codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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TO: Codex Contact Points
Interested International Organizations

FROM: Secretary, Codex Alimentarius Commission
FAO, Viale delle Terme di Caracalla, 00100 Italy

SUBJECT: **REQUEST FOR COMMENTS ON PROPOSED DRAFT GUIDELINES ON RESIDUES AT INJECTION SITES AT STEP 3**

DEADLINE: **31 January 2000**

COMMENTS:

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BACKGROUND

The Eleventh Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) considered a discussion paper entitled *Guidelines on Residues at Injection Sites* (CL 1998/4-RVDF). The Committee requested Australia to prepare *Guidelines on Residues at Injection Sites* based on the discussion paper (CL 1998/4-RVDF), information contained in the Report of the 48th Joint FAO/WHO Expert Committee on Food Additives (JECFA) and comments made at the Session (paras 111-115 of ALINORM 99/31) for circulation and comment at Step 3 prior to its consideration at the Twelfth Session of the Committee.

The following text and attached Proposed Draft Guidelines were prepared by Australia.

RATIONALE FOR THE DEVELOPMENT OF GUIDELINES

National regulatory authorities seek to ensure that foods of animal origin do not contain residues of veterinary drugs that might pose a health hazard to consumers. Maximum Residue Limits (MRLs) have traditionally reflected the maximum residue level in edible tissues, remote from the injection site, that is legally permitted or recognised as acceptable when the drug is used according to approved directions. To ensure that the MRL is not exceeded, a withholding period (WHP) may be set by national authorities.

MRLs are calculated taking into consideration several important factors. One important factor to be considered when setting MRLs is the Acceptable Daily Intake (ADI). The ADI of a drug is an estimate of the daily intake that can be ingested over a lifetime without appreciable risk. Other factors taken into account when establishing MRLs include good veterinary practice, other sources of residues that occur

in food of plant origin, clearance/metabolism of the chemical, and the extent to which practical analytical methods are available.

Despite the above measures some veterinary injectables leave residues above the MRL at the injection site after compliance with the WHP.

Governments are invited to comment on the attached Proposed Draft Guidelines on Residues at Injection Sites at Step 3. The comments should be sent to the US Codex Office with a copy to the Secretary of the Codex Alimentarius Commission **not later than 31 January 2000**. The Proposed Draft and comments submitted will be considered by the Codex Committee on Residues of Veterinary Drugs in Foods at its 12th Session in March 2000.

Attachment

PROPOSED DRAFT GUIDELINES ON RESIDUES AT INJECTION SITES[1]

(At Step 3 of the Codex Procedure)

INTRODUCTION

1. Some veterinary drugs exhibit a slow residue depletion profile from intramuscular and subcutaneous injection sites, partly due to their design as slow release or depot formulations. In some instances, the residue depletion may be slow due to excessive tissue reactions such as fibrosis, encapsulation or necrosis. The injection site reaction may not always be obvious on visual examination. Residues at the injection site result not only from long-acting products, but also from standard medicinal products that often are not long-acting or necessarily irritant.

2. Injection sites may contain elevated residue levels that may persist beyond the withholding period. Studies have demonstrated that the presence or absence of non-conforming residues in edible tissues may not be a reliable indicator of the persistence of such residues at the injection sites. Likewise the levels of residues at the injection site are not indicative of the residue levels elsewhere in the carcass.

3. Because consumption of an injection site is a rare event, non-conforming residue levels at injection sites do not normally present a human health hazard unless the chemical produces an adverse effect on the individual ingesting the injection site tissue. The main substances of concern are those with acute pharmacological or toxicological effects (eg β-blockers, β-agonists, tranquillisers, vasodilators, anaesthetics and corticosteroids) and substances that may lead to allergic reactions in hyper-sensitive individuals (eg, penicillins and chloramphenicol). Injection site residues with no potential for acute effects are not considered a consumer safety issue because they are rare events and do not lead to chronic exposure.

4. Notwithstanding the public safety aspect of injection site residues of those chemicals with the potential for acute effects, the issue of injection site residues occurring at levels higher than MRL has implications for residue monitoring and surveillance programmes, particularly port-of-entry inspection programmes. Non-conforming residue levels at injection sites detected during surveillance programmes are usually interpreted as meaning that non-conforming residue levels are present in all tissues. When such residues are detected, the product is legally contaminated and this leads to condemnation of the carcass, and possibly the whole consignment. There is often an adverse impact on domestic and international trade in meat.

1. SCOPE

5. These guidelines are intended to address the issue of residues of veterinary drugs at injection sites with particular reference to:

- ensuring consumer safety by minimising public health risks associated with injection site tissue containing residues of drugs with the potential to produce acute pharmacological or toxicological effects or acute allergic reactions;
- enhancing current sampling protocols for the control of residues of veterinary drugs in national residue monitoring and surveillance programmes, and the port-of-entry inspection sampling procedures for meat from food producing animals;
- assisting in the facilitation of domestic and international trade.

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[1] Prepared by Australia.

2. ABBREVIATIONS

ADI	Acceptable Daily Intake
Acute RfD	Acute Reference Dose
FAO	Food and Agriculture Organisation of the United Nations
FDA	United States Food and Drug Administration
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MRL	Maximum Residue Limit
NOEL	No Observable Effect Level
WHP	Withholding Period
WHO	World Health Organisation of the United Nations

3. PURPOSE OF GUIDELINES ON RESIDUES AT INJECTION SITES

6. These guidelines on injection site residues have two discrete but related purposes.

3.1 USING ACUTE REFERENCE DOSE VALUES

7. To establish a standard setting procedure for managing residues of veterinary injectable drugs that have the potential to elicit an acute toxicological or pharmacological effect or an acute allergic reaction using the principle of acute RfD. The aim is to set a WHP that allows tissue residues to decline below the MRL whilst at the same time allowing injection site residues to decline below the acute RfD. This procedure reflects the public health significance of residues with the potential to produce acute pharmacological or toxicological effects or acute allergic reactions occurring at an injection site.

3.2 SAMPLING PROTOCOL ENHANCEMENTS

8. To provide sampling protocol enhancements for current national residue monitoring and surveillance programmes and port-of-entry inspection programmes that take into account the potential for these programmes to select a meat sample that includes injection site tissue. These enhancements will limit the carcass/product rejection and subsequent increased inspection schedules that may follow the detection of non-conforming residue levels due to sampling muscle tissue from an injection site while not compromising the health of consumers.

4. SETTING STANDARDS FOR MANAGING INJECTION SITE RESIDUES

4.1 USING ACUTE REFERENCE DOSE VALUES

9. Currently, MRLs are set based on the assumption that the consumer may be repeatedly exposed to residues on a daily basis. This method does not accommodate the rare occasion where the consumer is exposed to residue levels from an injection site.

10. A standard setting process that reflects the public health significance of residues at the injection site involves sponsors presenting residue data from appropriately conducted trials to demonstrate:

- the likely maximum residue at the injection site;
- its variability; and
- the depletion of residues at the injection site when the product is used as proposed.

11. Sponsors should use these data in a risk assessment to demonstrate whether any appreciable risk to the consumer exists as a result of the rare occasion in which ingestion of such residues from an injection site may occur. In preparing such assessments sponsors should take into account the pattern of use for the product and its intensity of use in the market place. Such information should include species,

herd versus individual animal treatment, minor or major indication, seasonal use, and number of injections given.

12. Recognising that the consumption of an injection site residue is a rare event, the risk to the consumer should be based on the real probability of the actual hazards involved. The calculation of the risk from consumption of residues at the injection site could be based on the principle of an acute RfD. The concept of an acute RfD has been accepted and used by the JMPR. The acute RfD has also been referred to as the ADI-ACUTE or acceptable single dose intake.

13. The basic principles and methods used in establishing an acute RfD are similar to those for establishing an ADI. The acute RfD is calculated using the NOEL for acute single dose effects based on data from the toxicological-pharmacological database relating to acute effects. In comparison, the NOEL for an ADI is normally established from the toxicological database relating to chronic effects.

14. MRLs should then be established for all tissues in the standard food consumption package (i.e. a 300g muscle sample that excludes injection site tissue) based on the ADI. The WHP may then be set when residues have declined to below these MRLs with the added requirement that the injection site residues have declined to levels below the acute RfD.

15. As part of the assessment process JECFA should identify the at-risk subgroups of the population based on the acute toxicity or pharmacological endpoint(s) used to establish the acute RfDs so that the appropriate food consumption and body weight data can be used in the exposure risk assessment. The magnitude of the safety factor used should reflect the nature of the toxicity (i.e. the seriousness of the toxic or pharmacological effect or allergic response) and the quality and quantity of the database. Safety factors may be increased whenever there is any degree of uncertainty in the database. They may be decreased only when specific data are available to decrease uncertainty in the extrapolation. Thus, the assessment of the available data is biased in such a manner as to err on the side of caution and to recommend an acute RfD that can be fully supported as health-based reference values. Adverse health effects should not be assumed to ensue if the acute RfD is marginally exceeded due to the incorporation of the safety factor in the calculation of the acute RfD.

4.2 PROCEDURE WHEN THERE IS POTENTIAL FOR A SINGLE-DOSE EFFECT

16. The primary objective is to ensure that the average daily consumption of residues does not exceed the ADI and that one-off consumption on any day does not exceed the acute RfD. Thus, where the injection site residues of products, that are capable of producing acute effects, do not decline below the acute RfD, then it is recommended that the national authorities adjust the WHP to ensure that these injection site residues have declined to levels below the acute RfD. In these instances the MRL should be re-established to allow injection site residues to fall below the acute RfD. At this amended MRL, residues at the injection site should present no acute hazard. The enforcement of the new (lower) MRL should ensure compliance of the lengthened WHP.

17. The proposed approach is consistent with the method currently employed by JECFA on some occasions. For example, in establishing the appropriate basis for the safety evaluation of residues for carazolol (a β-adrenoceptor-blocking agent), JECFA based the ADI on the NOEL observed in acute pharmacological effects of carazolol.

4.3 PROCEDURE WHEN A SINGLE-DOSE PRESENTS NO ACUTE HAZARD

18. If there is no acute hazard, the injection site residue levels should not be the basis for setting the MRL and WHP. If no acute hazard is predicted by a single-dose (i.e. a calculation shows that the potential residue at the site does not exceed the acute RfD in a meal-sized portion), then WHP should be set such that the MRL for residues at the WHP does not exceed a figure based upon the ADI and the standard average consumption factor for the appropriate animal tissues. This is consistent with the method employed by JECFA in setting MRLs for isometamidium, a trypanocide.

5. SAMPLING PROTOCOL ENHANCEMENTS

5.1 RESIDUE SURVEILLANCE

19. Despite the suggested approach for the health-based assessment of residues at injection sites, the potential exists for non-conforming residue levels to be detected in domestic residue monitoring and surveillance programmes and port-of-entry inspection programmes. These programmes assume that a given consignment of meat is a homogenous product. However, based on current knowledge of injection site residues, homogeneity of residue levels within the meat product may not apply in all cases.

20. National residue monitoring and surveillance programmes provide both random (monitoring) and targeted (surveillance) testing for residues. Where data indicate a problem exists corrective measures, including investigation, regulation and extension activities, can be instituted to prevent further occurrences.

21. National residue programmes may potentially sample muscle tissue from an injection site. In these instances investigation procedures may determine that an injectable veterinary drug was used on the animal but the withholding period had been observed.

22. Port-of-entry inspection and product sampling are standard procedures used by many importing countries to ensure that imported meat commodities are produced to standards that are equivalent to those used by importing countries. They are used to ensure the safety and wholesomeness of the product and the accuracy of product labelling.

23. Port-of-entry inspection sampling may potentially sample tissue from an injection site. The *Codex Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods* (CAC/GL 16-1993) indicate that when non-conforming residue levels are detected then subsequent shipments of the same product group from the same exporting establishment are to be retained at the port-of-entry until laboratory results show compliance with the importing country's MRLs. All shipments from the exporting country may be placed on an increased schedule of port-of-entry inspection testing until a record of compliance with MRLs is re-established.

24. These increased measures, namely sampling on a 'test and hold' basis and increased inspection schedules, can present significant increased economic imposts on the exporting abattoir and/or country involved and an increased monitoring burden on the importing country. As a consequence these disruptions to normal inspection schedules can severely hinder trade.

25. When analysing the residues of meat products from food producing animals in national residue monitoring and surveillance programmes and port-of-entry inspection programmes, it is necessary to consider two classes of chemicals:

a) CLASS A[2] – residues with the potential for a single dose effect producing acute pharmacological or toxicological outcomes or allergic responses in sensitive individuals;

b) CLASS B - residues that have no potential for a single dose effect producing an acute pharmacological or toxicological or allergic consequence.

5.2 ENHANCEMENT FOR NATIONAL RESIDUE MONITORING AND SURVEILLANCE PROGRAMMES

26. The enhanced sampling protocol for national residue monitoring and surveillance programmes involves taking additional muscle samples when muscle tissue is the matrix of choice for testing. In addition to the usual musculature sampled in the monitoring programme, a sample is taken from the diaphragm musculature. The diaphragm muscle sample provides a secondary or back-up sample for confirmatory evidence of residue violations in the event of injectable drug residues being detected. The muscle samples are processed as follows:

a) sample muscle tissue in accordance with current national residue monitoring and surveillance programme requirements;

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[2] Examples of Class A chemicals are listed in appendix A

b) select a back-up muscle sample from the diaphragm musculature of the same carcass and retain in a frozen state;

c) process the usual muscle sample in the normal manner;

i) if the sampled carcass/product/lot is considered non-conforming;

ii) if the muscle sample contains non-conforming residue levels of a CLASS B chemical group, then analyse the back-up (diaphragm) muscle sample;

- if the back-up sample contains non-conforming residue levels of the same chemical detected in the first sample, then institute the current corrective measures for non-conforming residue detections;
- if the back-up sample contains non-conforming residue levels of a different chemical to the first sample, then institute the current corrective measures for non-conforming residue detections;
- if the back-up sample does not contain any non-conforming residue levels, then assume the first sample included tissue from an injection site. Using the normal residue monitoring and surveillance programme protocol, process the residue detection based on the laboratory test results from the back-up sample.

5.3 ENHANCEMENT FOR PORT-OF-ENTRY SAMPLING FOR MEAT PRODUCTS

27. Importing countries modify their current port-of-entry inspection sampling protocol by increasing the number of samples taken per product group/carton/shipment for drug/chemical residue analysis. These extra samples are considered secondary or back-up samples and are processed in the following manner:

a) take the usual muscle sample(s) in the port-of-entry inspection sampling programme;

b) select a secondary or back-up muscle sample(s) from the same product group/carton and retain in a frozen state;

c) analyse the usual muscle sample for drug/chemical residues;

i) if the muscle sample contains non-conforming residue levels of a CLASS A chemical group the sampled product/consignment is considered non-conforming;

ii) if the muscle sample contains non-conforming residue levels of a CLASS B chemical group, then analyse the back-up sample;

- if the back-up muscle sample contains non-conforming residue levels of the same chemical detected in the first muscle sample, then institute the current port-of-entry inspection corrective measures for non-conforming residue detections;
- if the back-up muscle sample contains non-conforming residue levels of a different chemical to the first sample, then institute the current port-of-entry inspection corrective measures for non-conforming residue detections;
- if the back-up muscle sample does not contain any non-conforming residue levels, then assume the first muscle sample included tissue from an injection site. Using the importing country's current port-of-entry inspection protocol, process the shipment based on the laboratory test results from the second sample.

5.4 INJECTION SITE RESIDUE MEASUREMENT FOR REGISTRATION EVALUATION

28. The method of sampling tissue at the injection site can affect the apparent concentration of residues and so it is desirable that such methods be standardised as far as is reasonably practicable. It is proposed that the FDA approach for measuring injection site residues contained in the *FDA General Principles for Evaluating the Safety of Compounds Used in Food Producing Animals, 1994* be considered as the basis for these guidelines.

6. ADDITIONAL RISK MANAGEMENT MEASURES

29. It is recommended that the following additional risk management measures should be taken with veterinary injectables:

- injections should be given in a specific site such as the neck, where it could be targeted for routine inspection at abattoirs, and could be detected, trimmed and discarded during the deboning process;
- injectables should not be given in volumes greater than 10 ml per injection site[1] and treated animals should be clearly identified in such a way that they can be tracked for the duration of the WHP;
- national authorities should restrict the use of injectables that have a particular propensity to cause irritation and persistence at the injection site; and
- industry should be encouraged to develop formulations that do not result in injection site residues.

APPENDIX A - CLASS A RESIDUES

Residues with the potential for a single dose effect producing acute pharmacological or toxicological outcomes or allergic responses in sensitive individuals.

E.g. β-blockers
β-agonists
tranquillisers
vasodilators
anaesthetics
corticosteroids
penicillins
chloramphenicol

APPENDIX B - BIBLIOGRAPHY

- Evaluation of certain veterinary drug residues in food: Thirty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives, 1991.
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- General Principles for Evaluating the Safety of Compounds Used in Food Producing Animals 1994; US Department of Health and Human Services Food and Drug Administration.
- Injection site residues CVMP Working Party on the Safety of Residues 1993.
- Jones PGH, (1994) Injection site residues: not a threat to consumers or free trade. European Veterinary Pharmacology and Toxicology, Proceedings of 6th International Congress Edinburgh, 7-11 August 1994.
- Recommendations for the revision of the guidelines for predicting dietary intake of pesticides residues: Report of a FAO/WHO Consultations, 1995.
- Residues of Veterinary Drugs at Injections Sites, Implications for Human Health and International Trade. COMISA, October 1996.

[1] Residues of Veterinary Drugs at Injections Sites, Implications for Human Health and International Trade. COMISA, October 1996.

APPENDIX C - GLOSSARY

MRL - Maximum Residue Limit[3]

The maximum residue limit is defined as the maximum concentration of a residue, resulting from the authorised safe use of an veterinary, or agricultural, chemical, that is recommended by the Codex Alimentarius Commission or national authorities to be legally permitted or recognised as acceptable in or on food, agricultural commodity or animal feed.

It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI) or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.

When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.

The concentration is expressed in milligrams per kilogram (mg/kg) of the commodity unless otherwise specified.

WHP - Withholding Period [4]

The withholding period is the period of time that must elapse between the last administration of a veterinary drug, including treated feed, (or application of agricultural chemical in the case of pesticide residues) and the collection of edible tissue or products from a treated animal that ensures the residue levels in food for human consumption comply with maximum residue limit requirements. The WHP is a statutory requirement. The withholding period is also known as the withdrawal period or withdrawal time.

Non-conforming Residue Level

A non-conforming residue level is any level of chemical residue that exceeds the MRL for that chemical.

ADI - Acceptable Daily Intake [5]

The acceptable daily intake of a chemical is the estimate of the amount of a substance in food or drinking-water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable health risk to the consumer on the basis of all the known facts at the time of the evaluation. It is expressed in milligrams of the chemical per kilogram of body weight (mg/kg**).**

Acute RfD - Acute Reference Dose

The acute reference dose of a chemical is the estimate of the amount of substance in food or drinking-water, expressed on a body-weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all the known facts at the time of evaluation. It is expressed in milligrams of the chemical per kilogram of body weight (mg/kg).

NOEL - No Observable Effect Level

The no observable effect level is the highest dose of a substance in experimental animal studies that does not cause any detectable toxic effects. The NOEL is expressed in milligrams of the substance per kilogram of body weight per day (mg/kg/day).

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3 The definition is in the *Codex Alimentarius Commission Procedural Manual* and in Section 4 of the *Codex Alimentarius*, Volume 3.

4 The definition of the term "withdrawal time and withholding time" is included in Section 4 of the *Codex Alimentarius*, Volume 3.

5 The definition is in Section 4 of the *Codex Alimentarius*, Volume 3, but slightly different from this one. The above definition is slightly different from the definition of "ADI" by JECFA.