should be made for post-marketing surveillance."~~	**Accepted**
C Hugnet	**480**	In oncology, body surface area (BSA) is not scientifically justified in dog, cat and human. Lots of publications indicate that is not a good way to approach dose calculation. BSA is not a mesured parameter but a calculated parameter. No validated method to determine it exists today. In paediatric medicine, BSA is not yet authorized. "Dose for paediatric patients may be defined in mg/kg." (EMEA/CPMP/EWP/569/02). **Proposed change :** A same sentence should be written in this veterinary guideline.	**Partly accepted.** It is agreed that there is no general agreement regarding the relevance of using BSA for dose determination purposes in animals. The current text indicates that the applicant should use the method that most accurately reduces variability in exposure and it is left to the applicant to justify his/her method. We believe this is the most relevant approach in the current situation. **No change to the text proposed.**
AVC	**506 (P7.3.1)**	Suggest the word "autopsy" is changed to "necropsy" or "postmortem examination"	**Accepted**

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M.J. Brearley	**536 (para 7.4) and 669 (para 7.6)**	Where Best Clinical Practice involves cytotoxic drugs (off-licence use of human drugs) it will be ethically difficult to deny patients this in favour of BSC or placebo. Therefore this will limit recruitment to patients having failed 'standard therapy' or where this is not possible on financial grounds. A mine-field!	**Not accepted**. It is acknowledged that it may be difficult to perform placebo controlled studies for ethical reasons in certain situations. Nevertheless, in the absence of an authorised anticancer veterinary medicinal product, such studies are of particular value and should be performed whenever possible. Any future authorisation of veterinary anticancer products will promote the possibility to perform reference controlled studies. In addition, the guideline in its present form gives some opening for other design option if appropriately justified. **No changes to the text suggested**
IFAH Europe	**557-558**	Validation is a concept that is difficult to apply as such to many diagnostic methods used in veterinary practice. How to validate histology or imaging techniques? **Proposed change:** Delete as follow: …"evaluable indicator of disease for which ~~*validated*~~ *diagnostic methods are available.*"	**Not accepted.** It is agreed that validation may be difficult for certain diagnostic tools but this is not considered a specific problem for methods used in veterinary investigations. In addition, it is considered crucial that the validity of any method used is ensured as far as possible. No change to the text proposed
IFAH Europe	**561-562**	The wording "as long as owner's informed consent is obtained" is confusing as owner's informed consent applies to all clinical trials. **Proposed change:** Delete: "studies, ~~*as long as owner's informed consent is obtained.*~~"	**Accepted.**
AVC	**589 (P.7.4.1)**	We are not clear what is meant by "evaluating adverse reactions at predetermined intervals". Are these intervals defined in relation to a pre-defined calendar or disease progression or other? **Proposed change :** Inclusion of example(s) describing the type of interval may help	**Accepted.** It is agreed that this expression is misleading and the sentence have been changed accordingly: "*The evaluation of adverse reaction should be conducted continuously*"
AVC	**594-595 (P. 7.4.1)**	We believe the word "activity" should be replaced by "efficacy" in this context. The presence of activity does not imply efficacy and what is	**Not accepted.** In the context of dose confirmation the demonstration

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		described in this section refers to the evaluation of the efficacy of the compound	of antitumoural activity could be a sufficient aim, implying the main goal is to demonstrate on short term basis that the product under study is able to affect the tumour to a reasonable extent. The use of any appropriate endpoint to reflect such activity could be accepted. Evaluation of efficacy is considered to be more connected to the demonstration of treatment benefit which is a more complex entity and confirmatory clinical trials are needed to fulfill this purpose. To demonstrate that the treatment is efficacious for the target disease endpoints should be selected to demonstrate the influence of treatment in several different aspects in comparison to the natural cause of the disease (or to compare benefit with an approved reference product). Thus, it is considered relevant to make a distinction between activity and efficacy and activity would be the proper expression in the current section. **No change to the text is proposed**
ECVIM - CA	**605-702**	Endpoints: ORR is given, but most often a PR is of no real benefit for the patient. Obtaining a CR is what counts, and related with that DFP is more important than TTP. Therefore, not only ORR and TTP should be assessed but also CR rates and DFP.	**Accepted.** The text regarding selection of endpoints has been amended to clarify the importance of CR. DFS and time of remission is already mentioned as potential endpoints
IFAH Europe	**633-636**	We can see no scenario where a placebo controlled study would be ethically acceptable. **Proposed change:** Delete: ~~*"To enable comparison…for all animals"*~~ and replace it by: *"Unfortunately the same assessment time-points is not ethically acceptable to enable comparison of animals tumour development."*	**Not accepted**. See response to M.J. Brearley (Ln 536)
J. Dobson	**634 and 673**	Use of placebo is unlikely to be considered ethical.	See above (response to M.J. Brearley, Ln 536)

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AVC	**673 (P.7.6)**	Although we understand the potential advantages of placebo controlled trials (e.g. reduction of sample size), we have some concerns from an ethical and animal welfare point of view for anticancer drugs. **Proposed change :** Suggest that a comparison of treated animals versus historical data (i.e. either published or within patient) be acceptable to the reviewers, if appropriately justified	See above (response to M.J. Brearley, Ln 536)
IFAH Europe	**673**	See comment 633-636 above. **Proposed change:** Proposal: *"…and reference ~~or placebo~~ controlled."*	**Not accepted.** See answer to comment for Ln 633-636 (response to M.J. Brearley, Ln 536)
Danish Society of Veterinary Oncology	**717-733:**	It is important that primary end points are well defined following criteria agreed upon by the international veterinary oncologic community (incl. relevant publications) and recorded for a particular drug. Quality of life measures as secondary end points are also crucial including the recording of resolvation of clinical signs resulting from the tumour or paraneoplastic disease incl haematological or biochemical or orther measurable parameters resulting from resolving cancer or paraneoplastic disease. Clinical signs relating to quality of life may differ greatly between cancers (i.e. osteosarcoma: pain and discomfort; gastrointestinal lymphoma: vomiting, weight loss and diarrhea). It may be worth while considering that an expert panel group defines minimally relevant criteria to be recorded for the most common canine and feline cancers and add these to the guideline. In addition, a consideration regarding which signs may be considered relating to the cancer as originally presented and which relating to the drug candidate to be tested (adverse effects according to VCOG criteria).	**Partly accepted**. A clarification has been added to stress that the endpoints selected should be well defined. The importance of monitoring quality of life is already emphasized in the current version. A sentence to clarify that the QoL endpoints should be relevant for the disease under study has been added. A reference to the VCOG criteria is already made in the current text. Establishment of an expert panel group to define criteria to be recorded for the most common cancers in dogs and cats would probably be useful but would take years and, therefore, doesn't contribute much to this guideline
IFAH Europe	**734-739**	This section is far too prescriptive and not relevant. There are too many exceptions that could be envisaged. As common practice the main focus for evaluating efficacy should be on the predefined relevant primary parameter. Quality of life (group C parameters) should not be diminished in an unacceptable manner. As Pointed out by Erik Teske during the focus	**Not accepted.** This paragraph clarifies that objectively measurable endpoints for disease development should be used as primary endpoint. However, it is made clear that the effect on life quality needs also to be presented. It is agreed that QoL parameters should not be diminished

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		group meeting, significant results regarding survival endpoints are generally very difficult to achieve and as anticancer treatments are not life style drugs, it seems to be unrealistic to expect overwhelming antineoplastic activity and improvement of QoL at the same time, especially as animals with starting cancer often do not suffer at all. In case of good and sustainable efficacy, more temporal side effects (also on QoL) may be acceptable for treating life-threatening diseases than for other diseases. **Proposed change:** *Delete: ~~"Primary and secondary endpoints….group C, is also required."~~*	to much but due to the fact such endpoints are often subjective in nature they are not appropriate candidates for a primary endpoint. The text leaves open for the applicant to justify any specific endpoint with these main points of view in mind. The text does not preclude that a positive risk benefit balance could be obtained for a product which causes temporal side effect, if sustainable effects are demonstrated. However, this is judgement made case by case and no general guidance can be provided. **No change to the text proposed**
AVC	**727** **(P.7.6.2)**	"The fact that these endpoints….." **Proposed change :** Suggest to be changed to "The fact that some of these endpoints…." (Bodyweight is an objective endpoint)	**Accepted.** A change to the text has been made.
IFAH Europe	**748 - 754**	Although this makes some good points it is still extremely difficult to see where a placebo controlled design would be ethically acceptable. **Proposed change:** *"~~However, a placebo controlled design should also~~ There will be very few occasions where a placebo controlled design could be considered, ~~since this~~, although this is…"*	**Not accepted.** See above (response to M.J. Brearley, Ln 536)
IFAH Europe	**755 - 767**	Although welcome, this section perhaps needs further clarification. For example, will it be acceptable to have an approved product that recommends on its label the use of 2, 3 or more other unapproved medicines for use concurrently in a treatment protocol? Equally, this area raises many other issues such as how would pharmacovigilance handle such a scenario. There are also questions about EIA and user safety – should the applicant assess all of the products recommended in the treatment protocol or only the one for which they seek approval? A good but difficult example could be where the authorisation is for a non-	**Partly accepted**. For a non-inferiority study it could be accepted to use a non authorised product as comparator, if sufficiently justified. The evaluation of a combination therapy can only concern a situation where the product under study is combined with products previously authorised for veterinary use. This fact has been further clarified in

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		cytotoxic substance whereas the SPC only recommends use alongside 2 human approved cytotoxic drugs. **Request for further clarification:** Further clarification is required because this discussion is highly hypothetical as the use of cascade drugs is blocked when a veterinary drug is available	the text. IFAH raises relevant questions regarding the possibility to accept combinations with non-authorised products. However, there is no legislative support for accepting a combination including products which are not authorized for veterinary use Scientific advice should be sought in case the intention is to evaluate a combination including non-authorised products.
IFAH Europe	**759 -761**	It should be more precisely indicated whether a non-approved reference product with sufficient evidence for support as explained in lines 743 to 747 can be also used in combination therapies. Is this approach really acceptable from a regulatory/legislative point of view? Multi-agent protocols are often more efficacious than single agent protocol. In the lack of approval of well-established chemotherapeutic regimens for veterinary oncology, this pragmatic approach would facilitate the development and approval of new drugs for veterinary oncology and could also overcome the ethical dilemma of using a placebo treated control group. In addition, such an experimental setting is also indicated for drugs considered to have an additive or synergistic effect. **Proposed change:** *… "If the experimental agent is added to an established <u>veterinary approved or non-approved</u> regimen (B), superiority of AB vs. B alone should be demonstrated and the benefit-risk balance should be shown to be favourable*	See above.
AVC	**761**	**Comments:** We think that either superiority or a positive benefit-risk balance should be shown, as in both cases, the patient will benefit **Proposed change :**	**Not accepted.** The demonstration of superiority with regard to effect and the demonstration of a positive benefit-risk balance are two different entities and should be considered separately. If superiority with regard to

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		Replace "and" by "or"	treatment effect is demonstrated for a certain product combination but the safety profile is inferior to the single substance to a significant extent it might be that the benefit-risk balance is regarded negative for the combination. Thus, both prerequisites have to be fulfilled. **No change to the text proposed.**
AVC	**774 (P.7.6.2)**	There is no mention of the use of concomitant treatments which will be used during the study (e.g. Corticoisteriods, NSAIDs, analgaesics, etc.) but which will influence the evaluation of some endpoints related to quality of life in particular. **Proposed change :** Suggest that a sentence is included stating that concomitant treatments will be allowed but must be registered and their effect should be evaluated. Alternatively certain products may be forbidden.	**Partly accepted.** The text has been modified.
IFAH Europe	**774 - 776**	Indeed, this is an extremely difficult area to assess and it is so wide that it is not helpful in such a guideline. **Proposed change:** Delete: ~~*"Interactions…should be addressed."*~~	**Partly accepted.** In case there is a well founded suspicion that such interactions may occur, they should be explored. **The text has been slightly amended to indicate such exploration is only needed when considered relevant.**
IFAH Europe	**779**	See the comment on lines 557-558. **Proposed change:** Delete: *"…properly* ~~*validated*~~ *tools…"*	**Accepted**. "Validated" has been replaced by "appropriate".
AVC	**791**	Animals are owned by their ownerd. Therefore it is to the complete discretion of owners, to allow necropsies. **Proposed change :** Add to last sentence: regardless of cause of death, whenever possible and allowed by the owner.	**Accepted.** A clarification has been inserted

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IFAH Europe	**Refs**	The VCOG guidelines are not referenced. **Proposed change:** Add: *"VCOG Guidelines"* references.	**Accepted** VCOG (Victorian Cooperative Oncology Group) organizes human oncologists and the guidelines produced by this organisation refer to human oncology Although the usefulness of these guidelines for exploration of veterinary medicinal products may be limited they have been added to the reference list.