Date of Approval Letter: April 21, 1999

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 140-951

CLINACOX™

(diclazuril)

"...broiler chickens: for the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. mitis (mivati),* and *E. maxima"*

Sponsored by:

SCHERING-PLOUGH ANIMAL HEALTH

I. GENERAL INFORMATION:

NADA Number:	140-951
Sponsor:	Schering-Plough Animal Health Corporation P. O. Box 529 Kenilworth, New Jersey 07083
Established Name:	diclazuril
Trade Name:	CLINACOX™ Anticoccidial Type A Medicated Article
Marketing Status:	Over-the-Counter

II. INDICATIONS FOR USE:

Broiler Chickens:

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. mitis (mivati),* and *E. maxima*. Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Diclazuril was shown in studies to reduce lesion scores and improve performance and health of birds challenged with *E. maxima*.

III. PRODUCT INFORMATION

A. Dosage Form and Amount of Active Ingredient:

CLINACOX™ is a Type A medicated article (premix) which contains 0.2% diclazuril.

B. Route of Administration and Dosage:

CLINACOX™ Anticoccidial Type A medicated article is administered to broiler chickens in a complete feed at 1 ppm that is fed continuously as the sole ration.

C. Mixing Directions:

One pound (1 lb.) of CLINACOX™ (0.2% diclazuril) is thoroughly mixed into each ton of complete feed to provide 1 ppm of diclazuril. It is recommended that an intermediary mix containing one part CLINACOX™ and not less than nine parts appropriate feed ingredient be thoroughly mixed before incorporation into the feed**.**

IV. EFFECTIVENESS:

A. Dose Determination (Field Isolate Battery trials)

1. Investigators:

Larry R. McDougald, Ph.D.
Georgia Poultry Research, Inc.
Athens, Georgia 30607

Barbara P. Siebert, V.M.D.
Pitman-Moore,Inc.
Washington Crossing, New Jersey 08560

2. Introduction

Sixty-six battery trials were conducted in two geographic locations, to evaluate the effectiveness of diclazuril in broiler chickens against single and mixed infections of six *Eimeria* species. Individual trial numbers, corresponding *Eimeria* species and trial locations are presented in Table 4.1 and 4.2.

Table 4.1. Dose determination studies testing various *Eimeria* species conducted in Washington Crossing, New Jersey, USA.

Eimeria spp.	Studies Numbers:
E. acervulina	CST-3, CST-7, CST-8
E. maxima (light infection)	CST-13
E. maxima	CST-4, CST-6, CST-12
E. mitis/mivati	CST-11
E. necatrix	CST-1
E. tenella	CST-2, CST-5, CST-10
Mixed Eimeria spp	CST-14

Table 4.2. Dose determination studies testing various *Eimeria* species conducted in Athens, Georgia, USA.

Eimeria spp.	Studies
E. acervulina	CST-113, CST-114, CST-130, CST-132, CST-133, CST-134, CST-135
E. brunetti	CST-104, CST-140, CST-141, CST-146, CST-147
E. maxima(light infection)	CST-109, CST-110, CST-111, CST-112, CST-121, CST-122, CST-123, CST-124
E. maxima	CST-105, CST-106, CST-107, CST-108, CST-117, CST-118, CST-119, CST-120
E. mitis/mivati	CST-127, CST-128, CST-129, CST-142, CST-143
E. necatrix	CST-144, CST-145, 88AVI024
E. tenella	CST-101, CST-102, CST-103 CST-115, CST-116, CST-125, CST-126, CST-136, CST-137, CST-138, CST-139
Mixed Eimeria spp	CST-148, CST-149, CST-150, CST-151, CST-162, CST-163

Fifty trials were conducted according to similar protocols, using single infections of different field isolates in each trial. Seven trials were conducted according to the same protocol using mixed *Eimeria* species infections. Approximately two-week-old chicks were placed in battery cages (Day -2), and fed diets containing 0.0, 0.5, 1.0, or 1.5 ppm diclazuril. Each treatment was replicated 4 times and each replicate contained 10 birds. Birds were experimentally infected with the appropriate *Eimeria* species on Day 0, and necropsied on Day 6. Variables evaluated to determine anticoccidial efficacy were intestinal lesion scores, droppings scores, weight gains, feed consumption, and coccidiosis mortality.

Nine additional trials with lighter infections of *E. maxima* isolates were conducted to determine the effect of diclazuril against oocyst passage. In these trials, fecal oocyst counts and weight gains were evaluated.

3. Results

Percentage improvement in weight gain, percentage incidence of mortality due to coccidiosis, mean lesion scores, and mean oocyst counts are presented in Tables 4.3 through 4.7. Birds fed diclazuril consistently exhibited improved weight gain, reduced mortality due to coccidiosis, lower lesion scores and lower mean oocyst counts per bird in comparison to the infected control birds.

Table 4.3. Percent weight gain improvement of diclazuril-treated birds over non-medicated birds challenged with oocysts of *Eimeria tenella, E. maxima, E. necatrix, E. brunetti*, *E. acervulina*, *E. mitis/mivati*, *E. maxima* (light infection), or mixed species in battery cage trials [a]

Treatment	Dose (ppm	*E. tenella*	*E. maxim*	*E. necatri*	*E. brunetti*	*E. acervulina*	*E. mitis/ mivati*	*E. maxima* (light)	Mixed Infection
Non-infected non-med.	0	45	54	37	96	41	82	5	150
Infected non-medicated	0								
Infected	.5	37	32	24	61	36	66	4	83
Infected	1.0	41	34	32	73	37	70	5	106
Infected	1.5	44	38	36	78	41	73	6	106

[a]Fifty-seven studies with 4 replicates/treatment and 10 birds/replicate

Table 4.4[a]. Mortality due to coccidiosis of diclazuril-treated and non-medicated birds challenged with oocysts of *Eimeria tenella, E. maxima, E. necatrix, E. brunetti*, *E. acervulina*, *E. mitis/mivati*, *E. maxima* (light infection), or mixed species

Treatment	Dose (ppm)	*E. tenella*	*E. maxima*	*E. necatrix*	*E. brunetti*	*E. acervulina*	*E. mitis/ mivati*	*E. maxima* (light)	Mixed Infection
Non-infected non-med.	0	0	0	0	0	0	0	0	0
Infected non-medicated	0	15.5	0	1.9	8.5	1.3	.8	0	25
Infected	0.5	0.2	0	0	0	0	0	0	0
Infected	1	0	0	0	0	0	0	0	0
Infected	1.5	0	0	0	0	0	0	0	0

[a]Fifty-seven studies with 4 replicates/treatment and 10 birds/replicate.

Table 4.5. Mean lesion scores of diclazuril-treated and non-medicated birds challenged with oocysts of *Eimeria tenella*, *E. maxima*, *E. necatrix*, *E. acervulina* *E. mitis/mivati*, or *E. brunetti* [a]

Treatment	Dose (ppm)	*E. tenella*	*E. maxima*	*E. necatrix*	*E. acervulina*	*E. mitis/ mivati*	*E. brunetti*
Non-infected non-med.	0	0	0	0	0	0	0
Infected non-medicated	0	3.35	3.55	2.31	3.65	3.47	3.07
Infected	.5	.13	2.66	.41	.24	.49	.83
Infected	1	.08	2.51	.32	.05	.11	.55
Infected	1.5	.07	2.39	.18	0	.1	.56

[a]Fifty studies with 4 replicates/treatment and 10 birds/replicate.

Table 4.6. Mean lesion scores in various regions of the small intestine and cecum in diclazuril-treated and non-medicated birds challenged with oocysts of mixed species of *Eimeria* [a]

Treatment	ppm	Upper	Middle	Lower	Ceca
Non-infect. non-med.	0	0	0	0	0
Infected non-med.	0	3.49	3.51	2.4	3.74
Infected	.5	.26	1.05	.02	.13
Infected	1	.02	.78	.03	.09
Infected	1.5	.03	.71	.05	.09

[a]Seven studies with 4 replicates/treatment and 10 birds/replicate.

Table 4.7. Number of oocysts in the feces of diclazuril-treated and non-medicated birds challenged with 1000 oocysts/bird of *E. maxima* [a]

Treatment	ppm	Million of Oocysts/bird
Non-inf. non-medicated	0	0
Infected non-medicated	0	37.95
Infected	0.5	0.31
Infected	1	0.16
Infected	1.5	0.29

[a]Nine studies with 4 replicates/treatment and 10 birds/replicate.

4. Conclusions

These trials provided a basis for concluding that diclazuril is efficacious at 0.5, 1.0, and 1.5 ppm against single or mixed infections of *Eimeria* spp. in broiler chickens. The lowest observed dose to provide optimal anticoccidial efficacy is 1.0 ppm. No adverse reactions were observed.

B. Dose Confirmation

1. Investigator: Larry R. McDougald, Ph.D.
Georgia Poultry Research, Inc.,
Athens, Georgia 30607

2. Introduction

A floor pen study was conducted to confirm the anticoccidial efficacy of diclazuril at 0 or 1 ppm against mixed *Eimeria* species in broiler chickens living under simulated growing conditions. Broiler chickens were infected with different field isolates of all six major *Eimeria* species (*E. acervulina*, *E. brunetti*, *E. necatrix*, *E. mitis*/*mivati*, *E. maxima*, and *E. tenella*) at 14 days of age. The

chickens were also administered the treatments at 14 days of age. The treatments were replicated eight times in a randomized block design.

3. Results

Table 4.8 summarizes the mean lesion scores, weight gain, feed efficiency, and percentage mortality due to coccidiosis at each location.

Table 4.8. Effect of diclazuril on mean lesion scores and mortality due to coccidiosis at Day 21 in floor pen studies in Georgia [a]

	diclazuril (ppm)	
Clinical Parameter	0	1
Mean Lesion Scores[b]		
Upper small intestine	2.96	1.00
Middle small intestine	2.58	2.23
Lower small intestine	1.71	0
Ceca	2.90	0
Total	10.15	3.23
Weight Gain, kg		
Days 14 to 21	0.115	0.220
Days 0 to 42	1.407	1.603
Feed Efficiency, gain/feed		
Days 14 to 21	0.339	0.554
Days 0 to 42	0.451	0.510
Percent Mortality		
Total	13.54	3.96
Due to coccidiosis	10.21	0

[a]Eight replicates containing 60 birds/replicate.

[b] Mean lesion scores are on a scale of 0 to 4 with 4 being most severe.

a. Upper, middle, cecal, and total intestinal lesion scores:

On Day 21, the diclazuril-treated birds had lesion scores lower than that of the non-medicated treatment.

b. Lower intestinal lesion score:

On Day 21, the diclazuril-treated birds had lesion scores lower than that of the non-medicated birds in the lower small intestine.

c. Weight gain and Feed Efficiency:

Weight gains and feed efficiency were calculated to demonstrate the performance effect associated with the anticoccidial action of diclazuril during the time of greatest infection and over the complete grow-out. The period from time of inoculation at 14 days on test to time of necropsy at seven days post infection (21 days on test) represents the period of greatest infection and most severe clinical signs of coccidiosis. The period from placement (day-old) to 42 days on test represents the complete grow-out. Weight gain and feed efficiency were improved in both periods by administration of diclazuril at 1 ppm.

d. Coccidiosis mortality:

The diclazuril-treated birds exhibited no mortality due to coccidiosis while birds in the non-medicated groups exhibited approximately 10% mortality due to coccidiosis.

4. Conclusions

Diclazuril at 1 ppm in the feed was highly efficacious against mixed infections with recent field isolates of *Eimeria* species in broiler chickens living under simulated commercial growing conditions. No adverse reactions were observed.

C. Field Studies

Investigators:

Phil Hargis Ph. D.	Jack Trammell	Michael D. Sims
Dept. of Poultry Science	3 T Enterprises	Virginia Scientific Research
University of Arkansas	114 South Railroad St.	Suite 327, 1790-10 East Market St.
Fayetteville, Arkansas	Hamilton, Texas	Harrisonburg, Virginia 22801

Approximately 222,600 broiler chickens were involved in three field studies in the states of Virginia, Texas and Arkansas. The birds were reared under commercial conditions typical for each area. The results of the grow-out of birds fed diclazuril were compared with the historical results in each house or contemporaneous controls in matched houses. Mortality, feed conversion and average final weight of the birds were recorded

1. Study No. P339-048 - Arkansas:

Approximately 91,600 broiler chickens were grown to market weight in four paired commercial broiler houses. Feed containing 1 ppm diclazuril was fed to birds in two randomly selected houses. The birds in the other two houses

received the standard anticoccidial and growth promotion, feed medication programs used at the site.

2. Study No. P339-046 - Texas:

   Approximately 123,000 broiler chickens were grown to market weight in eight identical commercial broiler houses. Feed containing 1 ppm diclazuril was fed continuously to birds in four randomly selected houses. The birds in the other four houses received the standard anticoccidial and growth promotion, feed medication programs use at the site.

3. Study No. P339-025 - Virginia:

   Diclazuril was included in the diet at 1 ppm and fed to approximately 8,000 broilers housed in one end of a commercial poultry house. Birds were treated with diclazuril for six weeks then fed non-medicated feed until seven weeks of age.

Results: There were no differences in morbidity or mortality from previous grow-out cycles. No adverse reactions associated with the use of diclazuril were observed in these studies.

Conclusions: Diclazuril at 1 ppm in the feed was effective against mixed infections of filed strains of Eimeria species in broiler chickens living under commercial growing conditions. Feed analyses show that diclazuril can be thoroughly mixed in broiler rations at proper level using the proposed Type A medicated article (0.2% diclazuril) under commercial feed mill conditions.

V. TARGET ANIMAL SAFETY STUDIES

A. Toxicity Test (1X, 12.5X and 25X label feeding level) Study No. V6536

   a. Investigators: L. Maes, W. Coussement, L. Desplenter, and R. Marsboom, Depts. of Veterinary Clinical Research and Toxicology, Janssen Pharmaceutica, Beerse, Belgium

   b. General Design: A commercial formulation of diclazuril (0.5% carrier-coated) was evaluated in 2,120 Hubbard broiler chickens (1,060 male and 1,060 female) at 1 ppm, 12.5 ppm and 25 ppm. The animals received the medicated feed from day-old until 37 days of age, followed by a drug-withdrawal period of 5 days.

   c. Results: During the trial, no drug-related effects on behavior, general appearance, litter wetness, mortality rate, growth performance and hematological parameters were observed. Pathological and histological examinations of various organs and tissues did not reveal any drug-induced alterations.

d. Conclusions: Diclazuril is safe for use in the feed of growing broiler chickens when fed at the recommended level of 1 ppm.

B. Safety under Field Conditions

1. General Design: Summaries of three field studies are found in Section V of this document, Effectiveness. Approximately 222,600 broiler chickens were tested in trials conducted in Arkansas, Texas and Virginia. Birds were reared under commercial conditions typical for each area. Results of the grow-out of birds fed diclazuril were compared with historical results in each house or contemporaneous controls in matched houses.
2. Results: Morbidity and mortality were similar to that of previous grow-outs or contemporaneous controls. No clinical signs of coccidiosis were reported.
3. Conclusions: Diclazuril is safe for use in the feed of growing broiler chickens under commercial conditions when fed at the recommended level of 1 ppm.

VI. HUMAN FOOD SAFETY:

A. Toxicity Studies

Pivotal Toxicity Studies were conducted by Janssen Pharmaceutica, Beerse, Belgium by the following investigators:

Dr. Coussement, Pathology
Dr. C. deMeester
Ms. P. Dirkx, Toxicology
Dr. Lampo, Toxicology
Dr. Marsboom, Director of Toxicology
Dr. Teuns, Toxicology
Dr. Van Cauteren, Toxicology
Dr. Vandenberghe, Pathology
Dr. Vanparys, Mutagenicity Dr. A Verstraeten, Toxicology

Additional investigators/facilities included:

Dr. Alain Leonard (Mammalian Genetics Labs SCK/CEN, Belgium)

Dr. P.J.J.M. Weterings (Notox, The Netherlands)

Dr. R. A. Young (Hazleton Labs, Kensington, Maryland USA)

The studies conducted are summarized in Table 6.1.

Table 6.1. Genotoxicity studies conducted for diclazuril:

Report Number	Type of Study	Initiation/ Termination	Results
ASR 89AVI029	Mouse lymphoma cell L5178/TK forward mutation assay	6/89 - 7/89	negative
V5964	*Drosophila* sex-linked recessive lethal test -	4/85 - 6/86	a no-test[1]
V6637	Chromosome aberrations in human lymphocytes	9/86 - 10/86	negative
V5909	Mouse dominant lethal test	8/85 - 10/85	inadequate[2]
V5868	SOS chromotest in *Escherichia coli*	9/85 - 9/85	negative
V6139	Micronucleus test in mice	9/86 - 9/86	inadequate[2]
V5834	Ames *Salmonella typhimurium*/microsome reverse mutation test	9/85 - 7/86	negative
V5597	Unscheduled DNA synthesis (UDS) test rat hepatocytes	5/85 - 6/85	negative

[1]A no-test due to questions regarding dose selection and monitoring of test article ingestion; no evidence of genotoxicity.

[2]Inadequate due to questions regarding dose selection; no evidence of genotoxicity.

Results: Collectively, the results obtained in the studies indicate an overall lack of genotoxicity related to diclazuril.

2. General Toxicity Studies

   a. One-Year Oral Toxicity Study in the Wistar Rat; Report #V6693; Initiation-Termination: 10/86 - 10/88

      Twenty rats per sex per group were treated with diclazuril in the food at dose levels of 0, 16, 63, 250 and 1000 ppm. Histopathologic changes were observed variously in the liver, lungs or mesenteric lymph nodes of either males or females of the 250 ppm and/or 1000 ppm groups. The no observable effect level is 63 ppm.

   b. Rabbit (New Zealand White) Oral Embryotoxicity and Teratogenicity Study Report #V6650; Initiation-Termination: 1/87 - 4/88

      An initial study was conducted at 0, 5, 20 and 80 mg/kg levels. No toxicity was observed. A second study was conducted at 0, 40, 80 and 160 mg/kg with 15 rabbits being gavaged at each dose level. No signs of toxicity were observed, either fetal or maternal. The treatment level of 160 mg/kg was accepted as the no observable effect level.

c. One-Year Oral Toxicity Study in the Beagle Dog
Report #V6694; Initiation-Termination: 1/87 - 11/88

Four dogs per group per sex were treated with gelatin ampoules daily at the levels of 0, 5, 20, and 80 mg/kg. Minimal hepatocyte changes were observed in the highest treatment group. The no observable effect level was set at 20 mg/kg for this study.

d. Rat (Wistar) Embryotoxicity and Teratogenicity Studies
Report #V582, Initiation-Termination: 5/85 - 5/87

A study was conducted at dose levels of 0, 12.5, 50.0, and 200 ppm, with the dose being administered in the feed to 24 rats per group. There was a slight decrease in fetal weight and maternal weight in the 200 ppm group. The 50 ppm dose level was set as the no observable effect level.

Report #V5989, Initiation-Termination: 3/86 - 5/87

A second teratology study was conducted at higher dose levels of 0, 200, 400, 800 and 1600 ppm. Although there was no evidence of teratogenicity, the compound appeared to be slightly fetotoxic at all doses (decreased mean body weight of fetuses).

e. Rat (Wistar) Oral 2-Generation Reproduction Study
Report #V6697, Initiation-Termination: 11/86 - 11/88

The compound was administered via the diet at dose/ levels of 0, 50, 200, and 800 ppm to groups of 24 rats/sex/dose. Diclazuril was slightly toxic to the dams and fetotoxic (body-weight depression) at the two highest doses. The no observable effect level was 50 ppm.

3. Carcinogenicity Studies

a. Carcinogenicity Study in Wistar Rats
Report #V6695; Initiation-Termination: 10/86 - 9/89

Wistar rats in groups of 50 per sex per dose were fed diclazuril in the diet at levels of 0, 16, 63, 250 and 1000 ppm for approximately 28 months. The maximum level (1000 ppm) was equivalent to 80 mg/kg for males and 61 mg/kg for females.

There was a positive dose-related trend for thyroid adenomas in the males and for hemangioendotheliomas of the soft tissues in females, but pairwise comparisons did not show a significant increase. The tumor incidence was not considered to be of biological significance. Minimal signs of toxicity were observed at the 250 and 1000 ppm level.

b. Carcinogenicity Study in Swiss Mice
Report #V6696; Initiation-Termination: 10/86 - 9/89

Swiss mice in groups of 50 per sex per dose were fed diclazuril in the diet at levels of 0, 16, 63, 250 and 1000 ppm for 104 weeks. The maximum level (1000 ppm) was equivalent to 185 mg/kg for males and 217 mg/kg for females. There were no treatment related increases in the incidence of tumors. Minimal signs of toxicity were observed at dose levels of 63 ppm and above.

c. Conclusions: Based on these results and the observations seen in three month and one year rat studies, a 90-day mouse study and pharmacokinetic studies in both species, both the rat and mouse carcinogenicity studies were considered acceptable negative studies.

B. Calculation of Acceptable Daily Intake (ADI)

The safe concentration is based on the no observable effect level (NOEL) of 50 ppm or 2.5 mg/kg body weight (BW)/day for fetotoxicity observed in the rat in both the teratology and two-generation reproduction studies. Because of the reversible nature of this effect, the safety factor (SF) to be applied to this study is 100.

$$\text{ADI} = \frac{\text{NOEL}}{\text{Safety Factor}}$$

$$\text{ADI} = \frac{2.5 \text{ mg/kg/day}}{100} = 0.025 \text{ mg/kg BW/day}$$

C. Calculation of Safe Concentration (SC)

The calculation of the safe concentration is based on the *General Principles for Evaluating the Safety of Compounds used in Food Producing Animals* (FDA/CVM, revised July 1994):

$$\text{Safe Concentration (SC)} = \frac{\text{ADI x Human Weight}}{\text{Consumption Factor}}$$

The average human weight is approximately as 60 kg. The daily consumption values of tissues are approximated as 300 g for muscle, 100 g for liver, and 50 g for fat or skin.

$$\text{SC (muscle)} = \frac{0.025 \text{ mg/kg BW/day} \times 60 \text{ kg}}{300 \text{ g/day}} = 5 \text{ microg/kg or } 5 \text{ ppm}$$

$$\text{SC (liver)} = \frac{0.025 \text{ mg/kg BW/day} \times 60 \text{ kg}}{100 \text{ g/day}} = 15 \text{ microg/kg or} 15 \text{ ppm}$$

$$\text{SC (fat)} = \frac{0.025 \text{ mg/kg BW/day} \times 60 \text{ kg}}{50 \text{ g/day}} = 30 \text{ microg/kg or } 30 \text{ ppm}$$

D. Total Residue Depletion and Metabolism Studies

^{14}C Diclazuril in Broiler Chickens: Total Radioactivity Depletion after Repeated Oral Dosing (V6252), Janssen Pharmaceutica, Beerse, Belgium

Groups of eight broiler chickens (4 male, 4 female) were dosed from day 28 to 41 of age with ^{14}C-diclazuril at 0.045 mg/kg (equivalent to 1 ppm in the feed). The groups of eight were sacrificed at 6 (practical zero), 24, 72, 120, 168 and 240 hours after the last dose. From each bird, liver, muscle and skin/fat were taken for radioanalysis. In addition, samples were analyzed for unchanged diclazuril using a GC/EC method. The results of the above study are summarized in Table 6.2.

Table 6.2. Concentration of diclazuril (ppb) in tissues of broiler chickens treated with 0.045 mg/kg ^{14}C-diclazuril at various times after the last dose

	6 hr		24 hr		72 hr		120 hr		168 hr		240 hr	
Tissue	TR*	UD*	TR	UD	TR	UD	TR	UD	TR	UD	TR	UD
Liver	386	370	240	202	187	138	107	85	63	42	36	20
Pectoral Muscle	58	52	31	27	23	19	13	13	7	<10	<5	<10
Skin/fat	193	158	110	85	83	59	49	41	29	22	17	<10

* TR = total residue

* UD = unchanged drug

The data in Table 6.2 show that 6 hours after the last dose (a practical zero withdrawal period) the total residue in each edible tissue is well below the applicable safe concentration for the tissue and the total residue essentially reflects unchanged diclazuril. Since the total residue essentially reflects unchanged diclazuril, a comparative metabolism study is not required to support approval of this application.

E. Assignment of a Zero Withdrawal Period

Because the total residue of diclazuril at practical zero withdrawal (6 hours after the last dose) in each edible tissue of chickens treated with diclazuril at the intended use level is more than ten-fold below the applicable safe concentration, no withdrawal period is required for birds treated per label directions with diclazuril medicated premix.

F. Regulatory Method and Tolerances

In order to provide guidance to Food Safety Inspection Service (FSIS) of the United States Department of Agriculture, which administers a national residue monitoring program, FDA is establishing tolerances for diclazuril in chickens of 500 ppb in muscle, 3000 ppb in liver and 1000 ppb in skin/fat as recommended by the World Health Organization/Food Agriculture Organization (WHO/FAO) Joint Expert Committee on Food Additives (JECFA). These tolerances are not based on the Agency's usual approach. However, these tolerances are less than the amount of drug residues permitted based on the ADI, are consistent with the labeled use of the product and can be monitored with the sponsor-validated GC/EC method. Therefore, edible tissues containing residues at or below the codified tolerances are safe for consumers. The sponsor's validated GC/EC method for diclazuril in edible tissue is on file with the Center for Veterinary Medicine.

VII. AGENCY CONCLUSIONS:

The data submitted in support of this original NADA for CLINACOX™ (diclazuril) satisfy the requirements of section 512 of the Federal Food, Drug and Cosmetic Act (FFDCA) and the implementing regulations at 21 CFR 514. The data demonstrate that diclazuril in the feed of broiler chickens at 1 ppm, when used according the label directions, is safe and effective for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mitis/mivati, and E. maxima*

The agency has concluded that this product can be approved for over-the-counter marketing status because directions for use are clearly written, and there is reasonable certainty that the conditions of use including mixing directions on the label, can and will be followed by producers.

An Acceptable Daily Intake (ADI) of 25 micrograms/kg body weight/day and safe concentrations of 5 ppm in muscle, 15 ppm in liver and 30 ppm in fat and skin have been established for diclazuril. Although a withdrawal time is not required for this use of diclazuril in chickens, tolerances of 0.5 ppm in muscle, 3 ppm in liver, and 1 ppm in skin/fat have been established for parent diclazuril.

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 findings of no significant impact (FONSI) and the evidence supporting that finding are contained in an environmental assessment, which may be seen in the Dockets Management Branch (HFV-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, Maryland 20852.

Under section 512(c)(2)(F)(i) of the FFDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

CLINACOX™ Anticoccidial Type A medicated article is under U.S. patent Number 4,631,278, which expires August 1, 2004.

VIII. APPROVED LABELING (attached)

Facsimile bag label - Type A medicated article

Specimen (Bluebird) label - Type B medicated feed

Specimen (Bluebird) label - Type C medicated feed