European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON USER SAFETY GUIDELINE FOR PHARMACEUTICAL VETERINARY MEDICINAL PRODUCTS (EMEA/CVMP/543/03-CONSULTATION)

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Organisation
1	IFAH-Europe

General overview
The CVMP adopted on 12 January 2005, following a 6-month period of public consultation, the user safety guideline for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL), following the recommendations for its Safety Working Party (SWP-V).

Comments were only received from IFAH-Europe

The main concern of IFAH-Europe was the absence of a concept paper before the work was started on the development of the guideline. IFAH-Europe had requested that this project should be taken back a step, to the level of a concept paper, so that there could be an adequate discussion on the scope, impact and framework of the proposed guideline.

The CVMP noted the request from IFAH-Europe but considered that the comment requiring the publication of a concept paper for consultation prior to further development of the guideline was not feasible in this case, as the work on the guideline had been initiated prior to the agreement of having concept papers systematically released for consultation.

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Table 2:Discussion of comments

GUIDELINE SECTION TITLE	
Comment	Outcome
General comment From a scientific point of view the section headings of the principles related to the risk and exposure assessments may be presented in a logical way. However, when taking into account what is happening in practice, the requirements of the proposed guideline are not realistic at all. The limitation of the guideline to newly developed products is welcomed; however if it is applied systematically to all new products without estimation of potential risk (exposure and degree of hazard), this would be a disproportionate measure putting further at risk the availability of veterinary medicinal products. We would regard it as essential that all requirements for studies are assessed on the basis of need, and kept proportionate to the risks, as judged from a simple and realistic initial risk assessment (c.f. decision tree for environmental impact assessment). No additional studies, beyond the standard toxicology package in Part III, should be necessary for low risk products.	The guideline is designed in such a way that restricts the data needs as much as possible. It also offers flexibility to applicants in terms of alternative methods and use of justifiable assumptions.
It has to born in mind, that human beings are not exposed to veterinary medicinal products (single or infrequent exposure) like other chemical products, such as detergents, heavy metals, etc (frequent or daily exposure). Furthermore most of the products with higher potential risk are administered by professional people and the amount of the product being administered is very low. These points must be adequately taken into account.	Professionals may come into contact with veterinary medicines on a daily basis, and are sometimes exposured to large volumes (e.g. sheep dippers). The type of user and the frequency and extent of exposure are indeed taken into account in this guideline.

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1. Scope of application In addition to clearly limiting the scope to new products, more guidance is needed on how the guidelines should be applied: • To ensure that excessive data requirements are not unnecessarily placed on inherently safe products; • To ensure that, where a risk is identified, the data requirements are proportional to the risks, and the risk: benefit assessment (e.g. also consider risk to animal or public health if the product is removed from the market). • The guideline focuses on biological risks, and does not take into account that some products may also pose a physical risk (e.g. some aerosol formulations may be flammable).	• the CVMP does not agree that the guideline demands excessive data requirements • normally consideration is first given to data requirements, then the provision of data allows for the identification of risks based on the assessment of that data. Hence, data requirements can not be based on the outcome of a risk assessment. In addition, risk:benefit assessment is done in the regulatory process, not in the risk assessment, and thus it is no part of this guideline. • the guideline requests relevant physico-chemical properties (like flammability).
2. Scientific requirements The scientific requirements and data to be provided are based on chemical substances used at a larger scale than veterinary medicinal products. Clear and specific guidance on exposure estimation relevant to the veterinary sector is needed. For the majority of products it should be considered whether the need for studies could be obviated by the inclusion of standard global safety warnings in the packaging.	The scientific requirements and data to be provided are veterinary medicines related. Regarding the exposure estimation: more specific guidance is very difficult to give because of the wide variety of products and uses. Including standard global safety warnings (not based on any data) is not justifiable. Warnings must have a relation to the actual risks, and safety measures must reduce these actual risks. Using standard warnings might warn users for risks that do not exist, or prescribe measures that are not needed. Nevertheless, applicants may omit the submission of studies as long as it will be adequately justified (see guideline chapter 5). Furthermore, published literature or handbook-information could replace studies as long as it provides adequate information.

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Comments on chapter 1: Introduction Paragraph 2: In fact the legislation does give guidance on the data requirements necessary to assess user safety. In Annex 1 to the veterinary Directive in Part 3 A Safety Testing, only part 3.1 – Single-dose toxicity - is identified as being relevant to user safety ("used to predict: - the possible effects of accidental administration to humans.") The studies are identified (normally studies in 2 mammalian species and two routes of administration). If "substantial exposure" is anticipated, these routes should include dermal and inhalation. The Directive then requires "a thorough discussion of any risks for persons preparing the medicinal product or administering it to animals, followed by proposal for appropriate measures to reduce such risks". In other words, no extra data is required, beyond making sure the routes of administration in single-dose toxicity studies are relevant if substantial exposure is anticipated. The user safety assessment is clearly based on the results of the safety studies, but is to be a paper exercise based on a thorough discussion of the risks. The Introduction to the guideline should be re-written to reflect this.	Single dose studies are indicated as being relevant in the Directive[1] for the user safety. But other studies are also relevant, e.g. studies on mutagenicity or local toxicity. However, there is no list of data-requirements for user safety assessment in the Directive. Hence the legislation is very unspecific about this. Clearly, a "thorough discussion of any risks" is only possible when adequate data are available. In addition, methods for risk assessment are not specified, nor are the options and recommendations for risk reduction measures. As a consequence, Member States may use or ask different studies, focus on different endpoints of toxicity, use different methods for risk assessment, and may recommend different measures for risk reduction. This guideline is developed to provide guidance on these matters, and to contribute to the harmonisation of user safety assessment and recommendations.
Comments to chapter 2: Scope Paragraph 3 should be re-written for the following reasons: Paragraph 3 confuses misuse and accidents. Only foreseeable accidents should be within the scope. All misuse is deliberate (either by commission because someone has decided to ignore the instructions for proper use, or by omission because that person has decided not to read the instructions and is therefore using the product incorrectly) and should be excluded. This paragraph should also be re-written to discriminate correctly between misuse and abuse. Accidental self-injection is an occupational accident; intentional self-injection of an animal antibiotic is misuse, and intentional self-injection of a narcotic drug is abuse. The reference to dangerous drugs is also misleading. In fact many drugs, including veterinary drugs, are not locked up because they are dangerous *per se*, or to prevent misuse as this sentence implies, but to prevent abuse.	The point that all misuse is deliberate is not accepted. What in the guideline is meant by foreseeable misuse is clearly defined in the glossary. However, because the wording may lead to debate, the proposal is accepted. The text of the guideline "foreseeable misuse (including oral misuse and accidental self-injection)" has been changed into "foreseeable accidents (including accidental ingestion by children and accidental self-injection)". The glossary will be changed accordingly, but the explanation given in the glossary will be retained. This means that the (foreseeable) use <u>not</u> according the instructions is still considered.

[1] Directive 2001/82/EC of the European Parliament and of the Council dated 6 November 2001

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Comments to chapter 3: Principles of assessment This section should be completely re-written for the following reasons: 1) The opening sequence is in the wrong order. Risk analysis texts recommend the following order: hazard identification, hazard characterisation, exposure assessment, and risk characterisation. In practical terms, this makes more sense for two reasons: a) If the hazard is characterised as being highly insignificant, there may be no need to waste time doing an exposure assessment, as the risk characterisation will be low anyway. b) The hazards are often identified and characterised long before a formulation is even developed. Toxicological studies are often carried out early in development; often before a product formulation has been developed. For veterinary medicines developed from human drugs, the hazards may have been identified and characterised long before the veterinary use was even envisaged.	It is recognised that the order of items in the risk analysis is slightly different from the usual order. This has been done on purpose. The reason being that it will prevent unnecessary testing. For example, a capsule administered by a veterinarian will not lead to oral, dermal, or inhalation exposure of this person. In such case a simple exposure assessment will indicate that no toxicity studies are needed to assess the user safety. Hence, the exposure assessment can not be considered a waste of time. If doing the safety studies first, without looking at the exposure (and relevant routes of exposure), studies with all routes of exposure would have to be provided, also for the capsule mentioned above.
2) The sentence "All anticipated exposure scenarios…." is unclear guidance. The applicant should only have to consider all realistic routes of exposure that might realistically occur with the product.	"all anticipated exposure scenarios" means only the exposure scenarios that are found to be relevant. The word "anticipated" will be substituted by "relevant" to make it more clear.
3) The same paragraph gives the distinct impression that the applicant will be expected to conduct additional studies. This should be re-written in line with the legal framework. Clearly the need for additional studies should be exceptional and justified only if "substantial exposure" with a significant hazard is anticipated.	Any additional studies will only have to be provided when there is a relevant exposure. This is the reason why the exposure assessment has to be done first. This has been ilustratted in table 2 of the guideline.
"The procedure for risk characterisation consists of comparing the exposure levels to which the user be exposed, with the exposure levels at which no adverse effects are expected". The guideline should make it clear that normally this comparison is done with the NOEL in the existing animal studies (or with ADI values when available).	The comment regarding the NOEL is not fully understood. NOELs may also be derived from human studies when available and appropriate. An ADI may not be the appropriate reference value in all cases. Other reference values like the acute reference dose and AOEL are offered in the guideline to use when appropriate and justified.

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Comments to chapter 3.1: Professional and non-professional users This section should be re-written as much of the content is controversial and open to debate. It is not the job of industry to protect users against mis-use beyond a general warning to store, use and dispose of the product as instructed; industry's responsibility is to provide appropriate safety warnings under the conditions of use. It can be emphasized that professional users are likely to routinely observe "the standard precautionary measures". Pharmacovigilance data suggest that many adverse reactions to veterinary medicinal products in humans arise not because of inadequate warnings or advice, but because of failure to follow that advice by professionals such as sheep farmers, cattlemen, and contract sheep dippers. The Guideline states "Professional users are also expected to read the package insert, whereas non-professional users may or may not do this". As an industry, we expect *everyone* who uses our products to read the product literature, not just professional users. However, if the Guideline is suggesting that professional users are *more likely* to read the package insert, label etc., then for reasons already explained, we as an industry would strongly dispute this. The reference to "children" as "non-professional users" is entirely inappropriate; they have no place in administering medicines to animals.	The distinction between the different types of users is important because it might lead to different exposure characteristics, like frequency of exposure. Also the level of training and experience may influence for example spillage scenarios. Please see Appendix I where this is illustrated. Regarding children, please see chapter 2 (scope) for explanation.
Comments to chapter 4.2: The tasks and situations that lead to exposure Table 1 could be improved by including more detail under "Administration to animals". IFAH-Europe will be pleased to submit detailed proposals to facilitate re-writing of the guideline.	The CVMP will consider additional information provided to improve current guidelines in the light of experience.
Comments to chapter 4.3: Exposure scenarios IFAH-Europe has proposals that it believes could significantly improve this section.	The CVMP will consider additional information provided to improve current guidelines in the light of experience.

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Comments to chapter 4.3.1: The type of user IFAH-Europe has proposals that could significantly improve this section. It doesn't really need "to be indicated" if the product is intended for use by professionals" etc. It is usually evident from the type of product (gaseous anaesthetic vs. flea-collar) and (to some extent) the legal classification (POM).	The CVMP will consider additional information provided to improve current guidelines in the light of experience. As explained above, the type of user may influence the exposure characteristics and therefore it needs to be indicated. The Committee agreeds that sometimes the type of user is obvious.
Comments to chapter 4.3.2: The routes of exposure The second bullet point is too extreme. Much of a non-respirable fraction is exhaled, or gets only a short way beyond the nostrils. This is particularly true with dusty feed formulations when much of the airborne material is inert vegetable matter, limestone etc. Each product should be evaluated based on its particle size, properties, and formulation but in the absence of other data it may be assumed that the non-respirable fraction will be swallowed.	Please see the glossary where respirable and non-respirable fractions are specified (in line with scientific consensus and use in other regulatory frameworks). Probably it is meant that the fraction that cannot be inhaled (aerodynamic diameter more than 100 µm). However, of the particles that can be inhaled (less than 100 µm), the larger particles (more than 1-5 µm) are being scrubbed in the nasopharyngeal region and subject to oral ingestion, whereas smaller particles (less than 1-5 µm) settle in the tracheobronchial or pulmonary regions, or are being exhaled. Of course, each product should be evaluated based on its particle size, properties, and formulation. However, in absence of any data (in particular the particle size distribution) it is impossible to determine which part of an inhalation exposure is non-respirable. It is evident that such data are available to the applicant and should therefore be submitted.
The next section is misleading and requires re-writing. • the warning "keep out of reach of children etc" will not prevent accidental ingestion by children; only *observation* of the warning will achieve this. However, an applicant could argue that a veterinary surgery is inaccessible to children under most circumstances, and so medicines that are only used there like anaesthetics and euthanasia agents present few risks.	The Committee agrees that it is only the *observation* of a warning that prevents ingestion. The text will be amended accordingly. It is correct to indicate that the applicant could argue that a veterinary surgery is inaccessible for children under most circumstances. However, the guideline states that accidental ingestion by children is considered only for consumer products, hence not for products like anaesthetics.

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• the risks of oral ingestion should be considered for all veterinary medicinal products (N.B. delete the reference to consumer products).	The CVMP did not consider oral ingestion by children for professional products, because professionals are expected to store the medicines properly.
• If the safety data suggest that there is adequate reason for concern, child resistant packaging should be considered (N.B. the guideline is about the assessment of user safety so child resistant packaging should be considered, recommended, mandated, but the guideline cannot give a blanket prescription that it must be "used").	The comment is accepted. The word "used" has been substituted by "considered".
Comments to chapter 4.3.3: The components of a product etc. The final sentence (To what users are exposed…) is very unclear and needs re-writing.	In agreement, the text has been amended "*For each exposure scenario, it should be specified to what (e.g. whole product, components, dilution) the user is exposed.*"
Comments to chapter 4.3.4: The likelihood of exposure This section should be re-written as it is does not give comprehensible guidance. As an example it says that there is a low probability that an accidental self-injection will happen, but a risk assessment for this is required. Does this mean that each perceivable exposure scenario has to be considered regardless of the probability of the event? It cannot be assumed that exposure will occur at each opportunity, or even that exposure will occur every time that the product is used. For example, a veterinarian using a product intended for euthanasia of small animals may be potentially exposed to the product if the bottles breaks on impact, from drips around the septum, by expelling excess product from the syringe prior to use, from accidental self-injection, and by needle-stick injury from the discarded needle - not to mention misuse (deliberate self-injection for pain relief) and abuse (barbiturate addiction). However, it is extremely unlikely that all of the "accidental" events would occur in anyone exposure incident, or that any one event would happen every time the product is used. The assessment report should address these issues.	The chapter says indeed that each perceivable exposure scenario has to be considered, but it also says that the probability that a scenario takes place in practice should be taken into account in the exposure assessment.
The next paragraph is also unclear and possibly too far-reaching: Does the applicant have to search and retrieve all data on the incidence of exposure events related to similar formulations? : ..."(type of) product ..". This does not seem reasonable.	It is not unreasonable that applicants retrieve and submit relevant data.

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Comments to chapter 4.3.4: The rate, extent, duration, interval and frequency of exposure IFAH-Europe received a considerable volume of expert comment to this section, indicating that there are significant concerns with it. Some of these comments are provided below to illustrate the need for more in-depth consultation with industry experts. This would most easily be achieved by asking them to provide alternative text for consideration by the CVMP and its working group.	The CVMP will consider additional information provided to improve current guidelines in the light of experience.
- We believe that the reference made to other chemical substances to calculate the exposure rate should be done carefully as the use, volume etc. of veterinary medicinal products cannot be compared to these chemicals falling in the scope of Dir. 93/67. - Third paragraph: The sentences regarding "measured exposure data" and the fact that "adequately measured and representative exposure data are preferred to model calculations" suggest that exposure of the user would have to be directly measured in a representative group of users. For ethical reasons, this request should be deleted. Generating such data in humans under "in use" conditions of new substances before MA would appear unethical and would be inconsistent with the aim of the Guideline to protect the user of the VMP. In most cases, models should be employed to assess the new substance, and measured exposure data could be provided later, from monitoring of some kind of users (e.g., professionals) subject to ethical committee approval. In the mean-time a model based on adequately measured and representative data of residue of substance (e.g., residue that can be dislodged from the fur of pets treated by topical products) could provide a valuable assessment of human exposure (e.g., skin exposure in the case considered), without necessitating effective exposure of a representative group of users (including, e.g., children, gestating women, elderly...). This is consistent with the usual toxicological assessment of a product (c.f. MRL Regulation), for which it is the rule to use animal-derived data in order to extrapolate them to humans, provided a safety factor is applied to ensure a satisfactory margin of safety for humans.	The CVMP does not agree with the comment. The expression "measured data" does not automatically refer to internal exposure of humans. It could for example also refer to a stroking test on the fur of dogs. Such experiments are not unethical. Still, the guideline allows for model calculations and assumptions. This implies for example that in absence of measured data and available models, the exposure may be estimated based on assumptions alone. In such case the assumptions have to be clearly indicated and justified.

GUIDELINE SECTION TITLE	
Comment	Outcome
- Reference to TGD and Dir 93/67: Reference to the TGD should be deleted as models described in the TGD are not applicable to VMPs on both a regulatory and technical point of view. This and the raft of related legislation directed at the protection of humans from exposure to chemicals was adopted for types of substances that should not be confused with pharmaceuticals, and this is specified in Article 1 of Directive 67/548/EEC which exclude medicinal products. This is also specified in 2.3.2.2 of the TGD showing that "many consumer products (e.g., pharmaceuticals) are subject to other EU legislation and the legislation (Directive 67/548) excludes from notification substances for which approval procedures exist and for which requirements are equivalent to those of Directive 67/548".	It is true that different legislation exists for different groups of substances. However, this does not imply the need for different methods of risk assessment. To the contrary, it would be beneficial to treat different kinds of substances in a similar way (but still taking into account the specific characteristics of the groups).
On a technical point of view, some of the exposure models proposed in the TGD are out of scope of the present GL for VMP; modelled data for e.g. inhalation exposure assessment are not yet fully rigorous; the model EASE (Estimation and Assessment of Substance Exposure Physico-chemical properties) should be regarded with caution, according to the TGD. As shown in 2.2.2.5 of the TGD, available models for "chemicals" are either specific mathematical models that cannot be used for more general application, or empirical/knowledge based models based on many years of accumulated experience (thus these would be hardy applicable to new VMP since no accumulated experience would be available). - Computer tools were developed for estimation of consumer exposure (TGD, Appendix II, section 4) but do not seem adapted to VMPs. More work is needed to validate the tools for VMPs.	The reference to the models mentioned in the TGD does not mean that each of these models are suitable for the assessment of Veterinary Medicinal Products. In fact, the CVMP guideline states to use these models “where possible”. It is suggested to change this into “where possible and applicable” to make it more clear. It was agreed that some models are not applicable. However, some models could be (and have been) used for Veterinary Medicinal Products (e.g. some models included in the ConsExpo tool). The CVMP has made reference to these models so that applicants and assessors can consider them (and their applicability).

GUIDELINE SECTION TITLE	
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Exposure factors in Appendix II: "- those found in Exposure Factors Handbook of the EPA" Values seems to be more specifically adapted to US populations (e.g., mean bw is 71.8 kg), and is non homogenous with current EU regulation on MRL (the recommended bw of adults for ADI calculation is 60 kg).	Indeed the human bodyweight figures are different. Please note that the EU TGD uses 70 kg for a standard human body weight. The CVMP has not established exposure factors to be used in the assessment of the user safety of veterinary medicines. Therefore, the CVMP had to fall back on other available exposure factors. It is preferable to use the European figures, however, when European figures do not exist for a specific factor, the figures of the EPA could be used.
The need to specifically address children should be deleted: children are not users. There is no request for a pharmaceutical product for adult human use to provide a risk assessment for children. In our opinion the risk of a child being exposed to a VMP is rather negligible when compared with a human pharmaceutical product stored in a family home.	Regarding children, see chapter 2 (scope) for explanation.
The sentence beginning "In some cases, …" is superfluous and should be deleted.	The CVMP considers that the sentence introduces the next one and therefore should be maintained.
The final paragraph "Irrespective of the method used …" is very unclear and is an example of where the current wording needs significant re-writing in order to deliver the objective of providing concise and clear guidance. It is unlikely that exposures to VMPs by each route occur simultaneously in each type of user/or person exposed. From a pharmacokinetic point of view, simultaneous exposure would also depend on the substance being significantly absorbed via different routes (e.g. dermally and orally). The sum of routes to calculate the total systemic exposure would be irrelevant if the product is not significantly absorbed through the skin.	If a substance is hardly absorbed following one of the routes, then this would be reflected in the calculated total systemic exposure, because absorption is taken into account when calculating systemic exposures.
From a toxicological / or toxicokinetic point of view: Summing exposure only makes sense if the toxicological effects via the different routes are the same. For example, if a substance induces a digestive effect by oral route but only dermatological effect by cutaneous route, summing exposure by oral and cutaneous routes would be irrelevant.	The total systemic exposure is calculated as an aid to assess the risks of systemic effects, not local effects.

GUIDELINE SECTION TITLE	
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• "Make aggregate exposure from both uses when a product (e.g., a flea treatment) is to be used to treat the animal and its environment (beddings etc)*" • "A URA should evaluate the risk for the user when apply the VMP under the MMA conditions" A licensed VMP is rarely (if ever) used to directly treat the environment of the animal and the animal. Secondly, even assuming both uses for a VMP, it should be noted that for VMPs the "high-end user" is generally considered for a user safety assessment. Aggregating exposure from both uses of a product would imply the assumption that the user would be exposed to the highest levels of the product simultaneously from both uses. The likelihood of this happening should be considered as exceptionally small and aggregate exposure could lead to unlikely and unrealistic combinations of residential exposure scenarios that could occur independently.	Examples of such products exist. It should be noted that the CVMP offered to include the likelihood of exposure in the exposure assessment. If the likelihood of being exposed to the highest concentrations of both uses is very low, then this has to be taken into account in the characterisation of exposure.
Comments to chapter 5: Hazard identification and characterisation This section completely ignores the fact that hazard identification will have been for the most part completed before exposure assessment is even considered. Therefore the exceptional need for additional studies will depend upon the existing toxicity assessment of the drug or product arising from data generated for Part III and, if relevant, to support an MRL application under Regulation (EEC) No. 2377/90. This is better reflected in Table 2.	A paragraph has been added in the guideline to reflect the comments: "*Generally, most of the toxicity studies are already part of a product dossier (part IIIA). The need for any additional studies depends on the exposure, as reflected in table 2. In some cases the nature of the substances indicate the need to focus on specific end-points of toxicity or pharmacology.*"
- First bullet point: The references to dose-response should be deleted (it should read "The no-observed effect level (NOEL), or, if this is not possible, the lowest observed effect level (LOEL) should be identified" (why introduce the NOAEL when NOEL is used for ADI/MRL evaluations?)	It is not explained why the reference to dose-response should be deleted. The CVMP has used both NOEL and NOAEL for ADI/MRL evaluations. Normally this would depend on whether non-adverse effects were present (and accepted) at lower doses.
- Second bullet point: "The systemic effects of the product have to be addressed". For most products it will be sufficient to consider those of the active material. However, in all cases, the applicant should consider the biological properties of the excipients and, if these raise cause for concern, these too should be discussed. On rare occasions, it may be necessary to consider conducting specific toxicity studies with the formulated product."	The guideline does not state "The systemic effects of the product have to be addressed". Instead, it states "the systemic effects have to be assessed for the active ingredients only". The tenor of the comment is however accepted, and it is believed that this is also already expressed in the text of the guideline.

GUIDELINE SECTION TITLE	
Comment	Outcome
Again, this is a guidance note so references to a regulatory authority asking for data are inappropriate. Moreover, this is patently not true. The Directive requires the risks arising from preparing the product and using it to be assessed. Clearly, if a product contains an organic solvent, then the biological and physical risk (fire, explosion) need to be evaluated.	The comment is agreed. The text has been amended accordingly, the reference to the regulatory authorities has been deleted.
- Last bullet point, it would make sense to include frequency: "...represent an adequate reflection of the duration/frequency of exposure...."	The comment is agreed. The text has been amended accordingly ("*frequency* " has been added).
There should be mention or cross reference to national, EU or international occupational limits, where these exist, for airborne dusts and gaseous products and vapours.	The comment is agreed and it is reflected in the last paragraph of Chapter 6.2.
- Table 2: The potential value of target animal safety (TAS) studies should also be considered. The requirements in Table 2 are rather rigid and not entirely clear. Especially the testing of the "whole product (active ingredient plus excipients) or components/ solutions/dilutions". **Dermal**: Photo toxicity: there are no well-established models, and this is only of concern if the product absorbs light at relevant wavelengths.	This comment is agreed. The demand for phototoxicity has been deleted.
Parenteral: Acute parenteral toxicity is only relevant if the product is acutely toxic, and this can often be determined by data from other routes e.g. oral. IFAH-Europe believes strongly that the industry should NOT have to test every injectable product for systemic parenteral toxicity because of recent adverse events in humans following accidental injection of an antibiotic formulation. For vaccines formulations (and for some pharmaceutical formulations) the adverse effects of concern do not relate to systemic activity, but to tissue damage following high-pressure automatic injection.	Indeed, accidental self-injection is a single exposure, and hence acute reactions are relevant. Route-to-route extrapolations are possible, as indicated in the guideline, as long as route-specific kinetics and metabolism is accounted for. Furthermore, it should be noted that acute systemic toxicity is not only determined from single dose toxicity studies. Depending on the substance, other acute effects (not observed in the standard LD_{50} studies) need to be considered (e.g. abortion for prostaglandins). Tissue damage is considered a local reaction. As indicated in the guideline, target animal safety studies may provide adequate information on both local and systemic effects following parenteral administration.

GUIDELINE SECTION TITLE	
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Inhalation: For respiratory irritation and sensitisation there are no standard models or methods available. The solution for sensitisation is kind of given, but why does it have to be repeated for the formulation when the properties of the active and the excipients are known?	Irritation and sensitisation are local effects that can be induced by the active ingredients as well as by the excipients. Consequently, for such local effects studies with the product would be preferred. However, the guideline also offers the possibility to deduce the effects of the product from the data on the single components of the product (see last bullet-point of chapter 5).
Listing the US EPA: IFAH-Europe companies have had mixed experiences with European regulators when using EPA protocols, as on occasions they are rejected when deviating from the EC standard.	The CVMP and its Safety Working Party have agreed on the current guideline, so such problems should not arise anymore in the future.
Comments to chapter 6.1: Qualitative risk characterisation This section needs to be re-written. We strongly disagree with the final statement in this paragraph - "...inability to make a quantitative risk characterization is that if hazards are identified, it must be assumed that the effects will occur at any exposure level". This contradicts the previous statement in the same paragraph. Some of the statements made in 6.1 are not entirely true. For example, irritancy can be scored, as can sensitising potency, and substances (for example) can be classed as irritants, severe irritants or as corrosive. This is certainly semi-quantitative, and some authorities would argue, quantitative characterisation. Furthermore "any exposure level" would not be scientific. Most effects have a threshold dose.	The CVMP agreed to amend the final statement to: *"If such information is not available, it must be assumed that the effects will occur at any exposure level"*. Although a proper quantitative risk characterisation is not possible, assessors should try to use all available information on severity of effects at relevant exposure levels to obtain a qualitative characterisation of the risk. Only when such information is not available, it has to be assumed that the effects will occur at any exposure level (despite the (unknown) threshold dose).

GUIDELINE SECTION TITLE	
Comment	Outcome
Comments to chapter 6.2: Quantitative risk characterisation This section can be improved in a number of ways. We consider the introduction of NOAELs to be unnecessary. In the second paragraph: "Where the exposure estimate is higher than or equal to the NOEL, the risk for the user is considered to be unacceptably high." This is too rigid. Often the NOEL is much lower than the LOEL, and the effects at LOEL may be marginal. Thus a valid argument could be made. And all the other factors may also have an influence on the need of additional safety margin. Risk management options may lead to acceptable risk as well.	The proposal in the guideline is similar to the assessment in other similar regulatory frameworks. When there is a huge span between NOEL and LOEL, it must be concluded that the dose levels in the study were not well chosen.
With reference to the two factors of 10 following the list of bullet points: the use of a x100 safety factor to a NOEL, amounts to the ADI value for drugs that are used in food animals and have EU MRLs. No guidance is provided on how to apply the WHO document (WHO, 2001).	Using a 100 safety factor on a NOEL does not automatically result in an ADI. That depends on the NOEL that is chosen (from a lifetime study, from an acute study, from an inhalation study, from a dermal study, …). The WHO document itself explains how chemical specific factors are derived. In essence: inter- and intraspecies extrapolation factors are subdivided into kinetic and dynamic subfactors. Information on characteristics of the chemical relevant for any of these subfactors could lead to chemical specific (sub)factors. In absence of such information the default factors are used.

GUIDELINE SECTION TITLE	
Comment	Outcome
Comments to chapter 7: Risk management Again, there are more unsubstantiated claims about the behaviour of non-professional and professional users, and the remarks made earlier are also relevant here. The public now have considerable access to potentially toxic or dangerous materials (pesticides, biocides, household chemicals, petrol) and most of them manage to use these materials safely. Patronising assumptions about the behaviour of different groups should be avoided.	Reference is made to the availability of other chemicals to the general public. It should be noted that also for such products a safety assessment for professional and non-professional use is made with comparable considerations (see e.g. the recent biocides guideline). In addition, non-professionals apply the products in a situation not relating to labour law, and we have no control whatsoever over the observation of warnings printed on the product label and package insert. It is also obvious that non-professionals have limited access to PPE. Therefore it is essential that products used by non-professional must be acceptably safe, or have an acceptable risk with limited protection. For professional users this is different: there are more tools to control the observation of warnings, and professionals have more access to PPE and more experience in using it. Therefore professionals can be trusted to handle more dangerous products with higher needs for risk reduction.
Comments to chapter 7.3: Risk control options The bulleted list of options and the list of criteria require refinement. For example, method of distribution does not necessarily mean restriction, nor does it protect veterinarians. Once dispensed, it matters little that the product was bought in a supermarket or pharmacy, or obtained via a prescription. Pet owners are free to have accidents with products or misuse them regardless of the supply chain. Some of the bullet points are inappropriate for new products and new applications for marketing authorisations.	In the case of prescription medicines, the veterinarian is obliged to inform the user about the product and instruct the user how to use it. This would give more assurance that a product will be used according to the instructions. The preferred option would be that certain products are restricted to use by veterinarians only. However, some Member States have no legal possibilities to achieve this.

GUIDELINE SECTION TITLE	
Comment	Outcome
Comments to chapter 7.3: Risk communication The user safety assessment should identify suitable and relevant warnings and safety measures for inclusion in the SPC and package insert. These should inform the user of the nature and extent of the risks. Global general precautions that can be applied to all veterinary medicines could be considered.	The CVMP agrees. The comment is in line with the guideline.
Medical and other treatment advice. No advice is given on this aspect in the Guideline. However, some exposures are best treated medically, and some are only treatable medically. This should be considered as part of the user safety assessment. For toxic materials, the user safety assessment should consider appropriate medical advice for users and medical advice for doctors, which should feature prominently in the product literature.	This would be covered in the Chapter 8 by point D: "What to do in the event of exposure".