DATE OF APPROVAL LETTER: FEBRUARY 10, 2000

FREEDOM OF INFORMATION SUMMARY

ADI and Tolerances for SAFE-GUARD® (fenbendazole) in Swine

I. GENERAL INFORMATION:

NADA Number:	131-675
Sponsor:	Hoechst Roussel Vet Perryville Corporate Park III P.O. Box 4010 Clinton, NJ 08809-4010
Generic Name:	fenbendazole
Trade Name:	SAFE-GUARD® (fenbendazole)
Dosage Form:	Type A medicated article
Marketing Status:	over-the-counter (OTC)
Pharmacological Category:	antiparasitic
Effect of Supplement:	This supplement provides for the revision 21 CFR 556.275 by establishing tolerances for residues in swine liver and muscle and adding allowable daily intake (ADI).

II. INDICATIONS FOR USE

Swine: For the removal of: adult stage lungworms (*Metastrongylus apri* and *M. pudendotectus*); adult and larvae ($L_{3,4}$ stages-liver, lung, intestinal forms): large roundworms (*Ascaris suum*); adult stage nodular worms: (*Oesophagostomum dentatum, O. quadrispinulatum*); small stomach worms (*Hyostrongylus rubidus*); adult and larvae ($L_{2,3,4}$ stages – intestinal mucosal forms) whipworms (*Trichuris suis)*; adult and larvae kidney worms (*Stephanurus dentatus*).

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

A. Dosage Form: Fenbendazole is supplied as a Type A medicated article in concentrations of 40, 80, and 200 grams fenbendazole activity per kilogram (18.1, 36.2, and 90.7 g fenbendazole/lb., respectively)

B. Route of Administration: oral, in feed

C. Recommended Dosage: Fenbendazole is added to swine feed at concentrations from 10 to 300 grams fenbendazole per ton to provide a total dose of 9 mg fenbendazole per kg body weight fed over a 3 to 12 day period in a complete feed which is fed as the sole ration for this period.

IV. EFFECTIVENESS:

Effectiveness was established in the original approval under NADA 131-675 and supplements, (49 FR 3846, January 31, 1984; 53 FR 48533, December 1, 1988; 55 FR 48231, November 20, 1990). No additional data were required for approval of this supplement.

V. TARGET ANIMAL SAFETY:

Animal safety was established in the original approval under NADA 131-675 (49 FR 3846, January 31, 1984; 53 FR 48533, December 1, 1988; 55 FR 48231, November 20, 1990). 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 Frankfurt, Germany and in the United States. No new toxicity studies were conducted to support this Supplement to NADA 131-675.

B. Acceptable Daily Intake

An Acceptable Daily Intake (ADI) of 40 micrograms per kilogram body weight per day for residues of fenbendazole is 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 swine 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	15 ppm	24 ppm
kidney	20 ppm	48 ppm
fat	20 ppm	48 ppm

D. Target Tissue, Marker Residue, and Liver Tolerance Assignments

The residue and metabolism studies submitted previously under this NADA support 6 ppm as the tolerance in swine liver measured as unchanged fenbendazole. These data showed that unchanged fenbendazole represented approximately 25% of the total residue in liver samples with total residues in the range of 10 ppm to 12 ppm (the highest total residue values reported in liver). Using that marker to total residue relationship, a value of 6 ppm parent fenbendazole was calculated as the tolerance in liver (25% of the 24 ppm liver safe concentration). No new residue studies were conducted for the Supplement. See Part F. Withdrawal Time and Regulatory Method for comments on the analytical methods used to measure residues of fenbendazole.

E. Muscle Tolerance Assignment

The residue studies previously submitted under this NADA contained only total residue measurements in muscle tissue. As a result, a fenbendazole muscle tolerance value of 2 ppm parent fenbendazole was estimated based on the metabolism data in swine liver. That value was obtained by taking 25% (the percentage of unchanged drug in liver at zero withdrawal). See part F. Withdrawal Time and Regulatory Method for comments on analytical methods used to measure residues of fenbendazole.

F. Withdrawal Time and Regulatory Method

The original NADA 131-675 for the use of fenbendazole in swine was approved with zero withdrawal and waiver of the regulatory method, although a proposed determinative analytical procedure based on the official method in cattle tissues was developed at that time. Approval of this supplement did not change those provisions of the NADA.

Several unofficial analytical methods are available for the determination of residues of fenbendazole in tissues. Those methods vary with respect to the analyte measured which may be parent fenbendazole only, parent drug plus its major metabolites measured individually, or combined parent plus its metabolites measured as fenbendazole sulfone. The liver and muscle tolerances established with this supplement correspond to parent fenbendazole as the analyte. For regulatory purposes, a method that measures parent fenbendazole in swine tissues should be used. The official method for the determination of fenbendazole in bovine tissues is recommended, and a copy of that method 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 establish or update the Acceptable Daily Intake (ADI), safe concentrations for fenbendazole total residues in swine tissues, and tolerances for parent fenbendazole in swine liver and muscle.

The ADI for fenbendazole is established at 40 micrograms per kilogram body weight per day. The safe concentrations for fenbendazole in swine have been revised to 8 ppm in muscle, 24 ppm in liver, 48 ppm in kidney, and 48 ppm in fat. The tolerances for fenbendazole in swine are 6 ppm in liver and 2 ppm in muscle, both measured as parent fenbendazole. The pre-slaughter withdrawal period of zero days in swine remains unchanged.

There is reasonable certainty that the directions for use on labeling can and will be followed in practice. Accordingly, the Agency has concluded that this product shall retain over-the-counter marketing status.

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. Blue Bird, Type B label 1000-17,740 g/ton active fenbendazole
#2 Blue Bird Type C label 10-300 g/ton active fenbendazole
#3. SAFE-GUARD ® facsimile 20% Type A medicated article (Premix) label
#4. SAFE-GUARD ® bag 8% Type A medicated article label
#5. SAFE-GUARD ® facsimile 4% Type A medicated article label

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