CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 6 (b) **CX/RVDF 12/20/6 Add. 2**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twentieth Session

San Juan, Puerto Rico, 7-11 May 2012

PROPOSED DRAFT MRLS FOR VETERINARY DRUGS

Comments at Step 3 of

Kenya, Thailand and IFAH

KENYA

Issues and observations

The AECRVDF agrees with the decision of CCRVDF to recommend to the 34th session of the Commission the advancement of MRL for antimicrobial drug Narasin in pig tissues to step 8 whilst retaining the MRL for Narasin in cattle tissues at step 7, in light of JECFA's assessment of the analytical method.

Comments

AECRVDF recommends the advancement of Narasin in pig tissues to step 8.

THAILAND

We have no objection on the proposed draft MRLs as mentioned in CX/RVDF 12/20/6 and CX/CCRVDF 12/20/6 corrigendum.

IFAH (International Federation for Animal Health)

The International Federation for Animal Health, IFAH, is pleased to submit the following comments on the draft maximum residue limits proposed by JECFA at their 75th meeting for residues of veterinary drugs. We wish to commend and thank the WHO and FAO Secretariats for their efforts in arranging the meeting of the 75th JECFA in a relatively short period of time which allowed many important compounds to be reviewed.

As expressed consistently at CCRVDF and Codex Alimentarius Commission meetings, IFAH is a strong supporter of science-based decision making, a precondition for a dependable regulatory environment that supports our industry. IFAH also acknowledges and supports the different roles of the JECFA, carrying out independent risk assessment and providing relevant advice to the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF), which ultimately recommends appropriate risk management measures for adoption by the Codex Alimentarius Commission (CAC).

In our view, as also expressed at the informal discussions at CCRVDF on how to improve the work of JECFA, CCVDF and Codex on residues of veterinary drugs, recommending ADIs for residues of veterinary drugs is a clear outcome of risk assessment, whereas the establishment of MRLs already is clearly within the responsibilities of risk management, addressing risks posed by residues of veterinary drugs to human health.

In alphabetic order, we offer the following comments on the compounds assessed at the 75th meeting of JECFA.

Amoxicillin:

We support the assessment and recommend that members of Codex consider advancement of the MRLs to Step 5/8.

Apramycin:

Whilst we recommend that members of Codex consider advancement of the proposed MRLs to Step 5/8, we would offer the comment that in view of the long record of safe use of the substance in the countries where it has been authorized with the current method, and considering that the substance has been out of patent protection the investment in the additional information requested by JECFA is difficult to justify. It is highly likely that further investment may not occur.

Derquantel:

With respect to derquantel, IFAH supports the advancement of this molecule to Step 5 of the Codex process and in anticipation of agreement from the Member Countries, will at the appropriate time at this meeting propose further advancement of derquantel to Step 5/8. Derquantel is or will be approved in several significant sheep producing countries and food commodities from treated sheep will enter international commerce. It is critically important that international standards be established for this molecule to avoid any technical barriers to trade.

While IFAH emphasizes that it wants to see derquantel advance, it is also asking CCRVDF to exercise its role as Risk Managers and consider a modification to the draft MRLs proposed by the 75th JECFA, should

the CCRVDF, as we hope, agree to advance the standards to the next step. IFAH recognizes that it does not need to remind the delegations that CCRVDF has two mandates. The first and top priority purpose is to ensure consumer safety while the second is to ensure fair practices on international trade. While JECFA has certainly proposed draft MRLs for derquantel that are protective of human health, IFAH is of the view that JECFA could have done considerably more with respect to the promotion of fair practices on international trade.

IFAH is far from being in complete agreement with the outcome of the JECFA assessment. While the ADI was set on a reasonable endpoint given the known toxicology of derquantel, a 300-fold safety factor was applied, which, again given the compound's safety profile, seems difficult to justify. In consequence, the MRLs are extremely low. IFAH would point out that the JECFA assessment is the most conservative (by a wide margin) of several global regulatory reviews of derquantel that have occurred over the past few years. For example, the JECFA recommended MRLs are approximately 10-fold lower than approved in the European Union (ADI=1 µg/kg; MRL (liver) = 20 µg/kg, MRL (kidney) = 5 µg/kg, MRL (muscle) = 2 µg/kg and MRL (fat) = 40 µg/kg).

IFAH is not seeking a re-evaluation by JECFA. While we do not agree with the conclusion in respect of the proposed draft MRLs, a risk management tool, we are prepared to accept the outcome of the risk assessment, the ADI decision; most importantly, as stated above, we would like to see derquantel advance at this session.

However, we note that the JECFA proposed draft MRLs, when considered in conjunction with the standard market-basket of edible tissues, only utilize 45% of the available (and very low) ADI (see Table 1). This provides an opportunity to explore whether these recommended MRLs, are appropriate in view of Codex's second mandate of ensuring fair practices in trade and we invite members to consider our proposal below.

Derquantel is not marketed alone but is only sold in combination with abamectin as the commercial product STARTECT (Pfizer Animal Health). Based on the draft MRLs proposed by the 75th JECFA and the application of standard statistical analysis techniques, the withdrawal time of STARTECT may be determined by either of the two active substances. The consequence of this recommendation is that member countries will need to incorporate both derquantel and abamectin into their surveillance programs as both substances will deplete to below their respective MRLs at similar time points. These programs are expensive and require investment in people resources and sophisticated technology and member countries will likely need to make critical decisions on how to allocate those scarce resources. Setting higher MRLs for derquantel that are still compatible with the ADI when estimating intake would enable countries to focus on the remaining substance determining the withdrawal period, i.e. abamectin.

IFAH proposes that CCRVDF double the draft MRLs proposed by the 75th JECFA for all edible tissues. As explained above, the consequence of this action for STARTECT would be that the withdrawal period would be governed by the residue depletion of abamectin, not derquantel. In other words, derquantel tissue concentrations would fall below its MRLs prior to the depletion of abamectin to its corresponding MRLs.

Modification of the draft MRLs proposed by the 75th JECFA per the IFAH proposal would have a significant impact to the promotion of fair practices on international trade. Member countries (if they chose to) would only need to monitor for abamectin in edible sheep tissues as derquantel assays would be unnecessary. As abamectin is a widely used substance, most surveillance programs would already have this assay well established in their laboratories. There would be no extra investment needed for member countries to establish, validate and implement a derquantel assay and financial resources could be channelled to more critical surveillance areas.

In the following, Table 1 lists the draft MRLs proposed by JECFA and the IFAH suggestion for the MRL modifications are shown in Table 2.

Table 1. JECFA calculations for the proposed draft MRLs for Derquantel

NOEL =	0.1 mg/kg bw	Safety Factor (SF) = 300			
ADI =	0.3 µg/kg bw	(NOEL/SF x 1000 µg/mg)			
(or) ADI =	18 µg/day	(ADI x 60 kg bw)			
Tissue	MRL (µg/kg)	Marker/Total Ratio	Total Residues (µg/kg)	Consumption Factor (kg)	Intake (µg)
Liver	2	0.03	66.7	0.1	6.67
Kidney	0.2	0.07	2.86	0.05	0.143
Muscle	0.2	0.06	3.33	0.3	1.00
Fat	0.7	0.15	4.67	0.05	0.234
Total Intake (µg) = 8.05 (TMDI)					
% of ADI = 44.7%					

Table 2. IFAH suggested revisions to the proposed draft MRLs for Derquantel

NOEL =	0.1 mg/kg bw	Safety Factor (SF) = 300			
ADI =	0.3 µg/kg bw	(NOEL/SF x 1000 µg/mg)			
(or) ADI =	18 µg/day	(ADI x 60 kg bw)			
Tissue	MRL (µg/kg)	Marker/Total Ratio	Total Residues (µg/kg)	Consumption Factor (kg)	Intake (µg)
Liver	4	0.03	133	0.1	13.3
Kidney	0.4	0.07	5.71	0.05	0.286
Muscle	0.4	0.06	6.66	0.3	2.00
Fat	1.4	0.15	9.33	0.05	0.467
Total Intake (µg) = 16.1 (TMDI)					
% of ADI = 89.2%					

IFAH recommends that CCRVDF adopt these increased MRLs for derquantel. This risk management decision is one that remains with the CCRVDF and CCRVDF does not need to go back to JECFA, as the scientific assumptions remain unchanged. The total maximum daily intake remains within the ADI established by JECFA and thus the revised proposed draft MRLs meet the first mandate of protection of public health. However, in addition the revised proposal for MRLs meets the second mandate of ensuring fair practices in trade by minimizing the need for import controls and by decreasing the discrepancy to existing MRLs, for instance, the EU MRLs. IFAH sees this as an opportunity to satisfy both Codex mandates.

To further clarify the rationale for this proposal, IFAH offers the following in a "Frequently Asked Questions" format:

What is the role of CCRVDF following a recommendation of MRLs by JECFA?

JECFA as the Risk Assessors propose draft MRLs based on their scientific review. CCRVDF as the Risk Managers can either (1) accept the proposal, (2) reject the proposal or (3) modify the proposal.

Has CCRVDF ever done this before?

Yes, at the 16th meeting in Cancun, JECFA proposed draft MRLs for pirlimycin in milk of 100 µg/kg. CCRVDF modified this recommendation and doubled the MRL to 200 µg/kg. The current IFAH proposal is similar to this previous action.

Why is the proposal for doubling the MRLs? Why not some other factor?

Currently the calculated withdrawal period (WDP) for STARTECT (the commercial product containing derquantel and abamectin) using the JECFA proposed draft MRLs can be determined by either active commodity. Fat and liver are the determining tissue for withdrawal and both active substances reach their MRLs on a statistical basis at approximately 14 days. If the MRLs are doubled, the withdrawal times for derquantel are shorter by 9 days in liver and about 2 days in the other tissues (final WDP = ca 12 days). But this adjustment is sufficient to allow derquantel residues to deplete to below its MRLs prior to when abamectin depletes to below its corresponding MRLs.

Then why not just adjust the liver and fat MRLs?

This would accomplish the IFAH objective but it would violate a standard principle of how MRLs are set. If only liver and fat were adjusted, the proportionality of tissue residues in the edible tissues, traditionally considered by JECFA in proposing draft MRLs, would be lost. As such, IFAH recommends adjusting all tissues by the same percentage.

Isn't this a rather large adjustment?

The IFAH proposal is for a 100% increase in the MRLs. However, on an absolute basis the proposal is for an increase from 200 parts per trillion to 400 parts per trillion in muscle and kidney, 0.7 parts per billion to 1.4 parts per billion in fat and 2.0 parts per billion to 4.0 parts per billion in liver. IFAH considers these as important but relatively small changes.

How will this benefit international trade?

Surveillance laboratories controlling imported commodities would not need to develop, validate and implement an analytical method for derquantel as part of their standard procedures (if they choose not to do so). The safety of sheep meat from STARTECT treated animals could be effectively controlled through monitoring for abamectin residues alone. The scarce people and equipment resources within the surveillance lab could be devoted to more critical concerns.

How much savings might be realized for surveillance programs?

Besides the people resources mentioned above, the derquantel assay requires that analytical instrumentation equivalent to a Sciex 5000 mass spectrometer be available to measure concentrations at the levels proposed by JECFA. These instruments can cost $400,000 to $500,000 in today's market. Laboratories, especially those in the developing markets, would need to obtain this instrumentation to implement the derquantel assay. If the MRLs are adjusted per the IFAH proposal, this purchase would be unnecessary. Furthermore, as abamectin is an old molecule, it is likely that surveillance laboratories already have this compound as part of their standard program. In this case, there would be zero additional expenses to set up and validate a derquantel assay.

Is the proposed adjustment to the derquantel MRLs safe?

This remains the most important question and the answer is an unequivocal YES. The revised MRLs would utilize only 89% of the available ADI and thus would remain consistent with the risk assessment of the 75th JECFA.

Monensin:

IFAH supports advancement of the proposed draft revised MRLs to step 5 and invites CCRVDF to consider advancement to step 5/8.

Monepantel:

IFAH supports advancement of the proposed draft revised MRLs to step 5 and invites CCRVDF to consider advancement to step 5/8. However, IFAH wishes to note that, as for Derquantel, the proposed draft MRLs amounting to an estimated intake of 17% of the ADI is exceedingly low. In the interests of trade, the MRLs should be increased to the MRLs currently set in Europe and in other countries, all of which have the same MRLs of 7000, 5000, 2000 and 700 µg/kg for fat, liver, kidney and muscle, respectively. The safety to the consumer is not at risk, as consumption of residues, based on median values, is still below the proposed JECFA ADI.

Narasin:

IFAH supports advancement of the proposed draft revised MRLs to step 5 and invites CCRVDF to consider advancement to step 5/8.

Triclabendazole:

IFAH commends JECFA for considering the possibility to extrapolate the existing MRLs in sheep and cattle to goats in consideration of the available information. To our regret, JECFA did not find itself able to undertake this extrapolation, and the MRLs in goat tissues that Codex members indicated were needed remain unavailable. We strongly urged JECFA to continue its work on defining conditions that would enable extrapolation of MRLs in order to ensure that more necessary standards can be developed to the benefit of consumers for old substances where data may be scarce.