I. GENERAL INFORMATION

A. File Number

NADA 139-189

B. Sponsor

Hoechst-Roussel Agri-Vet Company
Route 202-206 North
Somerville, New Jersey 08876

C. Proprietary Name

SAFE-GUARD

D. Established Name

fenbendazole

E. Dosage Form

20% Natural Protein deworming supplement (cold press) feedblock for beef cattle. This cold press feedblock is manufactured by V.M.S., Inc. Montgomery, AL. Each feedblock weighs 33.5 pounds and contains 730 mg fenbendazole per pound.

F. Dosage Regimen

1.67 mg fenbendazole per kg of body weight per day, for three (3) days. Total dose for the 3 day period of 5 mg/enbendazole per kg of body weight (2.27 mg fenbendazole per pound).

G. Route of Administration

The feedblock label contains complete directions for administration.

H. Species/Class

Cattle

I. Indication

Cattle dewormer for the removal and control of:

Lungworm: (Dictyocaulus viviparus).

Stomach worms: Barberpole worm (Haemonchus contortus), Brown stomach worm (Ostertagia ostertagi), Small stomach worm (Trichostrongylus axei).

Intestinal worms: Hookworm (Bunostomum phlebotomum), Threadnecked intestinal worm (Nematodirus helvetianus), Small intestinal worms (Cooperia oncophora and C. punctata), Bankrupt worm (Trichostrongylus colubriformis), Nodular worm (Oesophagostomum radiatum).

J. Effect of Supplement

The original approval provided for a 25 lb. medicated molasses block containing 750 milligrams of fenbendazole per pound as a beef cattle anthelmintic. The molasses block requires an 11-day withdrawal. This supplemental approval provides for a 33-1/2 pound cold press medicated 20% protein feedblock containing 750 milligrams of fenbendazole per pound as a beef cattle anthelmintic. The cold press 20% protein block requires a 16-day withdrawal period.

II. EFFECTIVENESS

This NADA relies on adequate well controlled studies showing the anthelmintic efficacy of fenbendazole in cattle included in the approved NADA 128-620 (Fenbendazole Suspension 10%, 48 FR 42809, September 20, 1983). The original NADA (128-620) provided for a dose of 3 mg fenbendazole/kg of body weight administered in a one (1) day treatment. This NADA demonstrates that the 5 mg dose given over a three (3) day period is equally as efficacious.

One study was conducted in cattle to demonstrate that the efficacy of fenbendazole in the feedblock formulation is equal to the suspension formulation when used at the same dose of 5 mg fenbendazole/kg body weight. It is appropriate to conclude that the feedblock formulation is equally efficacious.

Efficacy and consumption was demonstrated in these studies:

Efficacy Evaluation of Feedblocks Medicated with Fenbendazole

M. Blagburn, Auburn University, Auburn, Alabama

Twenty cattle naturally infected with gastrointestinal nematodes were identified and assigned to two groups of ten cattle each. One group remained unmedicated and one group was given fenbendazole via the natural protein cold press feedblock at a dose of 5 mg fenbendazole per kg of body weight over a 3 day period. Adequate numbers of parasites were recovered from the control animals at postmortem to evaluate and compare the effect of the feedblock formulation on the following species:

	% Reduction
H. contortus	100
O. ostertagi	99.9
C. punctata	100
O. radiatum	100
T. axei	100

Consumption rate by cattle of feedblocks containing Fenbendazole

Four feedblock consumption studies were conducted. The total number of mature cattle utilized for these studies was 195 head tested using the cold press feedblock. The studies were conducted in Alabama, Louisiana and Wyoming. To achieve the desired level of fenbendazole medicated block consumption, cattle require a period of time for adaptation to feedblocks. This adaptation period varied depending upon current and previous herd feeding and husbandry practices in addition to weather

conditions. From these studies, it was determined that specific medicated block treatment can be administered after 12-19 days adaptation period with non-medicated feedblocks.
The medicated feedblocks were given for a 3 day treatment period with the total fenbendazole consumption for the 3 day period calculated to be 5 mg fenbendazole/kg of body weight. The actual average consumption rate for fenbendazole averaged across the 3 locations was 4.55 (± 0.88) mg fenbendazole/kg body weight for the cold press blocks (see the following table).

AVERAGE FENBENDAZOLE CONSUMPTION CALCULATED FOR EACH LOCATION

Location	Cold Press Blocks - Consumption Averages Per Capita FBZ (mg/kg)
Wyoming	5.45
Louisiana	5.02
Alabama, Group 1	4.88
Alabama, Study 11, Group 1	3.19
Alabama, Study 11, Group 2	4.23
Average	4.55
Std. Deviation	0.88

These studies were conducted by:

Dr. Dean Danilson, Asst. Prof.
Auburn University
Auburn, AL. 36849-4201

Dr. Gene Luther
Dept. of Vet. Science
Louisiana State University
Baton Rouge, LA. 70803-6002

Dr. J. Waggoner Jr.
University of Wyoming
Dept. of Animal Science
Laramie, WY. 82071

The consumption and efficacy studies confirm that the feedblock formulation is efficacious when the total dose of 5 mg fenbendazole per kg body weight is given over a 3 day period.

The recommended treatment was found to be both safe and practical under field conditions.

III. TARGET ANIMAL SAFETY

This NADA relies on safety studies included in the approved NADA 128-620 (Fenbendazole Suspension 10%, 48 FR 42809, September 20, 1983), that indicated the maximum tolerance dose is greater than 2000 mg fenbendazole/kg body weight.

Therefore, as predicted, no visible adverse reactions were observed in any of the laboratory efficacy or clinical field trials conducted in cattle with cold press feedblocks containing fenbendazole.

IV. HUMAN FOOD SAFETY

A. Safe Concentration of Residues

The safe concentration for total fenbendazole residues in the uncooked edible tissues of cattle were established, based upon toxicology studies submitted under NADA 128-620 (48 FR 42809-9/20/83) as 5 ppm in muscle, 10 ppm in liver, 15 ppm in kidney and 20 ppm in fat.

B. Metabolism Studies

Under NADA 128-620 metabolism studies in cattle were conducted to select a marker substance and target tissue for fenbendazole. Cattle liver is the target tissue with parent fenbendazole being the marker substance. The tolerance (Rm) is 0.8 ppm parent fenbendazole for cattle receiving a single oral dose of 10 mg fenbendazole/kg BW, i.e. when total fenbendazole residues are 10 ppm in liver, there is 0.8 ppm parent fenbendazole as determined by the regulatory method. Acceptable comparative metabolism studies were described under NADA 128-620.

C. Regulatory Method

Under NADA 128-620, the method was developed for the determination of parent fenbendazole at the tolerance of 0.8 ppm concentration in cattle liver.

D. Withdrawal Time

Under NADA 128-620 (suspension 10%) it was determined that a withdrawal time of 8 days is necessary for the residues of fenbendazole to deplete to sale concentrations in all tissues.

Under this NADA a residue depletion study using the approved analytical method was conducted to determine when residues of the feedblock formulation deplete to or below the established safe concentration.

Twenty eight cattle were treated orally over a 3 day period with the feedblock formulation to provide a total dose of 10 mg fenbendazole/kg of body weight.

A statistical analysis using CVM's 99% tolerance limit with a 95% confidence interval on the data in the following table determined that fenbendazole residues were below the tolerance of 0.8 ppm 16 days after the end of the treatment period. The projected residue level at the end of a sixteen (16) day withdrawal period was 0.74 ppm. The Agency has reviewed the residue data and has concluded that this supplement will not alter the concentration and qualitative composition of the residue.

FENBENDAZOLE RESIDUES IN CATTLE LIVER AFTER A THREE DAY TREATMENT PERIOD USING THE COLD PRESS FEEDBLOCK FORMULATION WITH A TOTAL DOSE OF 10 MG FENBENDAZOLE PER KG OF BODY WEIGHT

Sacrifice Date after Treatment	PPM Fenbendazole(l,2)
1 day	14.56 (± 16.62)
3 days	13.75 (± 17.06)
5 days	3.92 (± 5.37)
7 days	1.67 (± 2.52)

1- Values are the average from seven (7) animals per data point
2- Standard deviation in ().

Therefore, it has been established that 16 days after treatment with a three day oral dose of 10 mg fenbendazole/kg b.w. in the cold press feedblock formulation is sufficient to confirm that no residues are present that may be harmful to human health.

V. USER SAFETY

Under NADA 128-620, studies were conducted which demonstrated that the drug would have no ill effects on persons handling it if the drug is used according to label recommendations.

VI. AGENCY CONCLUSIONS

This is a supplemental approval. NADA 139-189 provides for a 25 pound molasses block having 750 mg fenbendazole/pound. The supplement is for a cold press protein block of 33-1/2 pounds having 750 mg fenbendazole/pound. The data submitted in support of this NADA comply with the requirements of section 512 of the Act and demonstrates that fenbendazole (Safe-Guard) in a 20% natural protein deworming (cold press) feedblock when used under its proposed condition of use is safe and effective for the removal and control of lungworms, stomach worms and intestinal worms in cattle.

The Agency concludes that adequate directions for use have been written for the proposed over-the-counter use of this broad spectrum anthelmintic which is indicated for the removal and control of parasites commonly occuring in cattle. Fenbendazole premixes in swine and fenbendazole suspension, paste, and feedblock (containing molasses) in cattle are presently marketed over-the-counter as broad spectrum anthelmintic drug products. Fenbendazole medicated feedblock is currently codified in section 21 CFR 520.905e for use in cattle providing for the same concentration (750 mg/lb) and conditions of use with the exception of the drug withdrawal requirements (11 days for the molasses-containing block and 16 days for the cold press block). The Agency has reviewed the residue data and has concluded that this supplement will not alter the concentration and qualitative composition of the residue. Therefore, this supplement will pose no increased human risk from exposure to the drug.

Under the Center's supplemental approval policy (42 FR 64367), this is a Category II change which provides for an additional feed block formulation. This change is not expected to adversely affect the safety and effectiveness of the drug. Therefore, this action did not require a reevaluation of the underlying safety and effectiveness data in the parent application.

VII. LABELING (Attached)

1. SAFE-GUARD® (fenbendazole) product label

Copies of this label may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.