codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATIONS OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 10 **CX/RVDF 00/11**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
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GUIDELINES ON RESIDUES AT INJECTION SITE

Government Comments

CL 1999/35-RVDF invited Governments and interested International Organizations to comment on the Proposed Draft Guidelines at Injection Sites at Step 3.

Replies were received from the following countries: Canada, Denmark, Sweden, and the United States.

Canada

1. It is generally recognized that parenterally administered veterinary drug products, particularly those intended for prolonged action often deplete very slowly from the injection site tissue of the animals. It has also been documented in the literature that injection sites can contain very high residue concentrations that can persist beyond the withdrawal period established for the drug product. In Canada, public health and trade aspects of residues at the injection site are addressed by requesting the manufacturer to submit marker residue depletion data from the injection site and the residue levels are compared with residue levels in ordinary muscle.

2. The marker residue concentration at the injection site is taken into consideration when the withdrawal period is established. A Maximum Residue Limit (MRL) for injection site that is ten times that of muscle is used and this is, in our opinion, a better way of approaching the problem since there is no regulatory residue method for the Acceptable Daily Intake (ADI) or Acute Reference Dose (RfD), both of which relate to total residues of the drug. The proposed draft guidelines do not give enough detail as to how this obvious discrepancy is going to be addressed.
For drugs known to produce acute pharmacological or toxicological effects or allergic responses the procedure of applying a factor of ten to the MRL for muscle in evaluating the injection site residue could be waived.

3. We feel that our proposal to use flexibility in applying a factor of ten would simplify the approach to injection site residue problem. If during the monitoring for residues an injection site residue were detected and were less than ten times the MRL for muscle, additional sample from a different location on the same animal could be tested and MRL applied.

4. Canada supports the work of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in assessing certain veterinary drugs, ie, carazolol, on the basis of a no observable effect level (NOEL) for pharmacological effects that are relevant to their ingestion by humans as a residue in edible tissue. However, it should be recognized that the likelihood of human exposure to residue concentrations that exceed the MRL at injection sites is extremely small. Furthermore, the chance of sampling the injection site in the routine surveillance of muscle samples is a rare event. As such, the focus of the proposed draft guidelines may be perceived by national regulatory authorities as more trade orientated rather than concerns for public health.

5. While the acute reference dose (RfD) may have certain value in predicting acute hazard in humans, clarification is needed for the purpose of its use in this draft guidelines. Toxicologists are well aware that notwithstanding to the data from animal toxicity studies, information from humans including the physiological and pharmacological effects, pharmacokinetics and toxicity of the chemical should be taken into account in human risk assessment whenever possible. Species differences in response to chemicals represent an important issue in regulatory risk assessment and estimation. Identifying the mechanistic basis for species differences in response to chemicals is an important part of toxicology because only through a thorough understanding of these differences can the relevance of animal data to human response be verified. For example, residue of benzylpenicillin is regulated by our knowledge of the propensity of human hypersensitivity reactions to this drug and residues of carazolol, clenbutarol, ractopamine and other potent cardiovascular agents are regulated by our understanding of human pharmacology and toxicology of these adrenoceptor ligands.

6. It should be noted that the trypanocide, isometamidium, was first evaluated at the 34th Meeting (1989) of the JECFA. The JECFA was not able to establish an ADI because the results of adequate toxicity studies, including carcinogenicity (or genotoxicity) studies and teratogenicity and short-term studies of the drug, were not available, nor was there any information on the nature of the metabolites. At the 40th Meeting (1992) of the JECFA an ADI of 0-100 ug/kg bw for isometamidium was established based on the non-toxic dose level of 50 mg/kg bw/day in the 13-week rat study and a safety factor of 500. The JECFA chose this safety factor because of the marginal pharmacological effects seen at the lowest dose in rat study and the limited extent of the data available, although it recognized that neither the drug nor its metabolises were bioavailable when given by the oral route.

7. The proposal to re-establish the MRL under section 4.2 item 16 on page 5 of the Codex document is both unnecessary and impractical. There may be another formulation

of the same drug administered by a different route of administration in the same target species and the change in MRL would trigger re-evaluation of the withdrawal period.

8. It should also be noted that in the case of chloramphenicol, listed in Appendix AA≅ to the proposed guidelines, any concentration of this drug found in edible tissues is illegal in Canada.

9. Canada supports the additional measures outlined in section 6, item 29. Certain formulations, known to produce residues at injection sites, such as drug suspensions, oily based formulations and tissue irritating excipients should be discouraged from the market because, generally, these require long withdrawal periods.

Denmark

In the introduction of the circular letter it is mentioned that MRL's have traditionally reflected the maximum residue level in edible tissues remote from the injection site. This is not the case in EU, where injection site residues have to be in compliance with the MRL's. Therefore, the acceptance of the principle of an acute RfD as an enhancement of consumer safety depends on the starting point.

In the circular letter it is assumed that intake of an injection site is a rare event. This assumption needs documentation, also because injection sites are not always visible.

Denmark finds that for drugs where a single dose can have an effect on the consumer, e.g. pharmacological or allergic effects, this should be taken into consideration when establishing the ADI's, as it is normally done when establishing MRL's in EU. Doses giving these kinds of effects are mostly lower than the doses giving toxicologically effects. This means, that for these substances the basis of the ADI will often be the acute RfD.

For pesticides, the ADI is based on an average intake of different products. The acute RfD is introduced to take account on situations where individuals eat a high amount of a single product. For residues of veterinary drugs, the food package of 500 g meat and meat products takes these variations into account, since no 60 kg person can eat so much every day and still keep the weight at 60 kg.

It is true, that very long WHP can lead to incidences 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. A better solution is to follow the measures described in para 29 to make the WHP shorter.

Therefore, Denmark cannot support the principle of acute RfD for residues of veterinary drugs at the injection site as described, since it does not fulfil the first scope mentioned in para 5.

In addition, 5.2 and 5.3 needs some clarification. In 5.2 it should be described why the muscle sample has to be analysed first, since the conclusion is based on the diaphragm

musculature alone. In both 5.2 and 5.3 the text on levels of other chemicals should be explained. Normally, when a laboratory is verifying a result by analysing another sample, they will only look for the substance in question.

In 5.3 it should be taken into consideration that the second sample not necessarily comes from the same animal. This depends on the product imported, e.g. hams or sausages.

Sweden

Sweden supports the general outline of the Proposed Draft Guidelines on Residues at Injection Site prepared by Australia. There are, however, a few points which may be subject to discussion. For more detailed comments and suggestions, see the text below (bold type).

INTRODUCTION (p.3, sub-para 3, the next last sentence)

The examples of the substances should be expanded to include also other types/components of veterinary drugs with a potential for acute toxic effects arising from large amounts of residues present at the injection site.

Proposal: ” The main substances of concern are those with acute pharmacological or toxicological effects (e.g. b-blockers, b-agonists, tranquilisers, vasodilators, anesthetics, (and) corticosteroids **as well as vitamin A and selenium containing preparations)** and substances which may lead to allergic reactions.....”

4.1 USING ACUTE REFERENCE DOSE VALUES (p.5, sub-para 15, the last sentence)

It may be difficult to exactly understand what is meant by the formulation that... ”Adverse health effects should not assumed to ensue if the acute RfD is **marginally (?) exceeded** .....”

Proposal: **Delete the whole sentence starting with** ”Adverse health effects ..... should not be assumed .... in the calculation of the acute RfD”.

6. ADDITIONAL RISK MANAGEMENT MEASURES (p.8, sub-para 29, the second bullet point)

Some preparations, e.g. penicillin, spiramycin, tetracycline etc. are supplied in formulations with a therapeutic dose requiring quite a large injection volume. By recommending the divided doses of 10 mL, would mean a necessity for several injections at a time which puts a strain on the animal and is not always practical from the treatment point of view.

Proposal. ”injectables should not be given in volumes greater than 10 mL per injection site **where practicable,** and treated animals should be clearly identified.....”

United States

The Australian delegation has done a commendable job of presenting a rational approach to a difficult problem. Three areas are particularly well-considered:

1. The nature of the potential human exposure from injection site residues is identified;
2. A novel scientifically sound approach to assessing injection site toxicology is provided;
3. The inability of some compounds to produce acute effects at residue levels is recognized.

This document is soundly based on the pertinent scientific considerations.

We have some suggested changes. They are presented below as "major" and "minor", more or less in the order they are encountered in the document:

Major Changes

The major changes we suggest are:

- We suggest the document clearly state that an acute reference dose should be established for all compounds used injectably in food animals. Some parts of the guideline seem to imply that a RfD need not be established for compounds that do not have a potential for acute harmful effects at residue levels. Other parts imply that a RfD should be established for all compounds. We suggest addition of the following sentence at the end of the existing **Paragraph 7**: "*An acute reference dose should be established for all compounds that have an injectable use in food animals.*"

- **Paragraph 10:** We do not believe there is a need to establish the maximum level of residue at the injection site. This is not a requirement for other edible tissues. We suggest the three bullet points in this paragraph be deleted and the necessary remaining points be covered in a revised paragraph which reads as follows: "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 depletion and variability of residues at the injection site when the product is used as proposed*."

- The approach outlined in **paragraph 16** does not indicate which MRL would be changed, if needed, to establish withdrawal times that would allow the injection site levels to decline below the RfD. The suggested monitoring approaches (Section 5) clearly require that the muscle MRL must be changed. However, if non-muscle target tissues can be used in the residue surveillance procedures (a point not considered in Section 5) the MRL of the target tissue would be the one to change. We also suggest other clarifications in this important paragraph, suggesting it read as follows: "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 do not decline below the acute RfD, it is recommended that the national authorities adjust the WHP *of the monitoring tissue* to ensure that these injection site residues have declined to levels below the acute

RfD. In these instances, the MRL *for the monitoring tissue* should be re-established to *coincide with the withdrawal period where* injection site residues fall below the acute RfD. *This may give the sponsor opportunity to adjust the MRLs of other tissues.* At *these* amended MRLs, residues at the injection site should present no acute hazard. The enforcement of the new (lower) MRL *for the monitoring tissue* should ensure compliance *with* the lengthened WHP."

- We disagree that the approach described in paragraph 16 is consistent with the method JECFA employed when evaluating carazolol (see **paragraph 17**). When evaluating carazolol, the ADI was set based on acute pharmacological effects. This is a very different approach from changing the MRLs as proposed in paragraph 16, and is a new definition of "ADI" -- different from the definition given in Appendix C of the guideline. Hence, sponsors are left not knowing which approach is suggested by this guideline, and may be confused about the definition of ADI. We suggest paragraph 17 be deleted or, if kept, that the first sentence be replaced with the following:
  "*JECFA has previously used acute effects to establish acceptable residue levels.*"

- We disagree, for reasons described below, that a distinction needs to be made between CLASS A and CLASS B compounds in monitoring and surveillance programmes. We suggest **paragraph 25** be deleted along with all other references to CLASSES. We do believe, however, that Appendix A has value to provide examples, and should be referred to in **paragraph 3**.

- It is difficult to understand exactly what is intended in **paragraph 26**, partly because something appears to be left out of c)i). Presumably it should read more like the c)i) part of paragraph 27. Assuming that, we believe the process described in paragraph 26 can be simplified in either of two ways:
  1. If it can be assumed (as is apparently assumed in the second bullet point) that diaphragm musculature is not an injection site[1], the decision could be based on one sample taken from the diaphragm. It would not matter whether detected residue comes from CLASS A or CLASS B compounds. If the residue level is above the MRL[2] the carcass/product/lot is non-conforming. We suggest that use of one sample from the diaphragm muscle would be a simple and reasonable approach.
  2. If CCRVDF, for whatever reason, is unwilling to accept the process described in 1 above, then a second sample could be taken and used whenever the first sample contained residues above the MRL[2]. This second sample could come from

[1] Note that if diaphragm muscle can not be accepted as a non-injection site, the second bullet point is not an acceptable approach since a carcass/product/lot would be considered non-conforming based on one sample which could have been an injection site. In fact, knowing that the results of the first sample were not non-conforming (for the "different" chemical), the only reasonable conclusion is that the diaphragm sample was indeed from an injection site and the carcass/product/lot is acceptable. Note also that an assumption that diaphragm is not an injection site does not create opportunity for a producer to bypass detection of violative action; the probability of detection would be greater if the producer did inject in the diaphragm.

[2] This would be the "new" MRL of the monitoring tissue as established in paragraph 16.

anywhere on the carcass not proximate to the first sample. It would not matter whether detected residue comes from CLASS A or CLASS B compounds. If the residue level is above the MRL[2] in the first sample, then the second sample should be tested. If the second sample is non-conforming, the carcass/product/lot would be considered non-conforming; contrarily, a conforming result in the second sample would indicate a conforming product/carcass/lot and the assumption would be that the first sample came from an injection site. Note that although the carcass/product/lot can be accepted based on the result of one sample, there is never a situation where a carcass/product/lot would be rejected without testing two samples. Reliance on diaphragm muscle as a non-injection site (proposal 1) would save resources.

- The comments made in proposal 2 above regarding paragraph 26 also apply to **paragraph 27**, however, it should be noted that ground processed meat, where some homogeneity of the product can be assumed, could be considered non-conforming on the basis of one sample above the MRL. It should also be noted that in many port-of-entry sampling instances, a second sample is not of much value because it cannot be verified that the second sample comes from the same animal as the first. Although we do not have a complete solution to this problem, a partial solution could come from defining an acute MRL. The worst possible acute exposure situation is if the consumer is exposed to the maximum amount of injection site residue at one "sitting". This would occur if the consumer ate the full 300 g of muscle at one meal. Under that assumption we can calculate an MRL for acute exposure (MRL_{acute})[3]. If a monitor sample contains levels above this MRL_{acute}, the product/carcass/lot could be rejected without further sampling. We believe this approach should be considered, especially for port-of-entry sampling. This has the added advantage of eliminating the need to define "meal-sized"[4].

- We suggest the last two bullet points in **Paragraph 29** be deleted. Industry already strives to develop non-irritating products that do not result in injection site residues because such a product has marketing advantages. But we believe the availability of products is more important than these two restrictions, i.e., if the only product available to treat a certain disease is one that, despite industry efforts, is irritating and requires a long withdrawal time, the product should be available to treat sick animals.

- We suggest that in addition to the information in paragraph 13, an **Appendix D** be included that provides additional detail on how to establish the RfD. An Appendix D could be something like the following:

Proposed Appendix D

[3] For example, if an acute no effect level is established from lab animal studies at 10 mg/kg and a safety factor of 100 is used, the no acute effect level in humans would be 0.1 mg/kg or 6 mg in a 60 kg human. If this is consumed in 300 g of muscle, the concentration is 6 mg/300g or 20 mg/kg (20 ppm). This could be used as an acute MRL for monitoring purposes.

[4] This term appears in paragraph 18, but has no definition as far as we know.

Three types of host reactions have been identified as potential human health risks associated with the infrequent consumption of injection site residues of an animal medicine in edible tissues. The three types of host reactions are: 1) pharmacologic, 2) toxicologic, and 3) hypersensitivity. The types of data needed to determine the acute RfD for each of these three types of 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 which 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 antagonists, 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-pharmacology screening techniques. Compounds shown to be pharmacologically-active therapeutics via whatever route 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 nonrodent 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, diarrhea, 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 sensitization 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 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 sensitize humans orally. Specific studies to address oral hypersensitivity in the Guinea

pig would be required if it is shown that residues sufficient to elicit an allergic response possibly remain at the injection site after a classically determined WHP. A no-effect level could be determined and the 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 RfD used in practice would be the lowest of the RfDs calculated in the situations described above.
(End of Proposed Appendix D)

Minor Changes
The minor changes we suggest are:

- **CL1999/35 - RVDF (December 1999)** (This is the "Request for Comments on Proposed Draft Guidelines on Residues at Injection Sites at Step 3"): The next to the last paragraph of this document should read as follows:
  "Despite the above measures some veterinary injectables leave residues above the *muscle* MRL at the injection site after compliance with the WHP."

- **Title:** The title should be "Proposed Draft Guidelines on *Veterinary Drug* Residues at Injection Sites"

- **Paragraph 2**, as presently written, could be interpreted to imply that levels of residue in the non-injection-site muscle can not be used to monitor or predict residue levels at the injection site and *vice versa*. Yet, paragraph 16 and the suggested monitoring approaches (Section 5) clearly rely on a correlation between injection site levels and levels elsewhere, particularly in non-injection-site muscle. We suggest paragraph 2 be changed to read as follows:
  "Injection sites may contain elevated residue levels that may persist beyond the withholding period *established based on residue levels in non-injection site tissues.* Studies have demonstrated that *injection site residues are often much higher than those in other parts of the carcass.*"

- **Paragraph 4:** The first sentence should read: "Notwithstanding the public safety aspects of injection site residues of those chemicals with the potential for acute effects, the issue of injection site residues occurring at levels higher than *the muscle* MRL has implications . . . ."

- **Paragraph 9:** We suggest this paragraph read as follows:
  "Currently, MRLs are set based on the assumption that the consumer may be repeatedly exposed to residues on a daily basis *and that exposure to those residues is acceptable if daily ingestion is less than or equal to the ADI*. This method does not accommodate the rare occasion where the consumer *may be* exposed to residue levels

from an injection site *which would not be consumed on a daily basis, thus making the ADI irrelevant in this situation*."

- **Paragraph 15:** Because experts employed and contracted by the sponsor are the most knowledgeable about the compound, we suggest the following addition:
  Sentence 1: "As part of the assessment process JECFA should *use the information provided by the sponsor to* identify the at-risk subgroups . . . ."
  Because it is consistent with JECFA precedent, we suggest the following addition:
  Sentence 4: "They may be decreased only when specific data are available to decrease uncertainty in the extrapolation*, or if evidence is available indicating the animal model is sufficiently sensitive*."

- **Paragraph 18:** "MRL" in both the first and second sentences should be changed to "MRLs" (so the word "does" should be changed to "do" in the second sentence) and the word "appropriate" in the second sentence should be changed to "respective edible".

- **Paragraph 21:** The first sentence should read: "National residue programmes may potentially sample muscle tissue from an injection site *and find non-conforming residues.*"

- **Paragraph 25:** If it is decided to maintain the CLASS A and CLASS B distinctions (we suggest these distinctions not be used), each definition in this paragraph should replace the first word ("residues") with the word "chemicals" and the sentences should end with the added phrase "at possible residue levels".

- **Paragraph 29:** The second bullet point should be separated into two bullet points. The break should be right after the footnote number.

- We suggest the definition of "NOEL" as given in **Appendix C** be modified to include the possible use of human data, which, of course, can be very relevant if available. The definition would then read:
  "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/day)."

- The guideline, which is specific to animal use, could be made more understandable if **Appendix C** contained definitions that are specific to this situation. These definitions could be taken from the standard Codex definitions (and so referenced), but be adapted so they clearly refer to the animal usage inherent in this document. For example, the MRL definition should eliminate reference to "agricultural chemical" and the WHP definition should eliminate reference to "pesticide residues". All references to residues could include the phrase "in the edible tissue" to clearly specify the residues relevant to this document.

We appreciate the opportunity to comment on this guideline, and hope our comments are helpful and will be given due consideration.