Date of Approval Letter: July 3, 2000

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 131-675

SAFE-GUARD® (Fenbendazole) For Growing Turkeys

"For the Removal and Control of: Gastrointestinal worms: Round worms, adults and larvae (*Ascaridia dissimilis*); Cecal worms, adult and larvae (*Heterakis gallinarum*), an important vector of *Histomonas meleagridis* (Blackhead)."

Sponsored by:

Hoechst Roussel Vet

I. GENERAL INFORMATION

NADA Number:	131-675
Sponsor:	Hoechst Roussel Vet Perryville Corporate Park P.O. Box 4010 Clinton, New Jersey 08809-4010
Established Name	fenbendazole
Trade Name:	SAFE-GUARD®
Dosage Form:	Type A medicated article
Marketing Status:	Over-The-Counter
Pharmacologic Category:	Antiparasitic
Effect of the Supplement:	This supplement provides for the addition of growing turkeys to the previously approved SAFE-GUARD® Type A medicated article labeling.

II. INDICATIONS FOR USE

For the Removal and Control of Gastrointestinal worms: Round worms, adults and larvae (*Ascaridia dissimilis*); Cecal worms, adult and larvae (*Heterakis gallinarum*), an important vector of *Histomonas meleagridis* (Blackhead).

III. DOSAGE

A. *Dosage Form:* Fenbendazole is supplied as a Type A Medicated Article containing 20% fenbendazole activity per kilogram (90.7 grams per pound).

B. *Route of Administration:* Oral, in feed.

C. *Recommended Dose*: Fenbendazole is added to turkey feed at a concentration of 16 ppm (14.5 g/ton). The resultant complete turkey feed containing fenbendazole is then fed as the sole diet for six (6) consecutive days.

IV. EFFECTIVENESS

The following adequate and well-controlled studies demonstrate the effectiveness of SAFE-GUARD® (fenbendazole) for the given indications and dosage.

A. Dose Titration Study:

This dose titration study (#6225-01-01-93) was designed to determine the effectiveness of fenbendazole against both adult and larval forms of the predominant nematode parasites in turkeys.

Name and Address of Principal Investigator:

F. William Pierson, M.S., D.V.M., Ph.D., Diplomat ACPV
College of Veterinary Medicine
Virginia Polytechnic Institute and State University
Blacksburg, VA 24061

Name and Address of In-Life Investigator:

Mr. Michael Sims
Virginia Scientific Research, Inc.
Suite 327, 1790-10 East Market St.
Harrisonburg, VA 22801

Pertinent Study Features:

Study Design:	Complete randomized block
Number of treatments:	6
Number of replicates:	12
Species and Strain::	domestic white turkeys, Nicholas
No. birds per pen:	5 (same sex)
No. birds per treatment group:	60 (30/sex)
Total number of birds:	360
Feed Dose levels:	0, 8, 16, 24, 32 and 40 ppm
Treatment period:	fed continuously for six (6) days, at eight (8) weeks of age.

The objective of the dose titration study was to determine the effective dosage of fenbendazole when administered via the feed to growing turkeys. Effectiveness against adult and larvae of *Ascaridia dissimilis* and *Heterakis gallinarum* was evaluated. Three sources of poultry litter known to be contaminated with nematode ova (two turkey flock sources, one chicken flock source) were mixed together and used to produce parasite infections via natural exposure. Following establishment of parasite infection and prior to treatment, the turkeys were blocked by weight and randomly assigned within blocks to one of six treatments, with all treatments replicated twelve times (6 replicates/sex). The treatments consisted of 0 (control), 8, 16, 24, 32 or 40 ppm fenbendazole in the feed, fed continuously for six (6) days when the birds were eight (8) weeks of age.

On the fifth day after completion of the treatment period, the birds were sacrificed and intestinal contents collected. Worm counts (adults and immatures) were done blindly on samples from all turkeys. Effectiveness was calculated from the arithmetic mean worm burdens by the following formula:

$$\% \text{ Effectiveness} = [(\text{Mean}_{\text{control}} - \text{Mean}_{\text{treated}}) \div \text{Mean}_{\text{control}}] \text{ X } 100.$$

The results, summarized in Table 1, show that fenbendazole effectiveness (at least 90% compared to the control group) based on worm counts was achieved at a dosage of 16 ppm in the feed for six days against adult and larvae of *Ascaridia dissimilis* and *Heterakis gallinarum*.

TABLE 1
Effectiveness of Fenbendazole in Growing Turkeys Against
Ascaridia dissimilis and *Heterakis gallinarum* based on worm counts

			% Efficacy compared to control			
			Ascaridia dissimilis		*Heterakis gallinarum*	
Treatment	Pens per Treatment[1]	No. Birds per pen	Adults	Larvae	Adults	Larvae
0 ppm Control	12	5	-	-	-	-
8 ppm FBZ	12	5	100.00	40.04	55.75	28.11
16 ppm FBZ	**12**	**5**	**100.00**	**96.23**	**97.85**	**93.13**
24 ppm FBZ	12	5	100.00	99.82	99.24	98.28
32 ppm FBZ	12	5	100.00	99.64	97.60	99.79
40 ppm FBZ	12	5	100.00	99.64	100.00	99.57

[1]Six pens of males and 6 pens of females

B. Dose Confirmation Studies:

Two studies were conducted at two separate geographic locations. Since 16 ppm for six days was demonstrated to be the lowest effective dose against adult and larval *Ascaridia dissimilis* and *Heterakis gallinarum* parasites, the first dose confirmation study bracketed this dose. The second dose confirmation study consisted of 2 treatments; control and 16 ppm fenbendazole in the feed for 6 days.

STUDY #1 (Study #6225-02-01-95)

Name and Address of Investigator: Dr. Tom Yazwinski
University of Arkansas
Dept. of Animal Science Bldg.
Fayetteville, AR 72701

Pertinent Features of Study:

Study Design:	complete randomized block
Number of treatments:	4
Number of replicates:	8
Species and Strain:	domestic white turkeys, Nicholas
No. birds per pen:	12 (same sex)
No. birds per treatment group:	96 (48/sex)

Total number of birds	384
Feed Dose levels:	0, 8, 16, and 24 ppm
Treatment period:	fed continuously for 6 days, at 7 weeks of age.

The objective of this dose confirmation study was to confirm that 16 ppm fenbendazole in the feed fed continuously for six days is the lowest effective dose (>90% effectiveness) against adult and larval *Ascaridia dissimilis* and adult *Heterakis gallinarum* parasites.

Birds were infected by direct oral inoculation with infective ova. Following establishment of parasite infection and prior to treatment, the turkeys were blocked by weight and randomly assigned within blocks to one of four treatments, with all treatments replicated eight times (4 replicates/sex). The treatments consisted of 0 (control), 8, 16, and 24 ppm fenbendazole in the feed, fed continuously for six days when the birds were approximately seven weeks of age.

After completion of the treatment period, the birds were sacrificed and intestinal contents collected. Worm counts (adults and larvae) were done blindly on samples from all turkeys. The results, summarized in Table 2, are consistent with the results of the pivotal dose titration study.

TABLE 2
Effectiveness of Fenbendazole in Growing Turkeys Against *Ascaridia dissimilis* and *Heterakis gallinarum* based on worm counts

			% Effectiveness compared to control			
			Ascaridia dissimilis		*Heterakis gallinarum*	
Treatment	Pens per Treatment[1]	No. Birds per pen	Adults	Larvae	Adults	Larvae
0 ppm (Control)	8	12	-	-	-	-
8 ppm FBZ	8	12	99.42	81.85	100.00	29.33
16 ppm FBZ	8	12	100.00	98.79	100.00	58.91
24 ppm FBZ	8	12	100.00	99.45	100.00	66.25

[1]Four pens of males and 4 pens of females

STUDY #2 (study #96-0012)

The second dose confirmation study was conducted at Virginia Scientific Research to evaluate the efficacy of fenbendazole administered at the label dose of 16 ppm in the feed for six days in birds raised under commercial conditions.

Name and Address of Investigator: Mr. Michael Sims
Virginia Scientific Research, Inc.
Suite 327
1790-10 East Market St.
Harrisonburg, VA 22801

Pertinent Features of Study:

Study Design:	complete randomized block
Number of treatments:	2
Number of replicates:	4 (2/sex)
Species and Strain:	domestic white turkeys, Nicholas
Ave. no. birds per pen:	120 males, 101 females
Avg. no. birds per treatment:	442
Total number of birds:	884
Feed Dose levels:	0 and 16 ppm
Treatment period:	fed continuously for 6 days, at 8 weeks of age.

The objective of this dose confirmation study was to confirm the effectivness findings from the pivotal dose titration study.

The turkeys were grown on old litter known to be contaminated and infected with *Ascaridia dissimilis* and *Heterakis gallinarum*. Following establishment of parasite infection and prior to treatment, the turkeys were randomly assigned separately by sex within blocks to one of two treatments, with all treatments replicated twice per sex. The treatments consisted of 0 (control) and 16 ppm fenbendazole in the feed, fed continuously for six days when the birds were approximately eight weeks of age. On the fifth day after completion of the treatment period, the birds were sacrificed and intestinal contents collected. Worm counts (adults and larvae) were done blindly on intestinal samples. The effectivness results, summarized in Table 3, are consistent with the results of the dose titration study.

TABLE 3
Effectivness of Fenbendazole in Growing Turkeys Against *Ascaridia dissimilis* and *Heterakis gallinarum* based on worm counts

			% Effectiveness compared to control			
			Ascaridia dissimilis		*Heterakis gallinarum*	
Treatment	Pens per Treatment[1]	No. Birds per pen[2]	Adult	Larvae	Adult	Larvae
0 ppm (Control)	4	20	-	-	-	-
16 ppm FBZ	4	20	99.4	96.03	96.21	91.82

[1]Two pens of males and 2 pens of females
[2]Twenty birds per pen were necropsied

The claim for effectiveness against *Heterakis gallinarum* larvae was granted on the basis of these two studies, even though both studies did not demonstrate percent effectiveness

greater than 90%, because there is no effective drug available for the removal and control of this life stage of this important parasite.

C. Field Studies:

Two field studies were conducted. One at the University of Arkansas (#97-0011) and one at PARC Institute (#97-0012) to evaluate both the effectiveness and safety of fenbendazole administered at the label dose of 16 ppm for six days in birds raised under commercial conditions.

Field Study #1

Name/Address of Investigator:

Dr. Tom Yazwinski
University of Arkansas
Dept. of Animal Science Bldg.
Fayetteville, AR 72701

Pertinent Features of Study:

Study Design:	complete randomized block
Number of treatments:	2
Number of replicates:	4 (2/sex)
Species and Strain:	domestic white turkeys, Nicholas
Ave. no. birds per pen:	126 (same sex)
Avg. no. birds per treatment:	504
Total number of birds:	1013
Feed Dose levels:	0 and 16 ppm
Treatment period:	fed continuously for 6 days, at 5 weeks of age.

The objective of this field study was to assess the safety of the product under field conditions, and confirm the effectiveness findings from the dose titration and dose confirmation studies.

Separate sources of each genus of nematode ova were used. The birds were trickle infected by repeated exposure to the infective ova via the feed. An outbreak of histomoniasis (blackhead) occurred prior to the treatment period, reducing the numbers of birds in the study and compromising the cecae of the surviving birds. Hence, the numbers of *Heterakis* spp. worms following the histomoniasis outbreak were too low for meaningful worm count data. Following establishment of parasite infection and prior to treatment, the turkeys were randomly assigned separately by sex within blocks to one of two treatments, with all treatments replicated twice per sex. The treatments consisted of 0 (control) and 16 ppm fenbendazole in the feed, fed continuously for six days when the birds were approximately five weeks of age.

On the fifth and sixth days after completion of the treatment period, subsets of the birds were sacrificed and intestinal contents collected. Worm counts (adults and larvae) were done blindly on intestinal samples. The remaining birds were grown to market age and commercially processed. The performance results, summarized in Table 4, indicate

that fenbendazole is safe, and does not have a negative effect on the growth or feed efficiency of the turkeys but do not support a demonstration of effectiveness for feed efficiency. The effectiveness results, summarized in Table 5, are consistent with the results of the pivotal dose titration and dose confirmation studies.

TABLE 4
Commercial performance measurements from 28 days of age (1 week before treatment) until 97 days of age (61 days after start of treatment)

	Female Control 0 ppm FBZ	Female Treated 16 ppm FBZ	Male Control 0 ppm FBZ	Male Treated 16 ppm FBZ
Mean Final Body Weight (lb)	17.31	17.48	22.20	22.82
Feed Efficiency (Feed : Gain)	2.76	2.65	2.47	2.44

TABLE 5
Effectiveness of 16 ppm Fenbendazole fed to Turkeys for Six Days Against *Ascaridia dissimilis* infections

			% Effectiveness against *Ascaridia dissimilis* compared to control	
Treatment	Pens per Treatment[1]	Mean No. of Birds/pen	Adult	Immature
Control	4	126	-	-
16 ppm FBZ	4	126	>99.9	92.9

[1]Two pens of males and two pens of females per treatment group

Field Study #2

Name and Address of Investigator:

Dr. James L. McNaughton
PARC Institute, Inc.
P.O. Box 1161
Easton, MD 21601

Pertinent Features of Study:

Study Design: complete randomized block

Number of treatments: 2

Number of replicates:	4 (2/sex)
Species and Strain:	domestic white turkeys, Nicholas
Ave. no. birds per pen:	150 (same sex)
Avg. no. birds per treatment:	600
Total number of birds:	1200
Feed Dose levels:	0 and 16 ppm
Treatment period:	fed continuously for 6 days, at 6 weeks of age.

The objective of this field study was to assess the safety of the product under field conditions, and confirm the effectiveness findings from the dose titration and dose confirmation studies.

Separate sources of each genus of nematode ova were used. The birds were trickle infected by repeated exposure to the infective ova via the feed. Following establishment of parasite infection and prior to treatment, the turkeys were randomly assigned separately by sex within blocks to one of two treatments, with all treatments replicated twice per sex. The treatments consisted of 0 (control) and 16 ppm fenbendazole in the feed, fed continuously for six days when the birds were approximately six weeks of age.

On the fifth and sixth days after completion of the treatment period, subsets of the birds were sacrificed and intestinal contents collected. Worm counts (adults and larvae) were done blindly on intestinal samples. The remaining birds were grown to market age and commercially processed. The performance results, summarized in table 6, indicate that fenbendazole is safe, and does not have a negative effect on the growth or feed efficiency of the turkeys but do not support a demonstration of effectivness for feed efficiency. The effectiveness results, summarized in Table 7, are consistent with the results of the dose titration and dose confirmation studies.

TABLE 6
Commercial performance measurements from
38 days of age until 112 days of age

	Female Control 0 ppm FBZ	Female Treated 16 ppm FBZ	Male Control 0 ppm FBZ	Male Treated 16 ppm FBZ
Mean Final Body Weight (lb)	16.02	16.37	21.87	22.70
Feed Efficiency (Feed : Gain)	2.89	2.70	2.34	2.20

TABLE 7
Effectiveness of 16 ppm Fenbendazole fed to Turkeys for six Days
Against *Ascaridia dissimilis* and *Heterakis gallinarum* infections

			% Effectiveness compared to Control			
			Ascaridia dissimilis		*Heterakis gallinarum*	
Treatment	Pens per Treatment[1]	Mean No. of Birds/pen	Adult	Immature	Adult	Immature
Control	4	150	-	-	-	-
16 ppm FBZ	4	150	99.9	90.0	96.6	89.1

[1]Two pens of males and two pens of females per treatment group.

V. ANIMAL SAFETY

Study #95-0015

Name and Address of Investigator:

Beverly George, Ph.D.
Colorado Quality Reasearch.
400 E. County Road 72
Wellington, CO 80549

This target animal safety study was conducted using 528 turkeys (240 males, 288 females). The turkeys were 42 days of age when fenbendazole treatment was initiated. This age and weight represents approximately the age at which turkeys would be dewormed during the growing period.

Experimental Design:

Species and strain:	Turkeys, Nicholas strain
Number per group:	60 males and 72 females
Dosage form:	oral
Dosages used:	0, 20, 200 and 400 ppm fenbendazole in the feed
Duration of treatment:	Fed continuously for 18 days beginning at 42 days of age.
Start Date:	Feb. 29, 1996 (Poults received)
End Date:	April 29, 1996 (Last day of treatment)

General Measurements:

Test animals were observed twice daily (a.m. and p.m.) and any abnormal conditions recorded and reported to the study director. The daily observations included general flock condition, lighting, water, feed, ventilation, recording minimum-maximum temperature of the test facility and reporting of unanticipated events. Birds were weighed, on a pen basis on Day 1, individually weighed on Day 42 (at start of treatment diet feeding), and individually weighed on Day 60 (study end). Performance data was summarized by average weight per bird on Days 1, 42, and 60. The average feed conversion was calculated for Days 1 to 42 and 42 to 60 to demonstrate that the flock performed normally.

Hematology:

On Days 5 and 60 blood was collected for hematology assay (erythrocyte count, hematocrit, hemoglobin, leukocyte count, and differential count) and prothrombin time determination. Birds were randomly selected for blood collection. At five days of age, four samples (individual birds) per pen were collected. Two birds were used for the prothrombin time analysis samples and two birds were used for the hematology assays. Separate birds were required at the Day 5 sampling because of the small blood volume of this age bird. On Day 60, two randomly selected birds from each pen were sampled for both the hematology and prothrombin time assays.

On Day 60, the birds from which blood was collected were sacrificed and examined for gross pathology (see following section).

Gross Pathology/Histopathology

On Day 60, the two randomly selected birds from each pen were subjected to a complete gross necropsy. The following tissues were saved in neutral buffered formalin. All tissues indicated below, and any other tissues with gross lesions were examined histologically.

Adrenal glands	Bone and marrow	Brain
Bursa of Fabricius	Crop	Esophagus
Eye	Heart	Intestines (upper, middle,
Liver	Kidneys	ceca)
Ovaries & oviduct	Lungs	Parathyroid glands
Pancreas	Proventriculus	Pituitary gland
Spleen	Skin	Spinal cord
Testes	Thymus	Thyroid glands
Trachea	Ventriculus	

Gross Pathology on all remaining birds:

After the birds were weighed on Day 60 and after the two birds were removed for tissue collection as stated above, then all remaining birds (including the two from which blood was collected) were necropsied and examined for gross pathology. Any abnormal tissues were collected and preserved in formalin and submitted for histopathological examination. The following tissues were routinely examined.

Bone marrow	Brain	Bursa of Fabricius
Crop	Esophagus	Eye
Heart	Intestine	Kidney
Liver	Lung	Ovary (if present)
Pancreas	Proventriculus	Skin
Spleen	Testes (if present)	Trachea

Feed:

Feed samples were assayed for fenbendazole content. Results of assays confirmed the presence of fenbendazole at the expected dosage levels.

Results:

The turkeys remained healthy and exhibited no observable adverse effects in any of the treatment groups. Performance, clinical pathology, and histopathology parameters were measured in growing turkeys fed fenbendazole at 0, 20, 200 and 400 ppm fenbendazole via the feed for an 18-day period. Body weight and feed efficiency data were obtained at 42 and 60 days of age. Analysis indicated that these performance data were not influenced by any fenbendazole treatment when compared with the control group. Clinical pathology parameters were not influenced by any fenbendazole treatment when compared with the control group. Histopathological results indicated that there were no remarkable or consistent lesions present in the tissues. The hematology values were within normal biological ranges and were not different from the controls.

This target animal safety studies adequately demonstrates that there were no toxicological or biologically significant pharmacological effects on the turkeys. These results demonstrate that fenbendazole is safe when fed to growing turkeys at the approved use level.

VI. HUMAN SAFETY

A. ***Toxicity Studies:*** Toxicity and teratogenicity studies were presented in the original NADA 128-620 and were conducted in Hoechst Research Laboratories in Frankfurt, Germany and in the United States. Fenbendazole was determined to be safe to human health when food derived from treated animals is ingested (see 48 FR 42809, September 20, 1983). No new toxicity studies were conducted in support of this supplement to NADA 131-675.

B. ***Tolerance and Safe Concentrations:*** The safe concentrations for total fenbendazole residues in the tissues of turkeys were calculated by the procedure described in the *Federal Register,* Volume 59, page 27499, July 22, 1994, and are listed below.

muscle:	8 ppm
liver:	24 ppm
fat:	48 ppm

C. ***Total Residue Depletion and Metabolism:*** The study described below was conducted to determine the levels of total residues in tissues of turkeys following a six-day treatment with ^{14}C-labeled fenbendazole administered orally. The dosing rate in the study was 4.0 mg/kg bw/day, which is approximately four times the drug intake expected with the 16 ppm dosing level in feed for turkeys that is provided by this supplement to NADA 131-675.

Pivotal Study #6225-01-06-94

Study Director: Dr. Frederic W. Thalacker
Hazleton Wisconsin, Inc.
3301 Kinsman Blvd.
Madison, Wisconsin 53704

The ^{14}C-fenbendazole metabolism and residue study was conducted using 46 turkeys (23 males, 23 females). The turkeys were approximately 9 weeks of age when fenbendazole treatment was initiated. The experimental design was as follows:

Species and strain:	Turkeys, Nicholas strain
Number per group:	3 males and 3 females (control group) and 20 males and 20 females (treated group)
Dosage form:	oral via gavage
Dosages used:	0 and 4.0 mg ^{14}C-fenbendazole/kg body weight/day
Duration of treatment:	six days
Start Date:	September 7, 1994
End Date	February 14, 1996

The persistence and chemical nature of fenbendazole residues in the edible tissues of male and female turkeys were assessed following multiple daily oral administrations of ^{14}C-fenbendazole. Radiolabeled fenbendazole was administered in two daily doses by gavage for six consecutive days at a concentration equivalent to 4.0 mg/kg of body weight per day (treatment Group 2). Treatment Group 2 contained 18 males and 18 females. Four additional turkeys (two males and two females) were dosed with fenbendazole and served as potential replacements in case of illness or injury to turkeys in Group 2. Turkeys in treatment Group 1 (3 males and 3 females) served as controls and were dosed with 0.05% Tween 80 (w/w) in deionized water.

Turkeys in Group 1 were terminated after administration of the last dose. Turkeys in Group 2 were terminated at 6, 12, 24, 48, 72 and 96 hours (six turkeys per time point)

after administration of the last dose. Excreta and cage wipes were collected at 24 hour intervals (or at 12 hours after the final dose and/or at termination if less than 24 hours from the last collection) from the day prior to dosing (excreta only) until termination. At termination, whole blood, liver, breast muscle, skin with adhering fat (skin/fat), abdominal fat, and the gastrointestinal tract and contents were collected. Serum was prepared by centrifugation of the clotted whole blood.

Results:

Concentrations of radioactivity, fenbendazole and radiochemical purity of ^{14}C-fenbendazole in the dose solutions were verified before and after the dosing period. All samples were analyzed for total radioactive residues (TRR). Cage and paper wipes, serum, abdominal fat, and skin/fat were analyzed for TRR directly by liquid scintillation counting (LSC). All other sample matrices were analyzed for TRR by combustion and LSC. Excreta and edible tissue samples were analyzed for total extractable and nonextractable residues by exhaustive solvent extraction. Metabolites were characterized in the extracts by HPLC and in-line LSC.

No sex related differences were noted in the disposition of ^{14}C-fenbendazole. The values summarized in Table 8 are group means. The concentration of radioactivity in treated turkeys (Group 2) reached a maximum at 6 hours post-dose. The highest levels of radioactivity concentration in the examined tissues (Table 8) were in the liver (6.35 ppm), serum (1.80 ppm), abdominal fat (1.51 ppm), and skin with adhering fat (1.41 ppm). The breast muscle (0.933 ppm) also had detectable levels of radioactivity.

The concentration of radioactivity declined in the tissues with time through the final 96-hour post-dose collection. Detectable amounts of radioactivity were found in all matrices, except breast muscle at 72 and 96 hours post-dose. Group mean concentrations (ppm) of TRR in the edible tissues were as follows.

Table 8. Mean Concentrations (ppm) of TRR in Tissues Collected from Turkeys Treated with 4 mg/kg for Six Days

Withdrawal Hours	Liver	Breast Muscle	Abdominal Fat	Skin/Fat	Serum
6	6.35	0.933	1.51	1.41	1.80
12	5.14	0.586	0.836	0.954	1.22
24	2.83	0.228	0.346	0.408	0.459
48	0.978	<0.031	0.050	0.086	0.072
72	0.582	<0.031	0.027	0.107	0.023
96	0.431	<0.031	0.010	0.044	<0.010

<Indicates value below limit of detection for matrix.

The majority of the radioactivity was eliminated in the excreta by 24 hours post-dose. The radioactivity recovered in the excreta was 92.3% of the total administered radioactivity for the males, and 101% of the total administered radioactivity for the females (Group 2). All of the examined tissues had less than 0.01% of the total administered radioactivity at 96 hours post-dose, with the exception of liver (0.04% in males and 0.05% in females).

The high recoveries of radioactivity in excreta and the small fraction remaining in the tissues at 96 hours post-dose indicate no accumulation of ^{14}C-fenbendazole and/or its major metabolites in the major organ systems.

At zero withdrawal time (6 hour samples) the concentrations of TRR in the liver were well below the safe concentration of 24 ppm. Mean concentrations of TRR in muscle and both fat types were also below their respective safe concentrations at 6 hours (zero-withdrawal). The concentrations of TRR in all tissues, except liver, declined to less than 0.1 ppm within the tested withdrawal times. The concentration of TRR in the liver declined to 0.431 ppm at 96 hours after the final dose.

Extractable residues were the predominant fraction of the TRR in tissues and excreta. Radioactive residues were 83% to 98% extractable in excreta and 77% to 112% extractable in all tissues collected through 6 hours after the final dose was administered. The level of extractability of total radioactive residues did not change substantially through the 96-hour collection time for excreta, muscle, abdominal fat or skin with adhering fat. The levels of TRR extracted from liver declined significantly through time to approximately 43% to 50% at 96 hour withdrawal.

The extracts of the tissue samples were assayed by an HPLC procedure in order to determine the amounts of parent fenbendazole and its metabolites that were present. In all tissues, fenbendazole sulfone was the predominant radioactive residue. Liver was the organ with the highest concentration of fenbendazole sulfone and had the highest levels of total residues at the last withdrawal time point.

In tissues, fenbendazole is oxidized to oxfendazole (fenbendazole sulfoxide) and subsequently oxidized again to fenbendazole sulfone. Small amounts of unchanged fenbendazole were present in some of the early time point samples, especially fat samples. In excreta, fenbendazole was the predominant residue, making up approximately 50% of the TRR during the dosing period and at the 6-hour withdrawal point. Oxfendazole, fenbendazole sulfone, and hydroxy-fenbendazole were also present in excreta. The percentages and concentrations of fenbendazole metabolites found in the extracts of liver as determined by the HPLC analysis are listed Table 9 below.

Table 9. Fenbendazole metabolites present in the extracts of liver and muscle tissue of turkeys treated orally with ^{14}C-fenbendazole at 4 mg/kg bw for six consecutive days.

Sample	Fenbendazole Sulfone	Oxfendazole
6 hr pooled liver	85.5% (3.76 ppm)	14.2% (0.64 ppm)
12 hr pooled liver	97.6% (3.04 ppm)	2.4% (0.07 ppm)
24 hr pooled liver	92.8% (1.34 ppm)	0 %
48 hr pooled liver	79.2% (0.18 ppm)	
72 hr pooled liver	100% (0.04 ppm)	
6 hr pooled muscle	88.7% (0.75 ppm)	11.4% (0.09 ppm)
12 hr pooled muscle	100% (0.59 ppm)	0 %
24 hr pooled muscle	100% (0.23 ppm)	

D. ***Comparative Metabolism:*** Metabolism studies were conducted with fenbendazole in rats, rabbits, and dogs to support the original approval of fenbendazole in cattle (NADA 128-620). Animals were dosed with non-radiolabeled fenbendazole, and metabolite profiles were obtained by the HPLC analysis of serum. The results of those studies are summarized in Table 10.

Table 10. Concentrations of fenbendazole and its metabolites found in the serum of rats, rabbits, and dogs treated with non-radiolabeled fenbendazole.

	Rats	***Rabbits***	***Dogs***
Dose:	500 mg/kg	25 mg/kg	25 mg/kg
Post-treatment:	48 hrs	72 hrs	48 hrs
		Metabolites present	
FBZ + FBZ-NH2	0.36 ppm	Not found	0.53 ppm
oxfendazole	0.09 ppm	0.07 ppm	0.33 ppm
FBZ sulfone	0.11 ppm	0.41 ppm	0.10 ppm

A comparison of Tables 9 and 10 shows that the two fenbendazole metabolites identified in the liver tissue extracts of turkeys were observed in the serum of three laboratory species. Therefore, it is concluded that the metabolites of fenbendazole in turkeys have been adequately tested for toxicity in the laboratory species.

E. ***Withdrawal Time*****:** The residue data summarized in Section C show that total residues of fenbendazole in the edible tissues of turkeys are well below the safe concentrations for residues in turkeys that are listed in Section B. That finding qualifies this drug use for approval with no (zero) withdrawal restriction.

F. ***Tolerances for Residues in Liver and Muscle:*** The results of the HPLC assays for fenbendazole and its metabolites in Study No 6225-01-06-94 were used for the assignment of tolerances for residues of fenbendazole in turkey liver and muscle. Those data showed that 80 to 100% of the extractable residue in those tissues at short withdrawal times consists of fenbendazole sulfone, making that compound the marker residue of choice in both tissues.

Although residues deplete relatively rapidly from turkey muscle and liver, mean levels of fenbendazole sulfone were near the 1 ppm and 4 ppm levels at zero withdrawal (6 hours) in those tissues at the 4X dosing rate (Table 9). The results of statistical analyses of those data with an adjustment for the exaggerated dosing rate in the study indicated that peak levels of fenbendazole sulfone should be less than 2 ppm in muscle and 6 ppm in liver at zero withdrawal under the approved conditions of use. Accordingly, those values (2 ppm in muscle and 6 ppm in liver) are assigned as the tolerances for residues of fenbendazole sulfone in turkeys.

G. ***Analytical Methods for Residues Regulatory Method:*** A regulatory method and Method Trial were not required for this use of fenbendazole in turkeys because it qualifies for a zero withdrawal (Section E). Although an official tissue assay is not established, research methods based on HPLC are available to measure residues of fenbendazole and its metabolites in the extracts of tissues of turkeys.

VII. AGENCY CONCLUSIONS

The data 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, Code of Federal Regulations (21 CFR 514) to demonstrate that SAFE GUARD® (fenbendazole), when used under proposed conditions of use is safe and effective for the removal and control of adults and larvae of *Ascaridia dissimilis* and *Heterakis gallinarum*.

The available residue chemistry information supports the assignment of no (zero) withdrawal restriction for turkeys fed fenbendazole at 14.5 g/ton (16 ppm) for six (6) consecutive days. The safe concentrations for total residues of fenbendazole in turkeys are 8 ppm in muscle, 24 ppm in liver and 48 ppm in fat. The Agency has assigned tolerances of 6 ppm in liver and 2 ppm in muscle for residues of fenbendazole sulfone serving as the marker residue in these tissues.

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

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval of the supplement because the applicant contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food-producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of supplement and conducted by the sponsor.

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

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact (FONSI) and the evidence supporting that finding contained in an environmental assessment may be seen in the Dockets Management Branch (HFA-305), Park Building (Room 1-23), 12420 Parklawn Drive, Rockville, Maryland 20855.

VIII. APPROVED LABELING (attached)

Specimen Type A Medicated Article
Specimen (Blue Bird) labels - Type B and Type C medicated feed

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