CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 6b **CRD 27**

Original Languge Only

JOINT FAO/WHO FOOD STANDARDS PROGRAMME
CODEX COMMITTEE ON RESIDUES OF VETERIANRY DRUGS IN FOODS
Twentieth Session
San Juan, Puerto Rico, 7-11 May 2012

Comments submitted by:
IFAH

IFAH PROPOSAL FOR ADVANCEMENT OF DERQUANTEL

Since the submission of IFAH's previous comments on derquantel, questions have been raised with respect to the evaluation of this substance by the 75th JECFA to the point at which the current MRLs are unlikely to advance. Nonetheless, it is important from a trade perspective that a way forward is found to advance alternative MRLs at this meeting while at the same time allowing derquantel to be reconsidered by JECFA at its next meeting.

The uncertainty with the current JECFA approach revolves around the uncertainty of the marker to total ratios at the time JECFA elected to establish the MRLs. In order to provide greater assurance with respect to its safe use, IFAH offers the following alternative proposal to allow advancement of derquantel at the 20th CCRVDF, which differs from the JECFA assessment in that more conservative MRLs are being recommended. At the same time as suggesting these revised MRLs, IFAH would recommend to refer derquantel to JECFA for consideration of concerns to be put forward by any concerned Member Countries.

Total Residue Analysis

The derquantel residue depletion curve is biphasic and includes a rapid phase and then a slower phase starting at 4 days post-treatment. The Sponsor has total residue data from the slower depletion phase that includes values at 4 days (4 animals), 6 days (3 animals) and 28 days (1 animal). The residue data (µg/kg) as well as calculations showing total consumption based on the standard market-basket (0.1 kg liver, 0.3 kg mucle, 0.05 kg fat and kidney) are as follows:

Day	Liver	Kidney	Muscle	Fat	TOTAL
4	122.1	20.5	1.7	1.8	13.84
4	178.3	29.3	3.0	6.1	20.50
4	249.3	53.1	4.4	4.2	29.12
4	229.1	53.7	3.4	13.3	27.28
6	185.1	32.5	2.8	1.9	21.07
6	140.6	25.3	2.4	1.9	16.14
6	88.9	18.3	1.3	0.8	10.24
28	23.6	8.1	1	2.9	3.21
28	17.4	6.2	0.7	2.2	2.37*
28	11.4	3.9	0.5	1.4	1.56

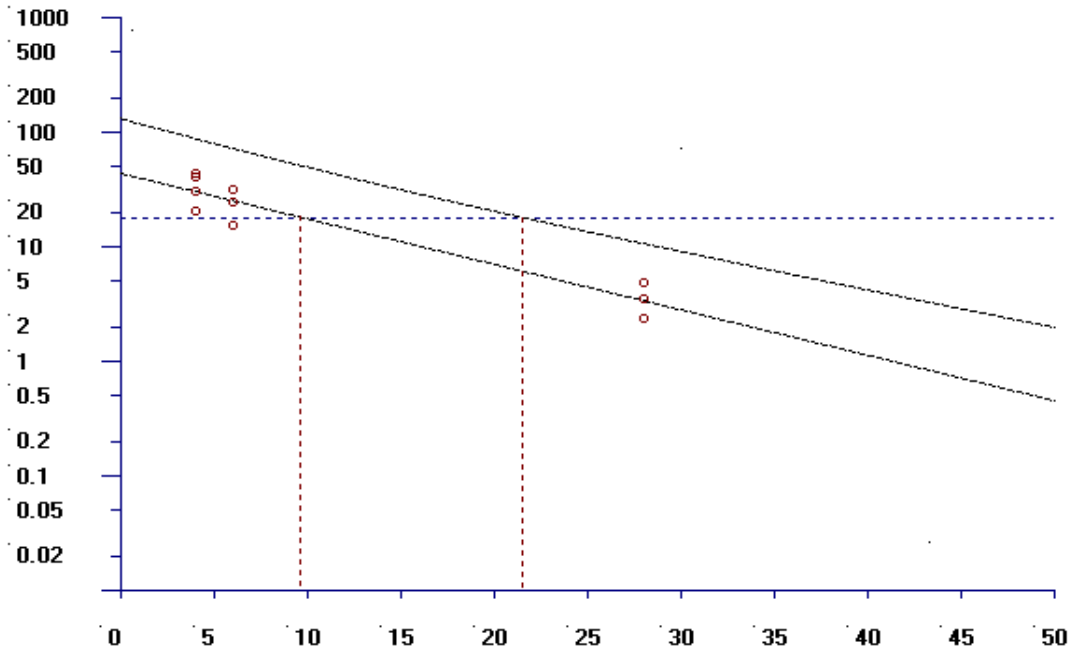
There was only one animal at Day 28 in the Sponsor study (2.37 µg*). In order for the statistical program to run (see below), three points are needed. As such, the Sponsor estimated the other two residue values using a coefficient of variation approximately equivalent to the other two time points.

The total residue data shown above were generated from animals treated at the label dose of 2.0 mg/kg derquantel. However, because of the weight ranges on the label, maximum doses during the normal pattern

of use may approach 3 mg/kg. To account for this, the total residue data above have been adjusted upward by a factor of 3/2 and are shown below as the sum or residues in the standard market basket of tissues.

WITHDRAWAL TIME (days)	TOTAL (µg/kg)	ADJUSTED TOTAL (µg/kg)
4	13.84	20.75
	20.50	30.75
	29.12	43.67
	27.28	40.92
6	21.07	31.61
	16.14	24.21
	10.24	15.35
28	3.21	4.82
	2.37	3.56
	1.56	2.33

The Adjusted Total Residue data were analyzed statistically using the CVMP program WT1.4 relative to the ADI elaborated by JECFA of 18 µg. The graph of the data is shown below:



The data indicate a withdrawal period of 22 days, which represents the time when total dequantel related tissues are safe for human consumption on a statistical basis.

Marker Residue Analysis (what MRL is required at 22 days)

The only tissue with significant levels of residues is liver. The Sponsor conducted a large marker residue depletion study with sheep sacrificed at time points from 6 hours to 35 days post-dose. As stated above, residue depletion is biphasic so only data between 4 days and 35 days were analyzed statistically. The SAS output for liver is shown below (the other tissues do not contribute significant residue amounts at the later withdrawal times):

2-DESOXOPARAHERQUAMIDE/ABAMECTIN STUDY SHEEP 0
STUDY: 14184Q005
LIVER RESIDUE CONCENTRATIONS - 2-DOPH
TOLERANCE LIMITS BASED ON REGRESSION

Days post administration	Predicted (log scale)	Tolerance limit 95th percentile 95% confidence (log scale)	Geometric mean (ug/kg)	Tolerance limit 95th percentile 95% confidence (ug/kg)	mrl	Tolerance below mrl
0	0.19	1.66	1.2	5.26	1	no
1	0.12	1.58	1.1	4.86	1	no
2	0.05	1.50	1.1	4.49	1	no
3	-0.02	1.42	1.0	4.16	1	no
4	-0.10	1.35	0.9	3.85	1	no
5	-0.17	1.27	0.8	3.56	1	no
6	-0.24	1.19	0.8	3.30	1	no
7	-0.31	1.12	0.7	3.06	1	no
8	-0.38	1.04	0.7	2.83	1	no
9	-0.46	0.97	0.6	2.63	1	no
10	-0.53	0.89	0.6	2.44	1	no
11	-0.60	0.82	0.5	2.27	1	no
12	-0.67	0.75	0.5	2.11	1	no
13	-0.75	0.67	0.5	1.96	1	no
14	-0.82	0.60	0.4	1.83	1	no
15	-0.89	0.53	0.4	1.70	1	no
16	-0.96	0.46	0.4	1.59	1	no
17	-1.04	0.39	0.4	1.48	1	no
18	-1.11	0.32	0.3	1.38	1	no
19	-1.18	0.26	0.3	1.29	1	no
20	-1.25	0.19	0.3	1.21	1	no
21	-1.32	0.12	0.3	1.13	1	no
22	-1.40	0.05	0.2	1.06	1	no
23	-1.47	-0.01	0.2	0.99	1	yes
24	-1.54	-0.08	0.2	0.92	1	yes
25	-1.61	-0.14	0.2	0.87	1	yes

The data show that at 23 days post-treatment, residues fall below 1.0 µg/kg, indicating that this would be an appropriate MRL for liver residues of dequantel.

SPECIFIC PROPOSAL

Elaborate MRLs for derquantel as:

- Liver = 1.0 µg/kg
- Muscle, Kidney and Fat = 0.2 µg/kg (2X the LOQ)
- Advance derquantel to Step 5 and Step 5/8 at the 20th CCRVDF (current meeting)
- Send derquantel back to JECFA for reassessment (in light of the concerns to be put forward by any concerned Member Countries)

This proposal is justified as total residues were determined to be safe at 22 days and the marker analysis computes a withdrawal time of 23 days.

Advancement of derquantel at this meeting would allow for continued registration activities by the Sponsor, including the pursuit of import tolerances, where appropriate, to facilitate trade. Additionally, returning the

molecule to JECFA for re-evaluation would allow the Sponsor an opportunity to submit a new toxicological assessment to increase the current recommended ADI.

IMPACT TO CURRENT MARKETING AUTHORIZATIONS

The European Union has evaluated derquantel and reached a significantly different conclusion with respect to the toxicology. An ADI was established at 60 µg, substantially higher than the 18 µg recommended by JECFA. New Zealand has an ADI of 300 µg, 5X higher than the EU. The Sponsor is aware that each region where STARTECT is currently approved will need to assess any potential impact to its Marketing Authorizations.