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Japan

Food and Agricultural Import Regulations and Standards

Japan Considering Changes to MRL for Tulathromycin, a Veterinary Drug

2006

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Report Highlights:
On April 14, 2006 the Japanese Ministry of Health, Labor and Welfare announced that it is accepting public comments on the proposed changes to the maximum residue limit for the veterinary drug, Tulathromycin. Comments are being accepted until April 28, 2006.

Includes PSD Changes: No
Includes Trade Matrix: No
Unscheduled Report
Tokyo [JA1]
[JA]

On April 14th, 2006 the Japanese Ministry of Health, Labor and Welfare announced the intent to change the maximum residue limits for Tulathromycin. Comments are being accepted until April 28th. If you have comments please send them directly to the following address:

Standards and Evaluation Division, Department of Food Safety,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
1-2-2, Chiyoda-ku, Kasumigaseki, Tokyo, 100-8916
Tel: 03-5253-1111
Fax: 03-3501-4868

Please also consider sending your comments, as early as possible, to the USDA Foreign agricultural Service (FSTSD@fas.usda.gov) for them to be considered for incorporation into official U.S. Government comments as well.

If this change is accepted, these will become the permanent MRLs and this substance will be removed from the list of provisional MRLs.

The text of the announcement follows:

Establishment of Maximum Residue Limits for Tulathromycin in Food

Discussion on the Establishment of Standards for Tulathromycin,
Veterinary Drug, in Food

Background
This activity is to respond to an application made by a foreign business for the establishment of standards, based on the Guideline for Application for Establishment and Revision of Maximum Residue Limits for Agricultural Chemicals Used outside Japan, published on February 5, 2004.

Tulathromycin is not permitted for use in food animals in Japan. The Ministry of Health, Labour and Welfare will newly establish standards for this substance to target imported animal products.

Summary report of discussion at the Joint Committee on Agricultural Chemicals and Veterinary Drug under the Pharmaceutical Affairs and Food Sanitation Council

1. Substance
Tulathromycin consists of an equilibrium mixture of two isomers (CP-472,295 and CP-547,272). CP-472,295 and CP-547,272 exist at a ratio of 9:1 in a solution in equilibrium state.

Chemical name
CP-472,295: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-a-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-Dxylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one
CP-547,272: (2R,3R,6R,8R,9R,10S,11S,12R)-11-(2,6-dideoxy-3-C-methyl-3-Omethyl-4-C-[(propylamino)methyl]-a-L-ribo-hexopyranosyl)oxy]-2-[(1R,2R)-1,2-dihydroxy-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-

(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one

2. Use as treatment of bacterial pneumonia
Tulathromycin is a semi-synthetic macrolide antibiotic. It is effective for pathogens of bovine and swine bacterial pneumonia, including Pasteurella (P. haemolytica, P. multocida),

The following site shows the details:
http://www.mhlw.go.jp/english/topics/foodsafety/dl/importguideline.pdf
Haemophilus soumnus, Actinobacillus pleuropneumoniae and Mycoplasma hyopneumoiae.
In the United states and European union, it is usually used with single subcutaneous dose of 2.5 mg/kg in cattle and single intramuscular dose of 2.5 mg/kg in pigs.

3. Acceptable daily intake (ADI)
Based on two-generation reproduction and teratogenicity studies in rats, the Food Safety Commission in the Cabinet Office determined that tulathromycin causes negative effects for liver weights and fetal body weights. In each study, the LOAEL (Lowest Observed Adverse Effect Level) of 15 mg/kg body weight/day was obtained. The commission established the ADI (Acceptable Daily Intake) of this substance at 0.015 mg/kg body weight/day. The ADI was calculated by dividing the LOAEL by a factor of 1,000, which consists of three 10-fold factors, one for interspecies differences, for interindividual variability in humans, and for additional safety factor. The assessment report from the commission is available in Japanese at http://www.fsc.go.jp/hyouka/hy/hy-hyouka-tulathromycin.pdf

4. Draft maximum residue limits (MRLs)
a. Target substance to regulate: Tulathromycin

b. The table shows draft MRLs. The MRLs were established taking into consideration requirements for standard setting and residue studies in the United State s and European union.

Tissue MRL (ppm)

Cattle		
	Muscle	0.3
	Fat	0.2
	Liver	5
	Kidney	3
	Other edible parts*	3
Pig		
	Muscle	2
	Fat	0.3
	Liver	4
	Kidney	9
	Other edible parts*	5

Note: The limits for “other edible parts” were based on residue study results for the lung.

c. Ratio of ADI

The table shows the ratios of the TMDI (theoretical maximum daily intake) to the ADI. The TMDI refers to the amount of tulathromycin that is estimated to be consumed a day, based on the National Nutrition Survey, when it is assumed that the substance remains in each food up to the draft maximum residue limit.

	TMDI/ADI (%)
National average-	10.31
Young children, aged between 1 and 6-	22.60
Pregnant women-	10.70

Food	MRL (ppm) (A)	Intake(g/person/day) (B)	Estimated intake (µg) of tulathromycin (A) × (B)
Cattle			
Muscle	0.3	19.71	5.91*
Fat	0.2		
Liver	5	0.12	0.60
Kidney	3	0.04	0.12
Other edible parts	3	0.42	1.26
Pig			
Muscle	2	35.83	71.66*
Fat	0.3		
Liver	4	0.17	0.68
Kidney	9	0.04	0.36
Other edible parts	5	0.36	1.80
Total (µg)			82.39
TMDI/ADI (%)			10.31

Note: Estimated intakes marked with asterisk: the MRL for muscle × (sum of intakes of muscle and fat).

d. Tulathromycin is appearing in the “list of maximum residue limits for substances used as ingredients of agricultural chemicals in foods,” which is specified in the Ministry of Health, Labour and Welfare Notification to revise the Specifications and Standards for Food, Food Additives, Etc (Notification 499, published on November 11, 2005). However, the MRLs given in the list, known to be provisional MRLs, will be deleted on the date of the enforcement of the new MRLs, given in section 4-b.