codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 7 **CX/RVDF 01/7-Add. 1**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
Thirteenth Session
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COMMENTS ON THE PROPOSED DRAFT GUIDELINES FOR RESIDUES AT INJECTION SITES

ARGENTINA

1. There are no technical objections in regards to the technical aspects of the determination of Acute Reference Doses, taking into consideration that, at the time of their implementation, it will be necessary to perform a prioritization for the establishment of the corresponding value for the active principles of use in veterinary medicine, for which prioritization criteria must be established.

2. Regarding the Sampling Protocol for Regulatory Enforcement Purposes, it is considered acceptable that the duplication of samples be performed within the inspection programs of the importing countries' ports of entry. It must be taken into account that it would be necessary to modify the sampling procedures duplicating the samples corresponding to muscle.

3. It is evident that the duplication of muscle samples for analysis will imply, without a doubt, a greater expenditure on behalf of the meat industry.

BRAZIL

4. Brazil supports the document.

CUBA

5. According to the document, compliance with the fundamental bases of this document will permit the protection of public health, and at the same time will permit the condemnation of only those carcasses that do not meet the corresponding criteria for the acceptable level of acute dietary ingestion and of chronic dietary ingestion.

CZECH REPUBLIC

6. We would like to draw your attention to a discrepancy in the enlistment of vitamin A and selenium to Annex II (council regulation 2377/90) and the requirement of determination of WHP for tissue after injectable application (with respect to injection sites).

DENMARK

7. Denmark supports the purpose of the Proposed Draft Guidelines for Residues at Injection Sites. However, Denmark cannot support the suggested $MRLVD_S$ for residues of veterinary drugs at the injection site as described in the proposed draft guidelines. From the Danish point of view, and as previously commented upon in the last proposed guidelines, the suggestion of a second muscle MRLVD will lead to a decrease in consumer safety.

8. Some injectable formulations contain ingredients that cause excessive tissue reactions, which can result in non-confirming residues at the injection site, despite the WHP being observed. The solution to this problem is not to introduce a $MRLVD_{IS}$, but to encourage the industry to develop formulations that do not cause tissue irritation. This would be the best solution both from a consumer point of view and in regard to animal welfare.

9. In the document it is mentioned that MRLVDs traditionally have reflected the maximum residue level in edible tissues remote from the injection site. Denmark suggests a change in this approach. One MRLVD for muscle tissue that also covers residues at injection site will in our point of view accommodate the best protection of the consumer. A non-confirming residue sample can then be condemned as illegal use of a veterinary drug. Depletion studies on injection sites should be requested from the applicant, and WHP can be set according to these studies. In long-acting formulations, residues at the injection site can persist for weeks, and this will result in long WHPs. This is not a consumer safety issue, but an economical problem for the farmer and therefore the length of the WHP will become a very important competition parameter for veterinary medicinal producers. It is true though, that very long WHP can lead to incidents where animals are slaughtered before the end of the WHP, but from an intake point of view the acute RfD will not solve the problem, it will only legalise the shorter WHP and the higher intake.

10. The suggested use of $MRLVD_{IS}$ based on the Acute RfD implies that the consumption of an injection site with level of residues above the muscle MRLVD is a “once in a lifetime” event. This assumption needs documentation, also because injection sites are not always visible. The occurrence of tissue damage from injections of medicines is highly connected to the skills of the producers when they inject the medicine. In 1996, there was found tissue damage from injection of medicine in 15 % of the slaughtered sows in Denmark, by education of the sow producers in injection techniques, and by focusing on the problem, this figure has been reduced to 1-2 % in 2000. Therefore, good practice in the use of veterinary drugs is a very important issue to avoid tissue damage and encapsulation of medicine.

11. The method of sampling tissue at the injection site can affect the apparent concentration of residues and therefore it is desirable to standardize the sampling method as far as reasonably practicable. Even if residues in a 300 g muscle sample containing a hidden injection site have depleted below MRLVD, there is still a risk of condemning the carcass, if the sample taken for analysis is small and contains the centre of the injection site and thereby the most concentrated part. This problem remains to be solved. Residues at the injection site do therefore pose a potential problem for residues surveillance, even if the injection site in the future is included in the muscle MRLVD.

12. The suggestion in paragraph 23, that in case of packed commodities the second sample can be taken from a different carton, implies that a higher level of veterinary drug residues will be accepted, because the non-confirmed sample may indicate illegal use of the drug. This implies a hidden acceptance of illegal use of veterinary drugs.

13. Paragraph 24 states that injectables should not be given in volumes greater than 10 ml per injection site. In cattle, this approach is not possible. A typical dose is 50 ml/day and with a treatment period of 3 days this would result in a total of 15 injections per cattle. Multiple injection sites should not be used as a way out of residue problems.

14. If these guidelines result in a recommendation for using an acute RfD, it should be noted that the microbiological ADI should also be used when setting the acute RfD. An acute RfD approach should not be taken into consideration, if the calculated acute RfD is higher than the pharmacological or the microbiological ADI.

FINLAND

15. In general Finland feels that the document should be processed to consider more consumer safety. Furthermore the document seems to be somewhat inconsistent to 'the from stable to table' principle. In addition to the short term exposure the significance of random long term exposure to residues is ignored. Long term exposure can sensitise to the residues, too. The possibility of combination of several drugs should also be taken into consideration.

16. The evaluation of MRLVD in injection sites might at first sight seem to be a good idea, but this a massive job which has to be financed by somebody even for old products. We feel that more stress should be loaded on the medical industry in order to encourage the development of such products that do not remain at the injection site.

17. The residues monitoring in the EU is targeted rather than random. Injection sites are not samples routinely. If the injection site has macroscopic changes, it is removed at the slaughterhouse. In the port of entry inspection it is not usually possible to sample injection sites since the meat is normally imported in pieces. We do not see the difference to the normal import control in the suggestion.

18. The idea of two samples in sampling protocol for regulatory enforcement purposes is unacceptable. The protocol would be too slow and costly to ever be impractical and one would need to know what substance to look for.

19. Paragraph 24: We support the idea of specific sites where injections would be allowed to be given. The proposed rule of maximum 10 ml volume per injection site is impractical and would either lead into even greater amount of injection sites or would either be ignored by the practising veterinarians. Multiple injections would not be feasible from the viewpoint of the treated animal. The wide area and number of injections would only widen the residue area.

SWITZERLAND

20. Is it intended to carry out particular studies for those veterinary drugs which are to be registered? Will there be any reconsideration of substances which have already been registered? Are only veterinary drugs included or also other substances or preparations (e.g. vaccines)? The draft should be limited to veterinary drugs administered only by the way of injection and not orally.

THAILAND

Port of Entry Inspection Programmes

21. Paragraph 20: We propose that the last sentence should be amended to read as follows: "All shipment of similar product from the same exporting establishment may be placed on an increased of part of entry inspection testing until a record of compliance with MRLVDis is re-establishment"

Proposed Sampling Protocol for Regulatory Enforcement Purposes

22. Paragraph 23: In the case of the second event, if the first sample is non-conforming with the respect to both the MRLVD and the MRLVDis, the carcass/consignment is failed, and there is no requirement to analyse the second sample for residues. The current corrective measures for non-conforming residue detection are instituted. We would like to propose that the second sample should be analysed for residues, since the product was already analysed from the exporting country . Therefore the result of analysis of the first sample which is different should be confirmed.

Additional Risk Management Measures

23. Paragraph 24: We propose to amend the second indent to read as follows: "injectables should not be given in volume greater than 10 ml/one injection (where practicable), and treated animals should be clearly identified in such a way that they can be tracked for the duration of the WHP." Reference: A recommendation of the Residue of Veterinary Drug at Injection Site, Implementation for Human Health and International Trade, COMISA, 1996

Appendix B-Glossary: WHP-Withholding Period

24. We would like to propose to delete "edible" in the first sentence, since the meaning of tissue is coverage edible tissue. Reference: Glossary of Terms and Definitions, Codex Alimentarius Volume 3-1995.

UNITED STATES OF AMERICA

25. The United States appreciates the excellent work on these proposed guidelines for residues at injection sites. We are pleased to offer some suggestions for consideration in finalising this document to facilitate compliance with Codex standards for foods in international trade.

Introduction

26. The U.S. suggests that the document should not limit potential causes of slow depletion of residues. We offer the following alternative for paragraph 1: "Some veterinary drugs exhibit a slow residue depletion profile from intramuscular and subcutaneous injection sites. This may be attributed to, among other things, their design as slow release or depot formulations, or irritation to tissues which may lead to excessive tissue reactions such as fibrosis, encapsulation or necrosis."

27. In paragraph 3, the U.S. suggests that the first sentence should make more specific reference for injection site residues for those veterinary drugs of major concern regarding acute pharmacological or toxicological effects. We suggest that the second portion of the first sentence be amended to cover other toxicological concerns. For example, following "selenium" insert: ", those with developmental toxicological effects and substances that may lead to allergic or hypersensitivity reactions in certain individuals (e.g., penicillins)."

Scope

28. In paragraph 5, the U.S. suggests that it is more appropriate to refer to the proposed guidelines as a safety assessment rather than a specific risk assessment for injection site residues as stated in the first narrative indent. We recognize that these guidelines are intended to address the issue of injection site residues in a manner that is consistent with safety assessment principles. Our second comment in paragraph 5 regards procedures "when applied" to national residue control programmes. Codex guidelines are applicable for products in international trade. However, it may be appropriate to suggest that the Codex injection site guidelines "may be applied" by individual Member States. This amended text should be considered throughout the document.

Purpose of Guidelines

29. In paragraph 6, while fully supportive of protecting public health of consumers, the U.S. suggests that here and elsewhere in the document our comments noted with regards to safety assessment versus use of risk assessment terminology and the appropriateness of applicability of draft Codex guidelines to national governments in paragraph 5 be considered.

Risk (Safety) Assessment of Residues at Injection Sites

30. In paragraph 7, the U.S. agrees that most JECFA safety assessments focus on low level, life-long exposures of residues in food and more limited assessments addressing occasional short-term exposure. We propose the following amendments for paragraph 7: Replace "risk assessment" with "safety assessment"; in the middle of the paragraph, insert "occasional" before "short term exposure"; and revise the sentence in line 5, beginning "In respect", with "With respect to the consumption of injection site residues, however, the published JECFA guidelines for recommending MRLs is not consistent with safety assessment principles applicable to dietary exposure that is of a occasional short-term nature." The third sentence, beginning with "The procedure", should make clear why establishing MRLVDs for chronic exposure is adequate (presumably what is suggested is that the model diet is sufficiently conservative).

Sampling protocol

31. The U.S. suggests that paragraph 8 should refer to "occasional short-term exposure scenarios". We again question the apparent focus of the paragraph on sampling protocols for national residue control programmes, however, we agree that member states may apply the Codex guidelines developed for product in international trade. Regarding a sampling protocol (comments noted below) the U.S. agrees that it is paramount that a sampling protocol will differentiate between non-injection site and injection site muscle. The condemnation of complying carcasses is not regarded as an acceptable means of achieving public health protection. We suggest an alternative for the last sentence: "With this approach, the emphasis remains on consumer safety while avoiding unnecessary condemnation of carcasses."

32. In paragraph 12, we suggest it would be helpful to include a reference or website address for interested parties, (e.g., http://www.fda.gov/cvm/guidance/guideline3toc.html).

33. Paragraph 13 suggests or assumes that the marker residue at the injection site will always be parent drug and will be equivalent to total residues of toxicological concern. The U.S. suggests that the appropriateness of the marker residue for the purpose of estimating the concentration of residues at the injection site must be confirmed. In general, injection site residues are comprised of a high proportion of administered compound, since post-absorptive metabolism has not occurred. Nevertheless, injection site residues need to be related to total radiolabeled residues (marker residue/total residue concept) for safety assessment purposes.

34. Paragraphs 14 through 16 reflect the most significant U.S. comments. As noted above, the U.S. suggests to insert "occasional" before "short-term exposure" and secondly, that in the safety assessment procedure, the residues should account for the ratio of injection site residues to total residues. The language from the previous U.S. comments, amended to correspond to the format of the current document, is still accurate. The previous U.S. comment proposes changing the MRLVD for the target tissue used for residue control programmes (at the minimum) so that depletion of residues will ensure that residues at the injection site are below the $MRLVD_{IS}$. Respectfully, we suggest the alternative language for paragraphs 14 to 16. In paragraph 14, consider using "Estimated Acute Intake (EAI)" as an alternative to Estimated Short Term Intake (ESTI). The equation in paragraph 16 should account for the relationship of injection site residues to total residues as measured by radiolabel studies (please see below).

35. The U.S. proposes that the paragraphs included in section 15 be deleted. The U.S. suggests paragraph 15 could be amended as follows: "The EAI is reconciled with the acute RfD. If the EAI exceeds the acute RfD, this situation needs to be re-evaluated, as appropriate."

36. In paragraph 16, the U.S. suggests that the equation needs to be revised since, as written, it equates EAI (ESTI) with acute RfD which is only the case if injection site residues are equivalent to total radiolabel residues. The equations would be as follows:

$EAI = MRLVD_{IS} * LP \div MR/TR$

Transposing, $MRLVD_{IS} = EAI \div LP * MR/TR$

37. The U.S. would draw attention to the value proposed for LP. The draft guidelines correctly refer to the JECFA model diet consumption of muscle tissue of 0.3kg. In the 52nd JECFA meeting, injection site residues were evaluated for doramectin (Ref.: *FAO Food and Nutrition Paper 41/12, page 32*). In this analysis JECFA indicated that residue concentrations were comparable for 0.3kg and 0.5kg samples of injection site tissue. This suggests little basis for selecting a larger sample size for residue analysis. However, other alternatives may be appropriate, for example, a statistical confidence interval approach, or the 97.5th percentile value for consumers of meat proposed by Australia.

National Residue Monitoring

38. In paragraphs 17 and 18, as indicated above, the U.S. suggests that discussion regarding a residue control programme at the national government level is not within the Codex terms of reference.

39. In paragraph 18, the U.S. suggests adding a concluding sentence, such as: "It is necessary to determine whether such non-conforming residues pose an adverse health concern to individuals that consume the injection site."

Proposed Sampling Protocol

40. In paragraphs 22 and 23, the U.S. suggests that guidance on sampling for analysis should be in accordance with the current requirements in Codex texts. Reference is made to *Codex Alimentarius, Vol. 3, Residues of Veterinary Drugs in Foods, Second edition, Section 3, Table A*. Specific guidance is noted for muscle tissue with regard to product submitted for residue testing. In those cases where the sampling instructions do not provide for the collection of two different muscle groups, Vol. 3 should be amended.

Additional risk Management Measures

41. In paragraph 24, the U.S. suggests that reference be made to safety assessment in lieu of risk management, and that the second highlighted note be divided such that the new entry would make a separate reference that "treated animals should be clearly identified in such a way that they can be tracked for duration of the WHP".

Appendix B – Glossary

42. The definitions should be reviewed to contain conforming language to the body of the document. Suggested definitions of acute RfD and EAI are provided below.

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43. Acute RfD: Revise the definition to indicate that this number refers to total residues in the same way that an ADI refers to total residues.

44. EAI - Estimated Acute Intake: Revise to conform to the terminology in document. indicating that the EAI is a percentage of the Acute RfD (the percentage should be corrected to total residues).

45. $MRLVD_{IS}$: Replace "short-term" with "acute" to account for the relevance to total residues as indicated above.

Appendix C - Methods for Establishing Acute Reference Dose

46. Australia has clearly indicated three possible scenarios. However, this section appears to place emphasis on the specific tests and, as a result, may diminish the larger issue of acute reference doses. The U.S. suggests that consideration be given to delete the three specific assessment categories and revise as follows:

> "The types of data needed to determine the acute RfD would depend on the drug product being evaluated and the manifested toxicological endpoints. In each case, the objective is to provide useful information upon which an estimate of the acute RfD can be made. Differences in the types of drugs, *in situ* metabolism and residue profiles, formulations, and potential for human exposure preclude *a priori* the establishment of a rigid list of studies that would be relevant for every situation."

47. In general, the agent being evaluated should be given orally in acute single-dose studies to determine a no-effect dose in a suitably sensitive, validated model animal species. If available, data on the effects of acute oral exposures in humans should also be evaluated.

48. The studies to determine the acute RfD would require adequate numbers of animals upon which valid scientific assessments could be made. The studies should be conducted under Good Laboratory Practices. The acute RfD adopted in practice would be based upon the RfD calculated from the most appropriate model system response."

49. Finally, we would suggest a general comment regarding harmonisation with other Codex Committees addressing acute reference dose concerns (e.g., CCPR).

CONSUMERS INTERNATIONAL

50. Consumers International supports the development of guidelines for residues at injection sites. We strongly support, as expressed in paragraph 6, that the first and foremost objective of these guidelines is the protection of public health. These guidelines can help ensure that consumers are protected from adverse effects associated with the consumption of animal products derived from the site where drugs are injected.

51. The report of the Twelfth session of the Committee states (ALINORM 01/31, para. 118): "The Observer from Consumers International expressed the view that in addition to acute effects, the document should address the potential for chronic effects resulting from consumption of the injection site, including chronic effects on a pregnant woman during a critical developmental period."

52. We continue to believe that the document should address this concern. Specifically, in paragraph 3 of the Proposed Draft Guidelines, the examples of drugs of concern due to acute pharmacological or toxicological effects appear for the most part to describe drugs by their particular pharmacological action. We are concerned about drugs that may result in long-term structural or functional deficits to the children of pregnant or nursing women who consume food derived from an injection site during a critical period of development. The timing of the exposure can be critical. Also of concern are drugs which may not provoke true allergic reactions but can lead to hypersensitivity reactions. We suggest that paragraph 3 be rewritten as follows:

"From a consumer safety perspective, the veterinary drugs of major concern with regard to injection site residues are those with acute pharmacological effects (e.g., B-blockers, B-agonists, tranquilizers, vasodilators, anesthetics), those with acute toxicological effects(e.g., preparations containing vitamin A or selenium, other neurotoxins or developmental toxicants), and substances that may lead to allergic or hypersensitivity reactions in certain individuals (e.g., penicillins, sulfas). The adverse manifestations observed are related to short-term dietary exposure and are, in the main, of an acute nature. However, the timing of the exposure (e.g., during a critical stage during pregnancy) can also be critical, and in such cases could lead to adverse effects observed over the long-term (e.g., impaired sexual or nervous system development)."

53. Furthermore, to ensure that sensitive subpopulations are adequately addressed, in paragraph 14 we suggest that the sentence state "BW = the average body weight for the population concerned (e.g., pregnant women, children)"

54. In paragraph 7, the second sentence states, "The procedure for establishing MRLVDs appears to adequately deal with drug residues of acutely toxic Compounds in the principal edible tissues included in the model diet." We suggest that the reasoning behind the statement should be clarified and confirmed.

55. The last sentence of paragraph 8 is unclear. We suggest deleting it, or rewording it as follows: "With this approach, the emphasis remains on consumer safety while avoiding unnecessary condemnation of carcasses."

56. In paragraph 12 there should be some indication as to how the 1994 FDA document which is referenced can be obtained. We note that it is not correct (in many cases) that the ESTI = Acute RfD.

57. In paragraph 16, it should be recognized that the 97.5th percentile is only one example of the consumption value that can be used. We suggest the following rewording: "Alternatively, national agencies may prefer to USE A HIGH percentile meat consumption value (E.G., 97.5th) for consumers, derived ... ."

58. In paragraph 18, we suggest that the following sentence be added to the end of the paragraph: "It is necessary to determine whether such non-conforming residues pose a threat to consumers who ingest the injection site."

59. in paragraph 24, we suggest that the last sentence be modified as follows: "It is recommended that the following additional risk management measures be taken with veterinary injectables to prevent consumers from ingesting injection site residues and to avoid disruptions to trade."

EUROPEAN COMMUNITY

60. The European Community would like to offer the following comments on the "Proposed Draft Guidelines for Residues at Injection Sites" based on the scientific evaluation performed by the Committee for Veterinary Medicinal Products in the European Medicines Evaluation Agency. (*The EC has submitted the scientific evaluation with these comments and they are posted in italics below).*

61. From a consumer point of view, main focus should be to minimise the risk of exposure to the injection site. Current European Community legislation is in conformity with this objective.

62. The draft Codex guideline on injection site residues can be considered as a basis for discussion but some of the fundamental concepts require further consideration. These points are summarised below.

63. The concept of $MRLVD_{IS}$ should be avoided as this would result in two different MRLs being established for muscle tissue. Problems with concerns among consumers as to which residue levels can be considered safe and trade disputes could be foreseen.

64. The concept of the Acute Reference Dose to be used specifically for evaluation of residues at the injection is not considered workable. There is only consensus in the scientific community on how to establish such reference doses for some classes of substances, mainly based on neurotoxicological endpoints. Other classes of drugs used in veterinary medicine and all toxicological end-points are not covered in the guideline (e.g. antimicrobial effects on the human gut, teratogenicity, aneugenicity, pharmacodynamic effects)[1].

65. The sampling protocol proposed is not supported as it can result in a number of practical problems and provides no guarantee that the injection site can be located. Among these are difficulties with identification of the injection site, cost of analysis and need for validation of the analytical methods over a wider concentration range or even the need for a new analytical method when the marker residue is not the same as the parent compound.

66. The additional risk management measures proposed are impractical. The restriction of the injection volume to 10 ml is not supported and the injection can not always be made in a specified area, although a short list of possible injection sites may be helpful in residue surveillance activities.

67. Although a risk assessment procedure for acute dietary intake may be applicable in some cases, the proposal is not substantiated by data and can not at present be supported[1]. Reliable information as to the likelihood of the consumer exposure to residues from injection sites should be obtained. The European Community supports further development of this area with the objective of managing potential acute risks for consumers.

68. The pharmaceutical industry should be encouraged to develop proprietary veterinary medicinal products with a low potential for persistence of residues at the injection site and improved local tolerance.

69. The European Community has harmonised the method for sampling of the injection site to be used in residue depletion studies with that of the United States of America since 1994.

Committee for Veterinary Medicinal Products (CVMP)

1. The CVMP would like to acknowledge the work of the Australian rapporteur and CODEX on the difficult topic of injection site residues. Scientific discussion of the subject has been taking place at the CVMP for several years. The CVMP considered that the draft guideline was a basis for discussion but some of the fundamental concepts required further consideration and refinement.

2. The draft Codex guideline proposes the establishment of an MRL for injection site muscle ($MRLVD_{IS}$). The implication of this proposal is that there could be two different MRLs for muscle. This could result in presentational problems with resulting concern among consumers over which residue level was to be considered safe and international trade disputes. The term $MRLVD_{IS}$ should be avoided.

[1] The European Community position is based on the decision taken at the 24th Session of the Codex Alimentarius Commission that "When there is evidence that a risk to human health exists but scientific data are insufficient or incomplete, the Commisison should not proceed to elaborate a standard but chould consider elaborating a related text, such as a code of practice, provided that such a text would be supported by the available scientific evidence." (Alinorm 01/41, para. 81).

3. The draft guideline includes a proposal for the establishment of Acute Reference Doses (Acute RfDs) for veterinary drugs. However there is no concensus within the scientific community on how to establish acute RfDs for some classes of substances. Many proprietary products intended for administration by injection are antimicrobials and the critical end point is the effect on the human gut flora which may be of an acute or (sub)chronic nature. Appendix C does not discuss how to deal with such end-points. Acute RfDs should not be established for substances for which the critical end-point is teratogenicity or aneugenicity. There is a lack of internationally agreed guidelines for the conduct of pharmacodynamic studies, the data available for veterinary medicines can vary in quality and quantity and identification of the most appropriate pharmacological end-point may not be straightforward.

3. The draft guideline relies on a proposed sampling protocol which could result in the following practical problems.

3.1 Identification of the site of injection may be impossible because some proprietary products do not result in a blemish at the injection site. Tissue sampling may result in only part of an injection site being sampled leading to results which would be difficult to interpret.

3.2 In some cases, the proposal would require further validation of the analytical method to be carried out over a wider range of concentrations.

3.3 Unless the parent substance has been identified as the marker residue, another method may have to be developed to monitor the injection site MRL (examples include metamizole (marker residue 4-methylaminoantipyrin), penethamate (marker residue benzylpenicillin) and dexamethasone esters (which must be subjected to enzymatic hydrolysis to release the dexamethasone marker residue)). Therefore, in such circumstances, the establishment of an acute RfDs would not be appropriate.

4. The proposed additional risk management measures may be impracticable. Injections cannot always be made to the neck and to restrict the injection volume to 10 ml is often not practicable. Some antimicrobial preparations which are intended for administration to large animals such as cattle need to be administered at volumes of up to 50 ml per animal and treatment may be continued for several days. The alternative would be repeated injections of small volumes resulting in numerous injection sites and consequent animal welfare problems. Multiple injection sites per administration should not be used as a way to deal with the problem of injection site residues. The recommendations should be practicable for the veterinarian otherwise there is a risk that the instructions may not be followed.

5. The draft guideline describes a risk assessment procedure that applies to the acute dietary intake of injection site residues. No data were provided to substantiate this approach. Processed meat products such as mince and sausages may be prepared from meat originating from areas of the carcass where injections are frequently administered. Some sectors of the population (e.g. children) may have a higher consumption of processed meat products. In these circumstances, there may be a need to consider repeated consumer exposure. There is only limited information concerning the consumption of an injection site as a single portion and the information that exists suggests that it is a "rare event". There is a limited amount of data on the occurrence of visible injection site blemishes at slaughter houses and the presence of residues of antimicrobial substances in these blemishes. Similar information for other classes of substances is not available. In order to assess the likelihood of the consumer exposure to residues from injection sites and consequently the risk to consumers, reliable information should be obtained on the frequency with which consumers are exposed to injection site residues.

6. Industry should be encouraged to develop proprietary products with a low potential for tissue irritation as well as products which do not result in persistent residues at the injection site.

7. For residue depletion studies, the EU has already harmonised with the method for sampling tissue at the injection site which is described in the FDA General Principles for Evaluating the Safety of Compounds Used in Food Producing Animals, 1994 (CVMP, Working Document: Injection Site Residues, III/5933-EN, Nov. 1994).

INTERNATIONAL FEDERATION FOR ANIMAL HEALTH (IFAH)

70. IFAH members would like to see the early completion of these guidelines, and would like to congratulate the Australian delegation for their work on these guidelines.

71. There is no reference to the fact that consumption of injection site residues is a rare event. Under these circumstances, it would be helpful to have some discussion in the paper on the frequency of injection site ingestion.

72. IFAH believes that it is necessary to state whether injection site residues are a real or perceived risk and the likelihood of a person ingesting an injection site that has residues of toxicological significance. Specific comments on the proposed guidelines:

73. Paragraph 1: Although formulation or tissue irritation may result in "higher" injection site residues this may have no consequence in relation to the consumption of this site. The last sentence of the paragraph should be deleted, as the phrase "conventional medicinal products" is ambiguous. Many conventional medicinal products may be slow release depot systems.

74. On line 3 of paragraph 1 delete the word "excessive" since this would be recognised as an adverse reaction and a component of pharmacovigilance.

75. Paragraph 3: IFAH questions the inclusion of "Vitamin A or Selenium" in line 3. We see no reason to highlight these two substances in particular.

76. Paragraph 7: We suggest a rephrasing of the next to the last sentence to read "… unless the need for such a risk assessment is deemed [or judged] to be unnecessary based on scientific grounds". The use of the phrase "… cannot be justified " does not seem appropriate in this context. Also, the word "short-term" should be replaced by "infrequent" or "occasional" in this paragraph and in paragraph 8.

77. Paragraph 12: In the final sentence, IFAH believes that it is appropriate to state explicitly that the FDA/CVM guideline requires a 500g sample be taken. In addition, it should be stated that the µg/kg value from the assay of this sample should be used for exposure assessments without further correction.

78. Paragraph 13-16: IFAH members have commented that the methods for determining Estimated Short-Term Intake (ESTI) is unclear. It is assumed that marker residue will be the same as total residue but this needs to be made clear in the text so that the appropriate correction factors can be used in situations where this is not the case.

79. The calculation in paragraph 14 for ESTI is based on the highest observed residue value at the withdrawal period. Certain members of CCRVDF may prefer to use a statistical confidence interval on the mean of the residues. Also in paragraph 14 it may be worth defining the average bodyweight for the population concerned. Is this 60kg or 70kg?

80. In paragraph 15, IFAH does not support the explicit sentence "limited to cases, where MRLVDs have not been established previously". Where MRLs are currently established a review of the data relative to the new guideline may result in an opportunity to alter the MRL and the Withdrawal Period (WDP). Where pharmacovigilance of an established product has failed to demonstrate any evidence of a hazard associated with an injection site residue there should be no requirement for any reassessment.

81. In paragraph 16, there is an opportunity for National Agencies to substitute alternative consumption values into the equation. A question has been asked in relation to the variability which this would permit in the system. This is particularly applicable in terms of International Trade of meat products.

82. Paragraph 24: Volumes greater than 10ml are frequently used in adult cattle. IFAH suggest that the final statement "… treated animals should be clearly identified …" should have a separate bullet point.

83. Appendix C - Page 10: No mention is made of what safety factors would be "appropriate". IFAH believes that a 10x factor has been discussed previously and would agree to this but another debate questioned whether a safety factor was necessary at all since consumption of an injection site is a rare event.