DATE OF APPROVAL LETTER:

FREEDOM OF INFORMATION SUMMARY

Muscle tolerance for PANACUR®/SAFE-GUARD® (fenbendazole) Suspension 10% in cattle and goats

I. GENERAL INFORMATION:

NADA Number:	128-620
Sponsor:	Hoechst Roussel Vet Perryville Corporate Park III P.O. Box 4010 Clinton, NJ 08809-4010
Generic Name:	fenbendazole
Trade Name:	PANACUR®, SAFE-GUARD® (fenbendazole) Suspension 10%
Dosage Form:	oral drench 100 mg/mL fenbendazole in 1000 mL and 3785 mL (1 gal) plastic containers
Marketing Status:	SAFE-GUARD® - over-the-counter (OTC) in cattle at 5 mg/kg (2.3 mg/lb.) PANACUR® - prescription in goats at the 5 mg/kg (2.3 mg/lb.) dose; prescription at 10 mg/kg (4.6 mg/lb.) in beef cattle
Pharmacologic category:	Antiparasitic
Effect of Supplement:	This supplement provides for the revision of 21 CFR 556.275 by establishing tolerances for residues in bovine and goat muscle (fenbendazole).

II. INDICATIONS FOR USE

Goats: 5 mg/kg (2.3 mg/lb.) for the removal and control of *Haemonchus contortus* and *Ostertagia circumcincta*.

Beef and Dairy Cattle: 5 mg/kg (2.3 mg/lb.) for the removal and control of:

Lungworm (*Dictyocaulus viviparus)*

Stomach worms (adults)
Ostertagia ostertagi (brown stomach worm)

Stomach worms (adult and 4th stage larvae)
Haemonchus contortus/placei (barberpole worm)
Trichostrongylus axei (small stomach worm)

Intestinal worms (adult and 4th stage larvae)
Bunostomum phlebotomum (hookworm)
Nematodirus helvetianus (thread-necked worm)
Cooperia oncophora, Cooperia punctata (small intestinal worm)
Trichostrongylus colubriformis (bankrupt worm)
Oesophagostomum radiatum (nodular worm)

Beef Cattle Only - 10 mg/kg (4.6 mg/lb.) for the removal and control of:
Stomach Worm (4th stage inhibited larvae): *Ostertagia ostertagi* (Type II Ostertagiasis)
Tapeworm: *(Moniezia benedeni)*

III. DOSAGE

A. Dosage Form: Fenbendazole is supplied as 100 mg fenbendazole /mL in 1000 mL (33.8 fl. oz.) and 3785 mL (1 gal) plastic containers.

B. Route of Administration: oral.

C. Recommended Dosage:

Goats: A single dosage of 5 mg fenbendazole per kg of body weight (2.3 mg/lb.).

Cattle: PANACUR®/SAFE-GUARD® (fenbendazole) is to be administered orally to cattle, including dairy cattle of breeding age, at the 5 mg/kg body weight dose (2.3 mg/lb.). PANACUR®/ (fenbendazole), in beef cattle only, 10 mg/kg (4.6 mg/lb.) dose to treat Type II Ostertagiasis and Tapeworms.

IV. EFFECTIVENESS:

Effectiveness in cattle was established originally under NADA 128-620 and its supplement (48 FR 42809; September 20, 1983, and 53 FR 40058; October 13, 1988). No new studies were conducted to establish effectiveness associated with the use of fenbendazole in dairy cattle of breeding age. For goats, effectiveness was addressed in PMF 5118 (56 FR 13650, April 3, 1991). No additional data were required for approval of this supplement.

V. TARGET ANIMAL SAFETY:

Animal safety in cattle was established originally under NADA 128-620 and its supplement (48 FR 42809; September 20, 1983, and 53 FR 40058; October 13, 1988). No new studies were conducted to establish animal safety associated with the use of fenbendazole in dairy cattle of breeding age. For goats, animal safety was addressed in PMF 5118 (56 FR 13650, April 3, 1991). No additional data were required for approval of this supplement.

VI. HUMAN FOOD SAFETY:

A. Toxicity Studies

Toxicity and teratogenicity studies were presented in the original NADA 128-620 for fenbendazole in cattle and were conducted in Hoechst Research Laboratories in Frankfort, Germany, and in the United States. No new toxicity studies were conducted to support this Supplement to NADA 128-620.

B. Acceptable Daily Intake

An Acceptable Daily Intake (ADI) of 40 micrograms per kilogram body weight per day for residues of fenbendazole has been assigned on the basis of the toxicity studies referenced above. The ADI of 40 mcg/kg bw/day was calculated from the no effect level for a six month dog study using a 100-fold safety factor.

C. Safe Concentrations

The safe concentrations for total residues of fenbendazole in cattle have been revised using the procedure described in the *Federal Register*, Volume 59, page 27499, July 22, 1994. The original and revised safe concentrations are listed below.

Tissue	Original Safe Concentrations	Revised Safe Concentrations
muscle	5 ppm	8 ppm
liver	10 ppm	24 ppm
kidney	15 ppm	48 ppm
fat	20 ppm	48 ppm

D. Tolerance in Liver

The tolerance for residues of parent fenbendazole in cattle liver was not recalculated with the approval of this Supplement, and the tolerance in cattle and goat liver remains unchanged at 800 ppb.

E. Muscle Tolerance Assignment

A muscle tolerance of 400 ppb is assigned as the tolerance for residues of fenbendazole measured as parent fenbendazole in cattle muscle. The residue studies conducted with ^{14}C-fenbendazole for the original approval in cattle showed that total residues in muscle tissue are well below the safe concentration of 8 ppm even at short withdrawal times following the approved conditions of use of the drug. The muscle tolerance value of 400 ppb is in the range of the maximum fenbendazole values expected in cattle muscle at one to two days post dosing. Residues of parent fenbendazole are not detectable by the official regulatory assay at the regulated withdrawal time of eight days for the paste and suspension formulations. The tolerance of 400 ppb will also serve as the tolerance in muscle tissue of goats, which are a minor species approved under NADA 128-620.

Residues of fenbendazole below 400 ppb in cattle or goat muscle indicate that total residues in muscle are below the safe concentration. However, residues below that level in muscle are not indicative of the safety of residues in other edible tissues.

F. Withdrawal Time and Regulatory Assay

The withdrawal times for the approved fenbendazole products are not affected by the recalculation of the safe concentrations for fenbendazole residues in cattle tissues. The official method for the determination of residues of fenbendazole in cattle or goat tissues is unchanged, and a copy is on file at the Center for Veterinary Medicine (HFV-199), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

VII. AGENCY CONCLUSIONS:

The information submitted in support of this supplemental application satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and implementing regulations at Part 514 of Title 21 of the Code of Federal Regulations (21 CFR 514), to enable FDA to revise 21 CFR 556.275 to establish a tolerance for residues of fenbendazole in cattle and goat muscle.

This supplement to NADA 128-620 has allowed the FDA to update the Acceptable Daily Intake (ADI) and the safe concentrations for fenbendazole total residues in cattle tissues and to establish a tolerance for residues of fenbendazole in cattle and goat muscle. The ADI for fenbendazole is established at 40 micrograms per kilogram body weight per day. The safe concentrations for total residues of fenbendazole in cattle have been revised to 8 ppm in muscle, 24 ppm in liver, 48 ppm in kidney, and 48 ppm in fat. The tolerance for residues of fenbendazole in cattle and goat muscle is established at 400 ppb, measured as parent fenbendazole. Other conditions of the approval (liver tolerance, withdrawal times, and regulatory method) are unchanged.

Federal law restricts PANACUR® (fenbendazole) Suspension 10% for Cattle and Goats to use by or on order of a licensed Veterinarian. The decision to keep PANACUR® (fenbendazole) Suspension 10% as a prescription product was made in 1988, based on the approval of the 10 mg/kg body weight dose for treating tapeworms and Type II Ostertagiasis in beef cattle (53 FR 40058, October 13, 1988). The 10 mg/kg dose is not for use in dairy cows of breeding age due to potential for violative milk residues. SAFE-GUARD® (fenbendazole) Suspension 10% is marketed as an over-the-counter (OTC) product. Goats are not on the SAFE-GUARD® (fenbendazole) Suspension 10% label, as it is an OTC product. The decision to keep SAFE-GUARD® (fenbendazole) Suspension 10% as an OTC product was made in 1988, based on the fact that it would not carry the 10 mg/kg cattle dose on its label.

In accordance with 21 CFR 514.106(b)(2)(x)&(xi), this is a Category II change that did not require a re-evaluation of the safety and effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals does not qualify for exclusivity because the supplemental application does not contain new clinical or field investigations (other than bioequivalence or residue studies) and new human food safety studies (other than bioequivalence or residue studies) essential to the approval and conducted or sponsored by the applicant.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action qualifies for a categorical exclusion from

the requirement to prepare an environmental assessment in accordance with 21 CFR 25.33(a)(1).

VIII. APPROVED LABELING (Attached)

#1. SAFE-GUARD ® (fenbendazole) Suspension 10% - 1000 mL (33.8 fl. oz.) plastic container
#2. SAFE-GUARD ® (fenbendazole) Suspension 10% - 3785 mL (1 gal) plastic container
#3. PANACUR ® (fenbendazole) Suspension 10% - 1000 mL (33.8 fl. oz.) plastic container
#4. PANACUR ® (fenbendazole) Suspension 10% - 3785 mL (1 gal) plastic container

Copies of applicable labels may be obtained by writing to the:
Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855