Date: December 5, 2019

FREEDOM OF INFORMATION SUMMARY

Import Tolerance

VMF 006-253

emamectin benzoate

salmonids

100 ppb emamectin B_1a (the marker residue) in muscle with adhering skin

Petitioner:

Intervet, Inc.

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I. GENERAL INFORMATION

A. File Number

VMF 006-253

B. Petitioner

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

C. Drug Established Name

Emamectin benzoate

D. Pharmacological Category

Antiparasitic

E. Species/Class

Salmonids

F. Import Tolerance for Drug Residues in Edible Tissues

100 ppb emamectin B_1a (the marker residue) in muscle with adhering skin

II. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

The Agency evaluated the need to address the impact of the use of emamectin benzoate on antimicrobial resistance among bacteria of public health concern in or on emamectin benzoate-treated salmonids. After reviewing information both submitted by the petitioner (literature, data, etc.) and available in the public domain, the Agency determined:

1. emamectin benzoate is not regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern in food-producing animals,
2. emamectin benzoate is not used to treat gastroenteritis or other bacterial diseases in humans,
3. emamectin benzoate (or a similar class representative) is not under development to treat bacterial diseases in humans, and
4. emamectin benzoate is not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined there was no need to develop or submit for review additional microbial food safety (antimicrobial resistance) information regarding the proposed emamectin import tolerance for salmonids.

B. Toxicology

1. Toxicology Studies

Toxicology studies considered in the determination of the acceptable daily intake (ADI) for total residues of emamectin are listed in Table C.1. below:

Table C.1. Summary of Toxicology Studies (test article: emamectin benzoate or emamectin hydrochloride)

Study Type	**Study Number**	**NOEL/NOAEL* (mg/kg bw/day)**
14-week oral toxicity study in rats	TT #88-059-0	0.5
14-week oral neurotoxicity study in rats	TT #91-006-0	1.0
14-week oral toxicity study in dogs	TT #88-060-0	0.25
53-week oral toxicity study in rats	TT #91-046-0	0.1
53-week oral toxicity study in dogs	TT #90-612-0 TT #90-612-1	0.25
2-generation oral reproduction toxicity study in rats	WIL-97056	0.6
Oral developmental toxicity study in rats	TT #89-716-0	4.0 (fetal) 2.0 (maternal)
Oral developmental toxicity study in rabbits	TT #89-715-0	6.0 (fetal) 3.0 (maternal)
105-week oral combined carcinogenicity and toxicity study in rats	TT #91-017-0	0.25**

*NOEL = no-observed-effect level
NOAEL = no-observed-adverse-effect level
** Emamectin was not carcinogenic under the conditions of the study.

The following genotoxicity studies were also considered, and it was concluded that emamectin is not genotoxic:

- Bacterial reverse mutation assay (Ames test)
  Study Number: TT #88-8013
- *In vitro* mammalian cell gene mutation test in Chinese hamster lung cells (V-79)
  Study Numbers: TT #88-8511 and TT #88-8519
- *In vitro* mammalian chromosome aberrations test in Chinese hamster ovary cells
  Study Numbers: TT #91-8632, TT #91-8633, and TT #91-8674
- *In vivo* chromosomal aberrations test in mouse bone marrow
  Study Number: TT #91-8680

2. Determination of Toxicological NOEL/NOAEL for Chronic Exposure

Based on the available toxicology studies, the no-observed-effect level (NOEL)/no-observed-adverse-effect level (NOAEL) of 0.1 mg/kg bw/day for neurotoxicity and weight gain from the 53-week oral toxicity study in rats (Study Number TT #91-046-0) was selected to be the most appropriate for

the determination of the toxicological ADI for chronic exposure of total emamectin residues to human consumers.

3. **Acceptable Daily Intake (ADI)**

The ADI for total residues of emamectin is calculated using the following formula based on the NOEL/NOAEL of 0.1 mg/kg bw/day from the 53-week oral toxicity study in rats. A safety factor of 100 was applied to account for a 10-fold factor for animal to human variability and a 10-fold factor for human to human variability in sensitivity to the toxicity.

$$\text{ADI} = \frac{\text{NOEL/NOAEL}}{\text{Safety Factor}} = \frac{0.1 \text{ mg/kg bw/day}}{100} = 0.001 \text{ mg/kg bw/day} = 1 \text{ µg/kg bw/day}$$

The toxicological ADI for total residues of emamectin is 1 µg/kg bw/day.

4. **Safe Concentration for Total Residues in Edible Tissues**

The calculation of the tissue safe concentration is based on our recommendations in the "General Principles for Evaluating the Human Food Safety of New Animal Drugs used in Food-Producing Animals" (FDA/CVM Guidance for Industry #3, June 2018). The daily consumption value of the edible tissue of fish (muscle with adhering skin) is 300 g. The safe concentration of total residues of emamectin in the edible tissue of salmonids (muscle with adhering skin) is calculated using the following formula:

$$\text{Safe Concentration} = \frac{\text{ADI} \times \text{Human Body Weight}}{\text{Food Consumption Value}}$$

$$\text{Safe Concentration (muscle with adhering skin)} = \frac{1 \text{ µg/kg bw/day} \times 60 \text{ kg}}{300 \text{ g/day}}$$

$$= 0.2 \text{ µg/g} = 200 \text{ ppb}$$

Therefore, the safe concentration for total residues of emamectin is 200 ppb in muscle with adhering skin in salmonids.

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Study

Title: SCH 58854: Residue depletion of SCH 58854 (SLICE™) following a multiple oral (dietary) 50 µg/kg dose regimen in Atlantic salmon (*Salmo salar*) maintained in seawater at 5 or 10 °C (Study No. 95707, Report No. P-6745)

Conclusions: The data demonstrated that the major component of total residues in muscle, skin, and fillet was emamectin B_1a (MAB_1a or 4"-deoxy-4"-epi-methylamino-avermectin B_1a). The data showed that at all timepoints, total residue concentrations were below 200 ppb and emamectin B_1a concentrations were below 100 ppb.

b. Comparative Metabolism Study

Title: The tissue distribution, metabolism and excretion of [^{14}C] 4"-deoxy-4"epimethylamino-avermectin B_1a (MAB_1a) benzoate in rats (Study No. ARM-6, Report No. A-27913)

Conclusion: The metabolic profile identified in the rat also was observed in salmon, indicating that the metabolic profiles of the rat and salmon are qualitatively similar.

2. Target Tissue and Marker Residue

The target tissue is muscle with adhering skin. The marker residue is emamectin B_1a.

3. Import Tolerance

We assign an import tolerance of 100 ppb emamectin B_1a (the marker residue) in salmonids muscle with adhering skin, harmonized with Codex international standards.

4. Withdrawal Period

A withdrawal period is not assigned when establishing an import tolerance.

D. Analytical Methods for Residues

Two methods are available for analysis of emamectin residues. The LC-MS/MS analytical procedure for emamectin B_1a in salmon tissue is described in Laboratory Information Bulletin (LIB) 4567. The multi-residue monitoring procedure for avermectins is described in LIB 4496. To obtain a copy of the analytical methods, please submit a Freedom of Information Summary request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/index.cfm.

III. AGENCY CONCLUSIONS

The Center for Veterinary Medicine assigns an import tolerance of 100 ppb for emamectin B_1a (the marker residue) in salmonids. The data submitted in support of establishment of an import tolerance for emamectin in salmonids satisfy the requirements of section 512(a)(6) of the Federal Food, Drug, and Cosmetic Act.