codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

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

Governments and international organizations wishing to submit comments on the following subject matter are invited to do so **no later than 1 September 2001** as follows: U.S. Codex Office, Food Safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th and Independence Avenue, S.W., Washington, DC 20250, USA (Fax No: +1.202.720.3157; e-mail: uscodex@usda.gov), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: Codex@fao.org).

BACKGROUND

1. The 12th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) considered proposed draft Guidelines on Residues at Injection Sites and agreed to return the text for redrafting by the delegation of Australia in light of the comments received and the Committee's discussions for circulation and consideration at the 13th CCRVDF (ALINORM 01/31, paras. 110-120).

2. The attached proposed draft Guidelines were prepared by the Delegation of Australia. The title of the Guidelines has been amended to *Guidelines on Veterinary Drug Residues at Injection Sites* in accordance with comments received at the 12th Session of CCRVDF.

RATIONALE FOR THE DEVELOPMENT OF GUIDELINES

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

4. MRLVDs are recommended after taking into consideration several important factors including the Acceptable Daily Intake (ADI), good practice in the use of veterinary drugs (GPVD), other sources of residues that occur in food, metabolism of the chemical, and the extent to which practical analytical methods are available. However, the use of some injectable formulations leaves residues at the injection site at concentrations above the muscle MRLVD. This may occur despite the WHP being observed.

5. As directed above, governments and international organizations are invited to comment on the attached proposed draft Guidelines on Veterinary Drug Residues at Injection Sites.

PROPOSED DRAFT GUIDELINES ON VETERINARY DRUG RESIDUES AT INJECTION SITES
(At Step 3 of the Codex Procedure)

INTRODUCTION

1. Some veterinary drugs exhibit a slow residue depletion profile from intramuscular and subcutaneous injection sites. This may be attributed to their design as slow release or depot formulations. Tissue irritancy, which may lead to excessive tissue reactions such as fibrosis, encapsulation or necrosis, is another potential cause of slow residue depletion from injection sites. By contrast, the use of conventional medicinal products seldom results in injection site residues at slaughter.

2. The residues at injection sites may be at higher concentrations, and of a more persistent nature, compared with those in non-injection site muscle. A consequence is that injection site residues may be non-compliant with the muscle MRLVD at the WHP. It is difficult to attribute non-compliance to an injection site residue because the latter is not always obvious on visual examination.

3. From a consumer safety perspective, the veterinary drugs of major concern are those with acute pharmacological or toxicological effects (eg β-blockers, β-agonists, tranquillisers, vasodilators, anaesthetics, corticosteroids, and preparations containing vitamin A or selenium) and substances that may lead to allergic reactions in hypersensitive individuals (eg penicillins). The adverse manifestations observed are related to short-term dietary exposure and are, in the main, of an acute nature.

4. Injection site residues have implications for residue monitoring and surveillance programmes. Currently, injection site residues occurring at levels higher than the muscle MRLVD are generally regarded as non-conforming and interpreted as meaning that non-conforming residue levels are present in all tissues. In this circumstance, the product is deemed legally contaminated, which leads to condemnation of the carcass, and possibly of the whole consignment. Disruptions to domestic and international trade in meat can result.

SCOPE

5. These guidelines are intended to address the issue of residues of veterinary drugs at injection sites in a manner that is consistent with risk analysis principles. The approach taken is to describe: -

- a risk assessment procedure that applies to the acute dietary intake of injection site residues. The procedure supplements the existing JECFA procedure for establishing MRLVDs. The latter appears to adequately deal with drug residues of acutely toxic compounds in the edible tissues included in the model diet; and
- procedures that, when applied to national residue monitoring and surveillance programmes, and to port of entry inspection programmes, reflect the intent of the risk assessments conducted on both acute dietary intake and chronic dietary intake of veterinary drug residues at injection sites. In essence, the approach ensures the safety of consumers while, at the same time, condemning only those carcasses/consignments that do not meet the criteria pertaining to acceptable acute dietary intake and chronic dietary intake.

ABBREVIATIONS

Acute RfD	Acute Reference Dose
ADI	Acceptable Daily Intake
ESTI	Estimated Short-Term Intake
FAO	Food and Agriculture Organization of the United Nations
FDA	United States Food and Drug Administration
GPVD	Good Practice in the Use of Veterinary Drugs
HR	Highest Residue
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LP	Large portion size for the commodity to be consumed
MRLVD	Maximum Residue Limit for Veterinary Drugs
$MRLVD_{IS}$	MRLVD for injection site muscle
NOEL	No Observable Effect Level

TMDI	Theoretical Maximum Daily Intake
WHP	Withholding Period
WHO	World Health Organization of the United Nations

PURPOSE OF GUIDELINES ON VETERINARY DRUG RESIDUES AT INJECTION SITES

6. These guidelines on veterinary drug residues at injection sites have two discrete but related objectives. The first and foremost is the protection of public health. The second objective is to design a sampling procedure for national monitoring and surveillance programmes, and for port of entry inspection programmes, which reflects the intent of the risk assessment process underpinning the public health standards. The overall approach must be consistent with the principles of risk analysis.

The stated objectives can be achieved by adopting the procedures described below. An additional factor that needs to be considered when formulating the proposed standard-setting procedure, which supplements the existing JECFA procedure, is that existing MRLVDs are not compromised.

RISK ASSESSMENT OF VETERINARY DRUG RESIDUES AT INJECTION SITES

7. The current JECFA procedure for calculating MRLVDs involves a risk assessment of veterinary drug residues in food, thereby ensuring the safety of consumers. The ADI, which applies to life-long dietary exposure to the residues, is pivotal to this approach. 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. In respect to the consumption of injection site residues, however, the procedure is not consistent with risk analysis principles applicable to short-term dietary exposure. Inclusion of an assessment of short-term dietary exposure in the procedure would provide guidance as to the acceptability, or otherwise, of potential acute adverse manifestations that may result from the consumption of injection site residues. A risk assessment of short-term dietary exposure should be mandatory for all injectable formulations, unless the need for such a risk assessment cannot be justified on scientific grounds. The procedure is based on the concept of the acute RfD (described elsewhere in these guidelines).

SAMPLING PROTOCOL FOR REGULATORY ENFORCEMENT PURPOSES

8. The sampling protocols for national residue monitoring and surveillance programmes, and for port of entry inspection programmes, should reflect the intent of the standard-setting process. The introduction of a risk assessment of the short-term dietary intake (based on the concept of the acute RfD) allows an MRLVD for injection site muscle ($MRLVD_{IS}$) to be calculated. When two standards are set for muscle tissue, *viz* the muscle MRLVD and the $MRLVD_{IS}$, it is paramount that a sampling protocol be devised that can differentiate between non-injection site and injection site muscle. Such a sampling procedure is described below. With this approach, the emphasis remains on consumer safety. However, the condemnation of complying carcasses is not regarded as an acceptable means of achieving this.

STANDARD-SETTING PROCEDURE FOR INJECTION SITE RESIDUES

9. Currently, JECFA recommends MRLVDs in the context of GPVD along with a consideration of the ADI. The dietary exposure assessment uses a model diet approach. If the Theoretical Maximum Daily Intake (TMDI) calculation reveals that the estimated dietary exposure to a veterinary drug residue exceeds the ADI, then the use of the veterinary drug is restricted to uses that implement practical withdrawal times, thereby ensuring that the dietary intake does not exceed the ADI. This dietary exposure assessment is appropriate when the hazard is long-term. It is appropriate that for all injectable formulations, the current JECFA risk assessment remains as the initial step in the MRLVD-setting procedure.

10. A discussion of the procedure for assessing the short-term dietary exposure to veterinary drug residues at injection sites follows.

11. Toxicological data are evaluated for the purpose of setting an acute RfD for the veterinary drug. The selection of appropriate acute toxicological end-points for determining the No Observable Effect Level

(NOEL) is pivotal to this process. The methods used to establish acute RfDs are detailed in Appendix C of these guidelines.

12. Injection site residues data that relate to the WHP under consideration are required for conducting the acute dietary exposure assessment. 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 much as is reasonably practicable. It is proposed that the FDA General Principles for Evaluating the Safety of Compounds Used in Food Producing Animals, 1994, be considered as the basis for these guidelines.

13. 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 parent compound, since post-absorptive metabolism has not occurred.

14. The acute toxicity of the veterinary drug is estimated from the Estimated Short-Term Intake (ESTI), which is calculated from the equation:

$$ESTI = LP \times HR \div BW$$

where LP = the large portion size for the commodity to be consumed (in this case, 0.3 kg of injection site muscle) during one meal or one day
HR = the highest residue reported in injection site muscle at the WHP under consideration
BW = the average body weight for the population concerned.

Utilising the injection site residues data that have been submitted, separate calculations of the ESTI are performed for each of the sampling times studied. In this regard, the shortest WHP that needs to be considered is the one that is applied to obtain compliance of residues in all non-injection site tissues with the respective MRLVDs.

15. The ESTI is reconciled with the acute RfD for the veterinary drug. Two possible outcomes of the reconciliation need to be considered as follows:

Firstly, if the ESTI exceeds the acute RfD for the veterinary drug, the WHP cannot be supported and the sponsor is notified that the acute dietary exposure is unacceptably high. The sponsor may wish to consider the available options for addressing the situation, such as modifying the use pattern or reformulating the product. Increasing the WHP to accommodate the injection site residues within the acute RfD may be an option, but is limited to cases where MRLVDs have not been established previously. This limitation is necessary, as it prevents the existing MRLVDs from being compromised and necessitating their revision.

Secondly, if the ESTI is equal to or less than the acute RfD for the veterinary drug, the WHP can be supported and the $MRLVD_{IS}$ is calculated.

16. The $MRLVD_{IS}$ is calculated from the following equation:

$$ESTI = \text{Acute RfD} = MRLVD_{IS} * LP$$

Transposing,

$$MRLVD_{IS} = \text{Acute RfD} / LP$$

The $MRLVD_{IS}$ is the concentration of the residue in injection site tissue that, if exceeded, will result in the ESTI exceeding 100% of the acute RfD. The $MRLVD_{IS}$ is used in national residue monitoring and surveillance programmes, and for port of entry inspection programmes (this aspect is described below). In the above equation, the value of LP is 0.3 kg (i.e. the meat consumption value in the JECFA model diet). Alternatively, national agencies may prefer to substitute the 97.5^{th} percentile meat consumption value for consumers, derived from the relevant national dietary survey data.

SAMPLING PROTOCOL FOR REGULATORY ENFORCEMENT PURPOSES

NATIONAL RESIDUE MONITORING AND SURVEILLANCE PROGRAMMES

17. 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 investigative, regulatory and extension activities, can be instituted to prevent further occurrences.

18. National residue programmes may potentially sample muscle tissue from an injection site and identify non-conforming residues. In these instances, investigative procedures may establish that an injectable veterinary drug was used on the animal, and the correct WHP had been observed.

PORT OF ENTRY INSPECTION PROGRAMMES

19. 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 of the importing country. These standards ensure the safety and wholesomeness of the product, and the accuracy of product labelling.

20. 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, 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 MRLVDs of the importing country. 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 MRLVDs is re-established.

21. These measures, namely sampling on a ‘test and hold’ basis and increased inspection schedules, can present significant 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.

PROPOSED SAMPLING PROTOCOL FOR REGULATORY ENFORCEMENT PURPOSES

22. The enhanced sampling protocol for regulatory enforcement purposes applies to both national residue monitoring and surveillance programmes, and port of entry inspection programmes.

23. Muscle tissue is sampled for analysis in accordance with the current requirements, except two samples are collected at the time of sampling instead of one. In the case of packed commodities, the two samples are collected from different cartons. In the case of carcasses, the two samples must originate from different muscle groups on the same carcass.

If the first sample conforms to the respective muscle MRLVD, the carcass/consignment is passed, and there is no requirement to analyse the second sample for residues.

If the first sample is non-conforming with respect to both the muscle MRLVD and the $MRLVD_{IS}$, 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 detections are instituted.

If the first sample is non-conforming with respect to the muscle MRLVD, but conforming with respect to the $MRLVD_{IS}$, evidence should be sought as to the likelihood of the sample originating from an injection site. In this situation, the second sample is subjected to residue analysis. If the second sample is conforming with respect to the muscle MRLVD, then it is concluded that the first sample was likely to be from an injection site, and the carcass/consignment is passed. By contrast, if the second sample is non-conforming with respect to the muscle MRLVD, it is likely that the first sample was non-injection site tissue. The

carcass/consignment is failed, and the current corrective measures for non-conforming residue detections are instituted.

ADDITIONAL RISK MANAGEMENT MEASURES

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

- injections should be given in a specific site, such as the anterior neck, which can be targeted for routine inspection at abattoirs, and can be detected, trimmed and discarded during the deboning process; and
- injectables should not be given in volumes greater than 10 ml per injection site[1] (where practicable), and treated animals should be clearly identified in such a way that they can be tracked for the duration of the WHP.

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

APPENDIX A - 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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Injection site residues CVMP Working Party on the Safety of Residues, 1993.

Jones PGH, Injection site residues: not a threat to consumers or free trade. Proceedings of the 6th International Congress of the European Association for Veterinary Pharmacology and Toxicology, 1994.

Recommendations for the revision of the guidelines for predicting dietary intake of pesticides residues: Report of a FAO/WHO Consultation, 1995.

Residues of Veterinary Drugs at Injections Sites, Implications for Human Health and International Trade: COMISA, 1996.

APPENDIX B - GLOSSARY

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 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 usually expressed in milligrams of the chemical per kilogram of body weight (mg/kg body weight).

ADI - Acceptable Daily Intake[2]
The acceptable daily intake is an estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard person = 60 kg). It is expressed in milligrams of the chemical per kilogram of body weight (mg/kg body weight).

ESTI – Estimated Short-Term Intake
The estimated short-term intake is a prediction of the maximum intake of a veterinary drug residue during one meal or one day, assuming that residues are present at the highest levels reported in residue trials, as occurring in injection sites. It is calculated as milligrams of the chemical per kilogram of body weight (mg/kg body weight), and is expressed as a percent of the acute RfD.

GPVD - Good Practice in the Use of Veterinary Drugs[3]
Good practice in the use of veterinary drugs is the official recommended or authorised usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.

MRLVD - Maximum Residue Limit for Veterinary Drugs[4]
The maximum residue limit for veterinary drugs is defined as the maximum concentration of residue (expressed in mg/kg or µg/kg, on a fresh weight basis) resulting from the authorised safe use of a veterinary drug that is recommended by the Codex Alimentarius Commission or national authorities to be legally permitted or recognised as acceptable in or on food.

It is based on the type and amount of residue considered to be without 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 and estimated food intakes.

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

$MRLVD_{IS}$ – Maximum Residue Limit for Veterinary Drugs at the Injection Site
The maximum residue limit for veterinary drugs at the injection site is proposed as a new concept in these guidelines. It is the maximum concentration of residue of veterinary drugs in injection site tissue that is legally permitted and recognised as acceptable when dietary exposure is short-term. It applies to all injectable veterinary drugs, including those that may potentially cause acute pharmacologic, toxicologic or hypersensitivity manifestations when consumed in the diet of humans. It is calculated as the concentration that results in the estimated short-term dietary intake being equal to 100% of the acute RfD. It is expressed in mg/kg or µg/kg, on a fresh weight basis.

NOEL - No Observable Effect Level
The no observable effect level is the highest dose of a substance in experimental animal studies or human 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 body weight/day).

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[2] The definition is in Section 4 of Codex Alimentarius, Residues of Veterinary Drugs in Food, Volume 3.
[3] The definition is in Section 4 of Codex Alimentarius, Residues of Veterinary Drugs in Food, Volume 3.
[4] The definition is in the Codex Alimentarius Commission Procedural Manual and in Section 4 of Codex Alimentarius, Residues of Veterinary Drugs in Food, Volume 3.

Non-conforming Residue Level
A non-conforming residue level is any level of chemical residue in the edible tissue that exceeds the MRLVD for that chemical.

TMDI – Theoretical Maximum Daily Intake[5]
The theoretical maximum daily intake is a prediction of the maximum daily intake of a veterinary drug residue, assuming that residues are present at the MRLVDs and that average daily consumption of foods per person is represented by the JECFA model diet. It is calculated as milligrams of the chemical per kilogram of body weight (mg/kg body weight), and is expressed as a percent of the ADI.

WHP - Withholding Period[6]
The withholding period is the period of time that must elapse between the last administration of a veterinary drug, including treated feed, 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.

[5] The definition is a modified version of the definition in the Food consumption and exposure assessment of chemicals, Report of a FAO/WHO Consultation, 1997.
[6] The definition of the term "withdrawal time and withholding time" is included in Section 4 of Codex Alimentarius, Residues of Veterinary Drugs in Food, Volume 3.

APPENDIX C – METHODS FOR ESTABLISHING ACUTE REFERENCE DOSES

Three types of host reactions have been identified as potential human health risks associated with the consumption of injection site residues of an animal medicine in edible tissues. These are: 1) pharmacologic, 2) toxicologic, and 3) hypersensitivity. The types of data needed to determine the acute RfD for each of these potential reactions will be discussed individually below. 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 the establishment of a rigid list of studies that would be relevant for every situation. For instance, a proteinaceous medicinal compound requiring parenteral administration for efficacy would be unable to elicit a pharmacologic reaction in a human following oral exposure, nor would a marketed product with twenty years of sales and no history of causing allergic reactions be likely to require new studies to show a lack of allergenic potential.

Pharmacologic Reaction Assessment: Pharmacologically active agents (β-agonists, β-blockers, etc) can be very potent; however, these activities are usually discovered very early in the development of a new animal health product through efficacy, toxicity, or safety screening techniques. Compounds shown to be pharmacologically active therapeutics should be given orally in acute single-dose studies to determine a no-effect dose in a suitably sensitive animal species. The highest no-effect dose tested, divided by an appropriate safety factor, would be the acute RfD.

Toxicologic Reaction Assessment: Acute oral toxicity studies are conducted on new animal health drug candidates. Investigations of oral toxicity are conducted as a means of selecting doses for longer-term rodent and non-rodent studies, as part of human food safety assessments. These acute oral exposures sometimes increase to doses of several thousand mg/kg to identify a dose. Such a dose would be unacceptably high for multiple dose studies. In the course of these studies, doses causing acute toxic reactions such as emesis, ptyalism, diarrhoea, lethargy, ataxia, dyspnea, prostration, seizures, coma, and death can be differentiated from a no-effect dose. The highest no-effect dose tested in these acute oral exposures, divided by an appropriate safety factor, would be the acute RfD.

Hypersensitivity Reaction Assessment: Hypersensitivity reactions require prior exposure followed by a time period necessary for antibody production before a true hypersensitivity reaction can be elicited; consequently, acute single dose studies are inadequate to assess this kind of acute exposure risk. For currently marketed products with no evidence of human sensitivities resulting from use, there would be no evidence to suggest that oral hypersensitivity studies in an animal model are required. For new compounds with no marketing history and unknown sensitisation potential, classical dermal Guinea pig hypersensitivity studies should be conducted. Negative results would suggest the lack of a potential problem and further work in animal models would be unnecessary. In that case, an acute RfD would not be established for hypersensitivity. Positive results in the dermal Guinea pig study would suggest the potential for sensitivities to occur; however, it is known that reasonably large doses of an antigen are required to sensitise humans orally. Specific studies to address oral hypersensitivity in the Guinea pig would be required if it were shown that residues sufficient to elicit an allergic response potentially remain at the injection site beyond the determined WHP. A no-effect level could be determined and the acute RfD could be calculated by dividing that level by an appropriate safety factor.

The above studies would require adequate numbers of animals upon which sound assessments could be made. The studies should be conducted under Good Laboratory Practices. The acute RfD adopted in practice would be the lowest of the acute RfDs calculated in the situation described above i.e. it is based on the most sensitive response.