codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 13 **CX/RVDF 00/14-Add.1**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
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DISCUSSION PAPER ON DATA REQUIREMENTS FOR THE ESTABLISHMENT OF MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS FOR MINOR SPECIES

EXTENSION OF MRLS TO COVER MINOR SPECIES AND MINOR USES

(Prepared by New Zealand)

BACKGROUND

1. The Committee at its 11th Session in 1998 was informed that the issue of data requirements for minor species was discussed at the 48th JECFA meeting. The Committee accepted the offer of the Delegation of New Zealand to prepare a discussion paper on data requirements for the establishment of Maximum Residue Limits for Veterinary Drugs for Minor Species for consideration at the 12th Session. The FAO Secretary to JECFA also agreed to present a document concerning the 52nd JECFA discussions on this subject for consideration by the 12th Session of the Committee. (ALINORM 99/31, paras 129-130)

2. The paper has been prepared in light of the instructions from the Codex Alimentarius Commission to committees:

(a) to develop and apply risk analysis principles and methodologies appropriate to their specific mandates within the framework of the Action Plan and report their progress to the commission on a regular basis

(b) that risk management should take into account the economic consequences and feasibility of risk management options in developing countries. Risk management should also recognise the need for flexibility in the establishment of standards, guidelines and other recommendations consistent with the protection of human health.

THE ROLE OF CCRVDF

3. The overarching purpose of the Codex Alimentarius Commission is to promulgate internationally adopted food standards which protect consumers' health and ensure fair practices in the food trade. Defining what may constitute good practice in the use of veterinary drugs is a national government's prerogative. CCRVDF has been tasked with recommending maximum levels of residues of veterinary drugs in foods consistent with ensuring human health will not unduly be adversely affected (as reflected by the ADI).

4. The procedural manual of the Codex Alimentarius Commission states that an MRLVD "is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the ADI" . "The MRL may be further reduced to be consistent with good practices in the use of veterinary drugs and the extent to which practical analytical methods are available".

5. It is thus important to recognise it is the ADI value which is important with respect to ensuring the protection of human health. MRLs are just one of the means used to help ensure the ADI is not likely to be exceeded at a frequency or level that may adversely affect human health.

6. CCRVDF has a role in:

i) Setting the risk assessment policy both with respect to data/information requirements and the appropriateness of any qualitative assumptions applied to that information.

ii) Setting up a risk management framework to better ensure the information provided back from the risk assessors (JECFA) can be dealt with in a standardised and transparent fashion.

DEFINING THE ISSUE

7. This Codex Alimentarius Commission has thus far adopted MRLs for 31 veterinary drugs as recommended by this committee[1]. The species breakdown is as follows: cattle (25), pigs (15), sheep (13), chickens (7), poultry (3), turkeys (2), ducks (1), goats (3), deer (1), fish (1), giant prawns (1), rabbits (1), and horses (1). Only 2 out of the 31 veterinary drugs have had MRLs established without reference to any particular species, 19 have MRLs for two or more species and 12 have MRLs for just one species. The MRLs for 16 of the 19 compounds used in multiple species are the same for all species.

8. In many countries the approved or authorised therapeutic use of these compounds extends well beyond those restricted species for which a Codex MRL exists. Experimental trials necessary to generate comprehensive data packages for multiple species are costly with respect to animal wastage, time and money. For a number of veterinary drugs these costs preclude comprehensive trials being completed in species other than those anticipated as being the predominant financially returning market for the drug. However, these same drugs often have an equally relevant and safe therapeutic use in species other than the one or more for which the full experimental work up can be financially justified.

9. Many national governments have recognised the above issue and set up mechanisms to extrapolate results from related species when approving recommended or authorised usage in other species. Assessing what may or may not be "good practice" in the use of veterinary drugs within their national borders is the national prerogative of each country. The primary consideration of CCRVDF is to ensure any food standards they recommend are consistent with ensuring human health will not be adversely affected (as reflected by the ADI). CCRVDF can of course still recommend lower MRLs for veterinary drugs where:

i) there is a consensus that no nationally authorised use should result in a level higher than the MRL, AND

ii) the setting of a lower level than required to satisfy the ADI is necessary to help identify gross abuses (human health risk related) of the drug eg the use of clenbuterol for growth promotion.

10. From a food safety point of view, because of the ways acceptable daily intake values (ADIs) are derived, and theoretical maximum daily intake values (TMDIs) are estimated, much of the information evaluated for one species is directly relevant and extrapolatable to other species. CCRVDF has recommended a number of generic food type MRLs in the past[2]. These include non-speciated MRLs for albendazole and sulfadimidine, and generic poultry MRLs. Other Codex Committees such as CCPR try where possible to recommend food group MRLs eg meat from mammals other than marine mammals (35 compounds) & Milks (54 compounds).

11. There is a clear need for more of a risk-based approach in the elaboration and application of MRLs for veterinary drugs. The application of zero tolerances or arbitrary defaults by importing countries in the absence of an international MRL for a particular species is generally not justified on food safety grounds, especially where a full toxicological work up has been done for one or more major

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1 http://apps.fao.org/CodexSystem/vetdrugs/vetd_q-e.htm

2 The CCRVDF received a report of the 38th meeting of JECFA that it would name all animal species individually and identify target tissues and food products. (ALINORM 93/31, para. 45)

species. Increased promulgation of generic food group MRLs would help reduce the potential for problems to arise associated with the trade in food from minor species without compromising human health.

12. Notwithstanding the above, where significant issues are identified food group MRLs could be recommended which specifically exclude certain or all other species eg meat from mammals or meat from mammals excluding marine mammals, or meat from ruminants only, or meat from pigs only. Countries can also continue to legitimately use their own consumption models when assessing the significance of extending the MRLs to minor species or minor uses in deciding whether to accept the recommended Codex MRLs or promulgate variants for imports. This principle is fully laid out in the section of the Procedural Manual titled: "Acceptance of Codex Maximum Limits for Residues of Pesticides and Veterinary Drugs in Foods".

TECHNICAL ARGUMENTS

i) Acceptable Daily Intake values (ADIs):

13. ADIs are usually derived from dose-response studies conducted in laboratory animals. Most commonly they correspond to 100 x less than the amount of the parent drug the laboratory animals can tolerate over an extended period of time without showing any adverse effects (NOAEL).

14. ADIs are usually expressed in terms of the parent drug, whereas people consuming tissues from treated food animals will consume a combination of the parent drug and/or its metabolites. However, because most species metabolise drugs in similar ways, unless there are reasons to suspect otherwise, it is assumed that the laboratory animal will have been exposed to a mix of parent drug and metabolites with at least the same toxic potential as that likely to be consumed by people consuming the tissues of subsequently treated food animals.

15. From a toxicological point of view it is the total amount of residues of the veterinary drug (parent drug + metabolites) that is thus more relevant for comparison, and not how the ratio of any particular marker residue varies between individual tissues or species.

ii) How MRLs and Total Residue Concentrations Relate to ADIs

16. MRLs are different from ADIs in a number of ways. Firstly, ADIs are amounts per human body weight whereas MRLs are amounts per weight of food. Conversion just of the units requires multiplication of the MRL by a weight of food likely to be regularly consumed then division by the relevant human body weight. However another difference is that the MRL is also often defined as a concentration of a metabolite of the parent drug (marker residue) as opposed to either a concentration of the parent drug or of a concentration of the total residues. This is usually done because most drugs tend to be extensively metabolised and choosing a marker residue simplifies monitoring. Conversion of a specific MRL to a total residue concentration requires division of the MRL by the proportion of the total residue that the specific metabolite(s) represents. The proportion of the total residue attributable to the marker residue can be crudely estimated from metabolism studies (using radiolabelled parent drug).

17. While total residue estimates are usually used for comparison with the ADI, it needs to be recognised these estimates are only very rough approximates. Metabolism studies are difficult to do and expensive and rarely reflect real life use scenarios for the drug. The actual ratios of parent drug and the various metabolites in real life scenarios vary significantly with (1) time post administration, (2) route and dose of administration, (3) tissue analysed, (4) physiological state, (5) between individuals, as well as between species. Accordingly, while using species specific metabolism studies to correct marker residue MRLs to total residue concentration may be a useful exercise to screen those MRLs for those species which make a substantial proportion of the dietary intake for the food group and where the drug is also likely to be extensively and routinely used, this exercise is a much less useful/necessary for consideration of the same MRLs in other species.

iii) MRLs, Total Residues Concentrations, ADIs and TMDIs

18. A simple measure of whether a series of MRLs will help ensure the ADI is not exceeded is the calculation of theoretical maximum daily intake values (TMDIs). JECFA calculates TMDIs by multiplying estimates of the total residues in each tissue type by arbitrarily chosen over-estimates of the maximum daily average amounts of consumption.

19. The dietary intake model JECFA currently uses for TMDI estimations is 300 g muscle, 100 g liver, 50 g kidney, 50 g fat, 100 g egg and 1.5 l of milk. The same model is used irrespective of the type or types of species JECFA considered data for. These TMDI estimations assume the residue will be routinely present (everyday) in the animal products of all species at the maximum levels set. Accordingly, they are a gross over-estimate of likely exposure.

20. From a human health point of view, the recommended MRLs arrived at after considering a comprehensive data set for one species arguably could be considered relevant for all species. This is especially so where either the percentage of recently treated animals at time of tissue harvest is likely to be small, or where the other species are relatively less important proportionately to the diet of the population (note arbitrary overestimates of generic food type consumption are already used in exposure estimations).

SUMMARY

21. While many national governments are taking a more flexible approach, current CCRVDF / JECFA policy is unduly restricting the elaboration of international standards which cover “minor species” and/or minor uses in other species. International trade in food commodities from such species is threatened by the absence of Codex veterinary drug MRLs.

22. While comprehensive residue depletion trials and metabolism studies may be desirable for those species that a specific veterinary drug is likely to be used most in, they are not essential from a human health perspective for the extension of the MRLs to other food animal species.

23. CCRVDF has been tasked with recommending maximum levels of residues of veterinary drugs in foods consistent with ensuring that human health will not unduly be adversely affected (as reflected by the ADI).

24. The inherent conservatism built into the current JECFA system for evaluating whether species specific MRLs will ensure the ADI is not exceeded at a level or frequency that may adversely affect human health allows a good deal of flexibility for CCRVDF to make decisions as to the appropriateness of extending the MRL to cover minor species or minor uses of the drug in other species.

25. Animal husbandry practices and disease challenge profiles vary between countries. Accordingly, defining what may constitute good practice in the use of veterinary drugs is predominantly the prerogative of national governments. Ensuring sufficient controls are in place to ensure the relevant MRL is not exceeded at a frequency or level that would jeopardise human health is also the role of national governments.

26. Except for where there are specific dietary exposure concerns, or a potential for gross abuse at the animal production level exists, generic food group MRLs for use in international trade should be sufficient to monitor whether sufficient drug use controls are in place to ensure the protection of human health as expressed by the ADI.

RECOMMENDATIONS

(1) For new veterinary drug evaluations, CCRVDF should ask national governments to submit information on all permitted uses of the drug within their borders.

(2) For new veterinary drug evaluations, CCRVDF should ask JECFA to identify whether there are any specific toxicological or intake concerns with setting a generic food group MRL for the drug.

(3) Additionally JECFA should report whether there have been approved use patterns reported by national governments which would result in residues in excess of the generic food group MRL. Where possible JECFA should provide an estimate of whether, and by how much, the MRLs required to encompass such uses in the specific species would likely affect dietary intake calculations.

(4) Where possible CCRVDF should recommend generic food group MRLs (eg muscle, liver).

(5) Where species specific concerns relevant to human health are raised, CCRVDF should attempt to recommend MRLs covering species groupings eg mammals, ruminants, seafood.

(6) CCRVDF only recommend species specific MRLs where there are substantial reasons to exclude all other species.

(7) CCRVDF should ask JECFA over a period of time to reassess the current MRLVDs according to these new criteria.

REFERENCES

1. Codex Alimentarius Procedural manual, tenth edition
2. Report of the 23rd Session of the Codex Alimentarius Commission
3. Food Consumption and Exposure Assessment of Chemicals; Report of a FAO/WHO Consultation Geneva, Switzerland 10-14 February 1977.
4. Residues of Some Veterinary Drugs in Animals and Foods, FAO Food and Nutrition Papers, various from the 41/ series.
5. Evaluation of Certain Veterinary Drug Residues in Food, various reports of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series.
6. Toxicological evaluation of certain veterinary drug residues in food, various, WHO food additive series 36.