codex alimentarius commission E

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 8 **CX/RVDF 09/18/8 Add.1**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Eighteenth Session

Natal, Brazil, 11-15 May 2009

DRAFT PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OF RE-EVALUATION BY JECFA AND WORKING DOCUMENT LISTING VETERINARY DRUGS OF POTENTIAL INTEREST

(Report of the electronic Working Group on Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation)

Comments Submitted by:

Argentina, Egypt, Iran, United States of America, International Federation for Animal Health (IFAH)

ARGENTINA

Argentina considers that within the HIGH PRIORITY category of substances, CHLORAMPHENICOL, NITROFURANS, NITROIMIDAZOLES, STILBENES AND THYROSTATIC SUBSTANCES, have already been sufficiently evaluated in the past.

Assuming the limitations related to the work of JECFA as well as the time invested in performing the evaluations, we consider that it would be appropriate to discuss before the Committee the banning of these substances in animals for human consumption without a new evaluation by JECFA.

EGYPT

Virginiamycin has been banned to be used as a growth promoter for avoiding bacterial resistance and consequently has become of no importance to be considered of priority to be discussed.

It makes no sense to evaluate and re-evaluate any veterinary drugs contained in pesticide or parasite with growth promoting hormones even if the compounds have a benefit complying with their contents as Zeranol that may cause carcinoma is prohibited in many countries.

It makes no sense to add vitamins and minerals to Ivermectin but we have to concentrate only on RVDs.

For the combination of Nonylphenol and Amitraz, it is the same case as mentioned above. So, it is recommended to evaluate and re-evaluate individual veterinary drugs only.

IRAN

Iran agrees with removing all the compounds from the priority list and returned to the starting list due to lack of adequate data.

Iran believes that scientific data (such as the history of safe use for a veterinary drug, good veterinary practices, and the threshold of toxicological concern) should be provided by cooperation of the drug manufacturers and this data must be available before the inclusion of a substance on CCRVDF Priority List.

We support the recommendation that “in future, only single compounds are nominated for evaluation".

Iran supports the recommendation that "in future, cleaner lists of compounds are nominated for inclusion on the Priority List for review and only compounds with sufficient available data are to be submitted for consideration".

UNITED STATES OF AMERICA

Annex 2 of the Report of the electronic Working Group on Priority List of Veterinary Drugs Requiring Evaluation or Reevaluation (CX/RVDF 09/18/8) lists many veterinary drugs and makes recommendations to the 18th Session of the Codex Committee on Residues of Veterinary Drugs in Foods. The recommendation for carbadox states that CCRVDF should confirm that this substance should not be used in food producing animals and agree that Codex does not recommend either an MRL or extra-label/off label use due to concern for toxicity to the human consumer. The United States does not agree with this recommendation. Carbadox is currently approved for therapeutic use in several countries and those national authorities have affirmed the safe use of carbadox in swine. The safe use of carbadox was questioned by at least one member of CCRVDF. In response to questions about the safe use of carbadox, the company committed to update the residue studies and analytical methods for carbadox. Interim reports of these non-GLP studies were submitted to JECFA. On the basis of these interim studies, JECFA recommended that the MRLs be withdrawn and CCRVDF agreed. Subsequent to the submission and evaluation of these studies, the company has discovered and communicated that the new analytical method was measuring an artifact in the tissues rather than carbadox. A new analytical method is being evaluated and new GLP residue studies are being conducted. The United States asserts that it is reasonable to expect that the new data will refute the data that the JECFA relied on to reach its conclusions. We would ask that a decision on carbadox be held in abeyance until the new data can be finalized and presented to the JECFA for reevaluation.

United States Proposal: Discussion on Accelerating MRLs

The United States previously submitted a proposal for discussion to the electronic Working Group on Priority which was not distributed with the report. As such, we would like to provide this paper with our comments. Please see Annex 1 of our comments for a paper entitled “United States response to CCRVDF Electronic Working Group on Priorities.”

In light of this discussion paper, an IFAH Member Company has a veterinary drug that they are interested in proposing for submission to the electronic Working Group on Priority List of Veterinary Drugs Requiring Evaluation or Reevaluation for use as a pilot consistent with the United States proposal.

This company has a complete toxicological and residue file with respect to a veterinary drug and is in the process of filing for Maximum Residue Limits in several countries in three distinct global regions. According to the current Codex procedure, this veterinary drug is not eligible for placement on the priority list as the veterinary drug has not been approved in any market at this time. In light of the United States proposal, the Company would like to offer its veterinary drug as a pilot molecule for placement on the current priority list for consideration at the next JECFA.

This veterinary drug is a new anti-parasiticide with broad activity against helminth infestations in livestock, including several drug resistant strains. Thus, it represents a product of high value to both public and animal health. The product is initially targeted for markets which rely heavily on their ability to export food products globally. Thus, the importance of establishing a food standard that reflects both consumer safety and facilitates international trade is of paramount importance.

As stated above, there is a commitment from the company to submit this complete dossier to the JECFA for evaluation and thus, it is requested that the compound be placed on the priority list.

Ractopamine

The United States would also like to offer comments on the MRLs for ractopamine in response to the Matters Referred by the Codex Alimentarius Commission (CX/RVDF 09/18/2). The Report of the 31st Session of the Codex Alimentarius Commission (ALINORM 08/31/REP, para. 58) reads:

It requested Members to submit relevant information on the availability of scientific data to the 18th Session of the Committee on Residues of Veterinary Drugs in Foods (May 2009) thus allowing for a decision by the Committee regarding the inclusion of ractopamine in the priority list of substances for evaluation / re-evaluation by JECFA.

In the absence of any new relevant scientific data, the CCRVDF should not include the MRLs for Ractopamine on the priority list and the MRLs should remain at the Commission at Step 8.

Narasin

The United States would also like to offer additional comments to those submitted on the MRLs at Step 3 (CX/RVDF 09/18/5 Add. 1). The US believes that the MRLs for Narasin should raise to 50 ug/kg for all tissues based on the reported LOD and LOQ of 10 and 25 ug/kg respectively. There is a table near the end of the monograph for Narasin with two method studies summarized (one by Elanco authors and the second by Ward, et al, as an AOAC International study). In the Elanco study, the LOD and LOQ were reported in the table as respectively, 10 and 25 ug/kg for skin/fat, muscle, liver and kidney (i.e. all tissues) while the AOAC study listed, 3 and 7 ug/kg. The MRLs were recommended as 2X the 25 ug/kg for liver and fat, but 2X the 7ug/kg for muscle and kidney. In the Ward, et al, paper, the table correctly reports the 3 and 7ug/kg values - however, the same paragraph in the paper indicates that these values are the optimal expected values and that for other laboratories, the practical performance values should be, respectively, 10 and 25ug/kg. Thus, both studies recommend LOD and LOQ values of 10 and 25ug/kg.

The United States would like to thank Australia for leading the Electronic Working Group on Priorities in preparation for the 18th session of the CCRVDF in Brazil in 2009. The United States previously submitted comments on October 31, 2008, to the Working Group on the proposed list and priority for substances that do not currently have Codex MRLs. In that document, the US requested that the CCRVDF consider a process whereby substances could be considered for the establishment of an ADI by the JECFA and MRLs by the Codex in advance of, or simultaneously with, any approval/registration by a national authority. We provide substantive elaboration on this proposal in this document. We would also like to propose that a physical Working Group be convened prior to the 18th session of the CCRVDF to further discuss this proposal, as there may be limitations in the quality of the discussions that can occur through multiple electronic exchanges.

With the increased focus on food animal product (meat, poultry and dairy) exports and imports, both in the developed and developing countries, there is increased awareness and sensitivity about substances used in food production. This has justifiably led to a discussion regarding setting JECFA ADIs and Codex MRLs for substances already on the market. However, individuals and firms involved in food production and export have a fundamental concern that they bear the brunt of trade sanctions, rejected shipments, and bans, particularly when the approved use of a veterinary drug in one country results in rejected food products in another country. Both industry and national authorities have, for the most part, taken a nationalistic view of approving substances, which has led to some of the trade issues. The Codex Alimentarius Commission is being looked to as an international standard setting body that through its process may resolve many of the differences in MRLs among countries by establishing internationally adopted MRLs. Developed countries often have well established local programs for assessing the safety of residues from substances used in food producing animals. These ADIs and MRLs are often established in isolation from other countries regulatory decisions, leading to multiple MRLs in the global market. Further, developing countries can become frustrated by the wide range of MRLs and have difficulty establishing their own standards based on these global discrepancies. The mandate of the Codex Alimentarius Commission is to establish standards for protecting consumers' health and facilitating fair trade practices. One of the criteria for nominating a veterinary drug for placement on the CCRVDF Priority List for referral to the JECFA is the requirement that the veterinary drug has been approved/registered by a national authority. This prerequisite requirement before establishment of a global standard is inadvertently creating trade issues as countries feel they must establish national standards for imported food products in the absence of a global standard. Arguably, some regional differences may continue to exist as national authorities approach the establishment of an MRL in a manner that is scientifically different than the JECFA.

The issue presented is not exclusive to veterinary substances. At the 40th Session of the Codex Committee on Pesticide Residues, held in Hangzhou, China, April 14 to 19, 2008, the United States presented a proposal on "Achieving Globally Harmonized MRLs Through Codex" (CX/PR 08/40/13; Agenda Item 10(iii), April, 2008). The United States would like the same arguments that were brought forward in the CCPR to be considered by the CCRVDF.

There are several advantages to having a global standard prior to the first approval of a veterinary substance by a national authority. If this were to be accomplished, a substantial number of trade issues could be avoided or minimized. It could be argued that a number of bans and other regulatory interventions could be avoided because global scientific assessments would already be completed and regulatory authorities would be aware of such outcomes. Many trade restriction actions are currently in place because substances were introduced into the market without adequate global assessments or global awareness, thus leading to precautionary measures by countries. If the substance could have a scientific review prior to any trade or political sanctions, many of these trade restriction actions would not likely occur. This would also support the Codex Alimentarius Commission mandate of science-based standards. In accordance with the SPS Agreements, countries would have a benchmark standard to follow and, if this benchmark was not acceptable, be able to focus on science if they did have a concern regarding the safety of a particular food product.

There are some issues that would need to be discussed in order for this to become a potential path forward.

Data Confidentiality: The Procedure Manual states that for the CCRVDF processes sponsor confidentiality will be maintained if so requested (Codex Alimentarius Commission Procedural Manual, 17th ed., pp. 141, para. 14). If the review process occurs toward the end of the product development cycle, knowledge of going to market should not be a major concern, as the sponsor should be in a position to know that they will be marketing the product.

Requirement for an approval by a national authority prior to a substance being placed on the priority list: The Procedural Manual states that for a substance to be placed on the priority list it needs to be available as a commercial product (Codex Alimentarius Commission Procedural Manual, 17th ed., pp. 141, para. 13). This could be open to interpretation if the intent is to get to an MRL concurrent with first approval. One thought would be that the sponsor company could certify in the dossier submitted for JECFA review that it has commercial GMP material available, and that it intends to launch the product after the first approval by a national authority. This is actually a different statement than that made by the CCPR, which states that a pesticide must be registered for use in a member country.

The time for the Codex to go through the 8 step procedure would essentially make it impossible for a pre-approval MRL procedure to be viable: There are mechanisms for priority review in the Procedure Manual (Codex Alimentarius Commission Procedural Manual, 17th ed., pp. 25-26). Also, the CCPR utilizes a process whereby, if a JMPR review indicates no scientific issues, the substance can go from Step 5 to Step 8 in one pass. Also, there are mechanisms in the Procedure Manual to do "out of cycle" reviews in the spirit of "speed to decision." These could be explored and

leveraged if this were to become a viable review. If both industry and national authorities cooperated in this process, it could very well support more predictable scheduling of the ad hoc JECFA meeting. As a continual string of innovation could be anticipated, there would be new veterinary drugs to add to the Priority List for Evaluation by the JECFA at each session of the CCRVDF.

Sponsors wouldn't have the total requisite data ready in time for the process to start and be completed prior to approval: Much of the safety and residue data is generated prior to the full scale target animal safety and effectiveness program, so the bulk of the information should be available. Assurance that the residue data were collected at the final dosing scheme would be necessary for an evaluation by the JECFA. Also, if the above process to speed up the review could be implemented, it would mean that sponsors would in fact have more time to collect the data prior to the dossier submission deadline to the JECFA.

Countries and the Codex would not want to invest WHO and FAO resources in a non-approved product for fear the sponsor would ultimately not want to market it after the review was complete: This concern should be allayed by the certification process described above. Additionally, the sponsor could be asked to contribute to a travel fund to support critical experts in getting to the JECFA meeting. The legal aspects of this would need to be vetted.

Not all MRLs would be established, as additional species are often added subsequent to a substances first use: Although this is a valid concern, the establishment of the ADI would be independent of the species to which the substance is being administered. Therefore, the toxicological assessment would be complete. The JECFA and the CCRVDF would need to be prepared to recommend and establish MRLs on subsequent species as they were provided by the sponsor. The CCRVDF should encourage sponsors to submit new species dossiers for priority review by the JECFA in advance of the first market approval for that species to also avoid any trade related issues.

The ultimate mandate of the Codex Alimentarius Commission is to set global standards to assure consumer protection and fair practices in food trade. This proposal represents a new approach that will ultimately facilitate the setting of standards in such a way that a standard can be established prior to any trade issues being raised. This has the benefit of providing safe and wholesome food to global markets without barriers resulting from an absence of international standards.

Proposal For the Priorities Working Group: The United States would like to recommend that a Physical Meeting of the Working Group be convened prior to the 18th session of the CCRVDF to further discuss this proposal.

IFAH (International Federation for Animal Health)

The International Federation for Animal Health (IFAH) appreciates the opportunity to comment on the work of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) Working Group on Priorities. Annex 2 (Starting Point for a Priority List of Veterinary Drugs for Discussion at the 18th CCRVDF) of CX/RVDF 09/18/8 contains many veterinary drugs with recommendations to the 18th Session of CCRVDF. The recommendation for Carbadox states that CCRVDF should confirm that this substance should not be used in food producing animals and agree that Codex does not recommend either an MRL or extra-label/off label use due to concern for toxicity to the human consumer. IFAH does not agree with this recommendation. The recommendation ignores the fact that Carbadox is currently approved for therapeutic use in several countries and has a substantial body of information demonstrating conditions of safe use in swine. Codex has previously affirmed the safe use of Carbadox in swine. The safe use of Carbadox was questioned by at least one member of Codex based on incidences of misuse of Carbadox, a standard that had never been applied by Codex in the safety evaluations of veterinary drugs. In response to questions about the safe use of Carbadox, the sponsor committed to update the residue studies and analytical methods for Carbadox. Interim reports of these non-GLP studies were submitted to JECFA. On the basis of these interim studies, JECFA recommended that the MRLs be withdrawn and Codex complied. Subsequent to the submission and evaluation of these studies, the sponsor determined that the new analytical method was measuring an artifact in the tissues rather than Carbadox. A new analytical method is being evaluated and new GLP residue studies are being conducted. The sponsor intends to submit this new data on the safety of Carbadox to CCRVDF and JECFA for a re-evaluation. Meanwhile, IFAH believes it inappropriate and premature for CCRVDF to recommend Carbadox not be used due to concern for the human consumer.

In previous comments on veterinary drugs with MRLs at step 3, IFAH recommended Monensin and Narasin be included on the priority list of drugs for JECFA re-evaluation. IFAH has no additional drugs for the priority list; however, IFAH supports the US Delegation's proposal to accelerate the approval of Codex MRLs by submitting human food safety data to JECFA prior to the first national approval. If this proposal is accepted by CCRVDF, a member of IFAH has committed to providing JECFA the human food safety necessary to establish an ADI and MRLs. Under the present criteria for placing veterinary drugs on the priority list, this compound would not qualify as it is not registered in any country.