FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-099

CYDECTIN®
(moxidectin)
Pour-On for Cattle

Sponsored by

Fort Dodge Animal Health

January 1998

®**Registered trademark of American Cyanamid Company**

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I. GENERAL INFORMATION

NADA Number: 141-099

Sponsor: Fort Dodge Animal Health
P. O. Box 400
Princeton, N.J. 08543-0400

Established Name: moxidectin

Tradename: CYDECTIN® (moxidectin) 0.5% Pour-On for Cattle

Marketing Status: Over-the-counter (OTC)

II. INDICATIONS FOR USE:

Effective in the treatment and control of the following internal and external parasites.

Gastrointestinal Roundworms

Ostertagia ostertagi - Adult and fourth-stage larvae (including inhibited larvae)
Haemonchus placei - Adult
Trichostrongylus axei - Adult and fourth-stage larvae
Trichostrongylus colubriformis - Adult
Cooperia oncophora - Adult
Cooperia punctata - Adult
Bunostomum phlebotomum - Adult
Oesophagostomum radiatum - Adult
Nematodirus helvetianus - Adult

Lungworms

Dictyocaulus viviparus - Adult and fourth-stage larvae

Cattle Grubs
Hypoderma bovis
Hypoderma lineatum

Mites

Chorioptes bovis
Psoroptes ovis (*Psoroptes communis* var. *bovis*)

Lice

Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus
Bovicola (Damalinia) bovis

Horn Flies

Haematobia irritans

CYDECTIN® (moxidectin) 0.5% Pour-On for Cattle has been proven to effectively control infections and to protect cattle from reinfection with *Ostertagia ostertagi* for 28 days following treatment and *Dictyocaulus viviparus* for 42 days after treatment.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. Form: CYDECTIN® (moxidectin) 0.5% Pour-On for Cattle is a ready-to-use topical formulation which contains 0.5 mg moxidectin per mL of solution.

B. Route of Administration: The product should be applied directly to the hair and skin along the top of the back from the withers to the base of the tail. Application should be made to healthy skin avoiding mange scabs, skin lesions or extraneous foreign matter.

C. Recommended Dose Rate: The recommended rate of administration is 1 mL for each 22 lb (10 kg) of body weight which provides 5 mg moxidectin for each 22 lb (10 kg) of body weight.

IV. EFFECTIVENESS

A series of dose determination studies were conducted at a variety of locations in the United States to establish the recommended effective dose of moxidectin pour-on for the control of nematodes, mange mites, and lice. This dose was further evaluated in a series of dose confirmation and field efficacy trials which confirmed the appropriateness of the recommended dose against a broad spectrum of parasites, and demonstrated effectiveness under field conditions.

Efficacy of moxidectin pour-on against parasites was calculated as the reduction in the number of a specific stage and species of parasite in treated animals as compared to the number in vehicle or untreated control animals. Percent efficacy or percent reduction was calculated using arithmetic means in the following formula.

$$\% \text{ Efficacy} = \left(\frac{\text{mean parasite count in control group - mean parasite count in treated group}}{\text{mean parasite count control group}}\right) \times 100$$

For each parasite claim which appears on the product label, the following criteria were applied:

a) at least six control animals were infected/infested with that specific stage and species of parasite;
b) treatment with the recommended dose resulted in at least a 90% reduction in the parasite count as compared to controls; and
c) these results were duplicated in at least two independent studies.

These studies indicated that a dose of 0.5 mg moxidectin/kg body weight administered as a single topical application along the backline of the animal gave the optimal efficacy against all ecto- and endoparasites which are listed as label claims.

A. Endoparasite Claims

Dose Determination - Endoparasites

Two experiments (B-90-38 and B-91-4) were conducted to determine the effective dose against gastrointestinal nematodes in cattle. In both studies, cattle were treated with doses of 0 (vehicle-treated controls), 0.25, 0.5 and 0.75 mg moxidectin/kg body weight and necropsied 13 to 15 days later for nematode recovery and identification. In Experiment B-91-4, there was no difference in the efficacy of any of the three dose levels tested. In Experiment B-90-38, the dose of 0.25 mg/kg was not as effective as the higher doses against *Cooperia* spp. and *Cooperia punctata*. There were no other differences between any of the doses in either study. Based on the doses tested in these two dose determination trials, 0.5 mg moxidectin/kg body weight was found to be the optimal dose for effective control of gastrointestinal nematodes.

Individual Dose Determination Studies

Study Number B-90-38

1. Type of Study: Dose determination study in cattle with naturally-acquired gastrointestinal roundworm infections.

2. Investigator: C. E. Couvillion, D.V.M., Ph.D.
   Mississippi State University
   Mississippi State, MS

3. General Design:

   a. Purpose: This study was designed to evaluate the dose required for effective control of natural nematode infections in cattle.

   b. Animals: Forty mixed beef breed steers, weighing between 129 and 190 kg, were randomly assigned to one of four treatment groups (10 animals per group) based on pretreatment body weight.

   c. Housing: Animals were maintained in outdoor concrete-floored pens by treatment group and exposed to ambient weather conditions.

   d. Infection: All cattle had naturally-acquired nematode infections.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg moxidectin/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, 1.0 or 1.5 mL/10 kg body weight providing 0.25, 0.5 or 0.75 mg moxidectin/kg body weight, respectively.

   h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1.5 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

   i. Test Duration: Necropsy was on Day 14 or 15 posttreatment

   j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on (mg/kg) 0.25	0.5	0.75
Ostertagia ostertagi, adult*	1038	100	100	100
Ostertagia ostertagi, inhibited EL_4	228	100	100	100
Trichostrongylus axei, adult	950	100	100	100
Haemonchus placei, adult	136	100	100	100
Cooperia punctata, adult	200	81.0	95.0	100
Cooperia spp., adult	1036	78.0	97.7	99.8

*Includes developing L_4's

5. Adverse Reactions:

   No adverse reactions to treatment were observed. At necropsy, it was observed that three of 40 calves had areas of hair loss (3 to 12 inches in diameter) along the midline of the back. Two animals were in the 0.25 mg/kg group and one animal was in the 0.5 mg/kg group. In this study, the pour-on site was not observed pretreatment. Therefore, no conclusion could be made whether or not this was a preexisting condition or if it was related to treatment. These patches of hair loss were not related to either the volume of vehicle applied or dose of moxidectin pour-on because no such observations were observed in the control group or the 0.75 mg/kg group which received the highest volumes of product.

Study Number B-91-4

1. Type of Study: Dose determination study in cattle with naturally-acquired gastrointestinal roundworm infections.

2. Investigator: J.A. DiPietro, D.V.M., M.S.
   College of Veterinary Medicine
   University of Illinois
   Urbana, IL

3. General Design:

   a. Purpose: This study was designed to evaluate the dose required for effective control of natural nematode infections in cattle.

b. Animals: Forty calves, weighing between 149 and 302 kg, were randomly assigned to one of four treatment groups (10 per group) based on pretreatment fecal nematode egg counts and body weight. Cattle were a mixture of purebreds and crossbreds of the following breeds: Angus, Shorthorn, Charolais, Brangus, Polled Hereford, Hereford and Jersey.

c. Housing: Animals were maintained in outdoor gravel lots by treatment group and exposed to ambient weather conditions.

d. Infection: All cattle had naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, 1.0 or 1.5 mL/10 kg body weight providing 0.25, 0.5 or 0.75 mg moxidectin/kg body weight, respectively.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1.5 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Necropsy was on Days 13, 14 or 15 posttreatment

j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

	Arithmetic Mean in	% Efficacy of Moxidectin Pour-on (mg/kg)		
Nematode species and stage	Control Cattle	0.25	0.5	0.75
Ostertagia ostertagi, adult	3606	96.0	100	100
Trichostrongylus axei, adult	1323	99.0	92.7	100
Trichostrongylus axei, L_4	417	98.8	99.8	100
Bunostomum phlebotomum, adult	5	100	100	100
Cooperia oncophora, adult	2917	95.9	94.4	98.5
Oesophagostomum radiatum, adult	380	100	100	100

5. Adverse Reactions: No adverse reactions to treatment were observed.

Dose Confirmation - Endoparasites

Seven pivotal nematode dose confirmation experiments were conducted in the United States and Canada, including trial locations in Idaho (B-93-5), Illinois (B-93-12), North Carolina (B-93-10), Louisiana (B-92-14), New Jersey (B-90-29), Wisconsin (0863-B-US-15-96) and Quebec (0863-B1-CN-03-92). Four studies included doses of 0.25 and 0.5 mg moxidectin/kg body weight and thus provided additional data on potential dose limiting species of nematodes. The cattle in the Illinois, Idaho and Quebec trials were naturally infected with nematodes; cattle in the Louisiana and North Carolina trials had induced infections superimposed on natural infections; and cattle in the New Jersey and Wisconsin studies had induced infections. These studies consisted of critical nematode trials in which worms were counted and identified. The results confirmed that moxidectin 0.5% pour-on at a dosage of 0.5 mg moxidectin/kg body weight was highly effective against a broad spectrum of endoparasites.

Individual Dose Confirmation Studies

Study Number B-93-5

1. Type of Study: Dose confirmation study in cattle with naturally-acquired gastrointestinal roundworm infections.

2. Investigators:

E.G. Johnson, DVM	G.L. Zimmerman, DVM, Ph.D.
Johnson Research	Zimmerman Research
Parma, ID	Livingston, MT

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose for the control of natural nematode infections in cattle.

   b. Animals: Twenty-four mixed beef breed heifers, weighing between 177 and 334 kg, were randomly assigned to one of three treatment groups (8 per group) based on pretreatment fecal nematode egg counts.

   c. Housing: Animals were maintained in outdoor pens with dirt floors by treatment group and exposed to ambient weather conditions.

   d. Infection: All cattle had naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, or 1 mL/10 kg body weight providing 0.25, or 0.5 mg moxidectin/kg body weight, respectively.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Necropsy was on Day 14 or 15 posttreatment.

j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on (mg/kg) 0.25	0.5
Ostertagia ostertagi, adult males	1312	99.8	100
Ostertagia spp. adult females	1495	99.7	100
Ostertagia spp., inhibited EL_4	698	53.0	95.7

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number B-93-12

1. Type of Study: Dose confirmation study in cattle with naturally-acquired gastrointestinal roundworm infections.

2. Investigator: J. A. DiPietro, D.V.M., M.S.
College of Veterinary Medicine
University of Illinois
Urbana, IL

3. General Design:

a. Purpose: This study was designed to confirm the effective dose for the control of natural nematode infections in cattle.

b. Animals: Thirty mixed beef breed calves, weighing between 138 and 223 kg, were randomly assigned to one of three treatment groups (10 per group) based on pretreatment fecal nematode egg counts and body weight.

c. Housing: Animals were housed indoors in pens with concrete floors by treatment group.

d. Infection: All cattle had naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, or 1 mL/10 kg body weight providing 0.25, or 0.5 mg moxidectin/kg body weight, respectively.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Necropsy was on Day 14 or 15 posttreatment.

j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on (mg/kg) 0.25	0.5
Haemonchus placei, adult	135	100	100
Ostertagia ostertagi, adult	10060	100	>99.9
Ostertagia ostertagi, L_4	3714	100	100
Trichostrongylus axei, adult	10635	100	100
Bunostomum phlebotomum, adult	254	100	100
Cooperia oncophora, adult	8602	>99.9	>99.9
Cooperia punctata, adult	3490	>99.9	>99.9
Nematodirus helvetianus, adult	1279	100	100
Oesophagostomum radiatum, adult	163	100	100

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number 0863-B1-CN-03-92

1. Type of Study: Dose confirmation study in cattle with naturally-acquired gastrointestinal roundworm infections.

2. Investigators: S. Ranjan, B.V.Sc., Ph.D.
and R.K. Prichard, B.Sc., Ph.D.
McGill University
MacDonald Campus
Ste-Anne de Bellevue
Quebec, Canada

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose required for the control of nematode infections in cattle.

   b. Animals: Twenty-four mixed beef breed male calves, weighing between 129 and 160 kg, were randomly assigned to one of three treatment groups (8 per group) based on pretreatment fecal nematode egg counts.

   c. Housing: Animals were maintained on pasture until treatment and then commingled in a barn following treatment.

   d. Infection: All cattle had naturally-acquired nematode infections.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, or 1 mL/10 kg body weight providing 0.25, or 0.5 mg moxidectin/kg body weight, respectively.

   h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

   i. Test Duration: Necropsy was on Day 14 or 15 posttreatment.

   j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on (mg/kg) 0.25	0.5
Ostertagia ostertagi, adult	129	100	100
Ostertagia ostertagi, inhibited EL_4	503	99.8	99.8
Trichostrongylus axei, adult	497	97.1	95.8
Trichostrongylus axei, L_4	20	100	99.4
Cooperia oncophora, adult	3261	99.1	98.9
Cooperia punctata, adult	159	99.4	99.2
Nematodirus helvetianus, adult	4500	99.9	99.4
Nematodirus helvetianus, L_4	1326	100	99.6

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number B-93-10

1. Type of Study: Dose confirmation study in cattle with naturally-acquired and experimentally-induced gastrointestinal roundworm infections.

2. Investigator: L.R. Cruthers, Ph.D.
   Professional Laboratory and Research Services, Inc.
   Corapeake, NC

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose for the control of nematode infections in cattle.

   b. Animals: Thirty mixed beef breed calves, weighing between 168 and 255 kg, were randomly assigned to one of three treatment groups (10 per group) based on pretreatment fecal nematode egg counts.

   c. Housing: Animals were maintained in outdoor pens by treatment group and exposed to ambient weather conditions.

d. Infection: Thirty six days prior to treatment, cattle were infected with approximately 10,000 third-stage larvae from the following nematode genera: *Nematodirus* (2,000 larvae), *Cooperia* (3,000 larvae), *Ostertagia* (3,600 larvae) *Trichostrongylus* (1,200 larvae) and *Haemonchus* (200 larvae). These induced infections were superimposed over any naturally-acquired nematode burdens carried by these cattle.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, or 1 mL/10 kg body weight providing 0.25, or 0.5 mg moxidectin/kg body weight, respectively.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Necropsy was on Day 14 or 15 posttreatment.

j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on (mg/kg) 0.25	0.5
Cooperia oncophora, adult	1130	77.2	98.9
Haemonchus placei, adult	35	100	100
Ostertagia ostertagi, adult	838	99.3	100
Trichostrongylus axei, adult	90	100	100
Trichostrongylus colubriformis, adult	84	90.5	100

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number B-92-14

1. Type of Study: Dose confirmation study in cattle with naturally-acquired gastrointestinal roundworm infections and induced infections of hookworm and lungworm.

2. Investigator: J.C. Williams, Ph.D.
   Louisiana State University
   Baton Rouge, LA

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose for the control of nematode infections in cattle.

   b. Animals: Twenty mixed beef breed heifers, weighing between 122 and 184 kg, were ranked by pretreatment fecal lungworm larval counts, paired and randomly assigned to either the moxidectin pour-on treated group or the control group.

   c. Housing: Animals were maintained in outdoor pens with concrete floors by treatment group and exposed to ambient weather conditions.

   d. Infection: Cattle were infected with approximately 2,316 hookworm L_3 larvae on Day -77. On Day -29, cattle were infected with approximately 1,509 third-stage hookworm larvae and 1,080 third-stage lungworm larvae. These experimentally-induced infections were superimposed over naturally-acquired nematode infections.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

   h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

   i. Test Duration: Necropsy was on Day 14 or 15 posttreatment.

j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on 0.5 mg/kg
Dictyocaulus viviparus, adult	23	100
Haemonchus placei, adult	1500	100
Haemonchus placei, larvae	126	100
Ostertagia ostertagi, adult	2402	100
Ostertagia ostertagi, larvae	303	100
Bunostomum phlebotomum, adult	89	100
Cooperia pectinata, male adult	210	100
Cooperia punctata, male adult	4555	99.8
Cooperia spatulata, male adult	317	100
Cooperia spp., female adult	7299	99.5

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number B-90-29

1. Type of Study: Dose confirmation study in cattle with experimentally-induced gastrointestinal roundworm infections.

2. Investigator: J. A. Pankavich, Ph.D.
Cyanamid Agricultural Research Center
Princeton, NJ

c. General Design:

a. Purpose: This study was designed to confirm the effective dose required for the control of nematode infections in cattle using 4 different formulations.

b. Animals: Thirty Angus, Hereford and Angus X Hereford cross heifers weighing between 158 and 228 kg, were randomly assigned to the control and moxidectin treated groups (6 per group) based on pretreatment fecal nematode egg counts.

c. Housing: Animals were housed in a barn in pens by group following treatment.

d. Infection: Twenty-eight days prior to treatment, cattle were infected with third-stage larvae from the following nematode genera/species: *Cooperia* (19,800 larvae), *Ostertagia* (38,600 larvae) *Trichostrongylus axei* (34,400 larvae). *Trichostrongylus colubriformis* was present in the inoculum as a contaminant.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

h. Controls: Untreated control animals were used.

i. Test Duration: Necropsy was on Day 16 posttreatment.

j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals administered the formulation intended for marketing are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on
Ostertagia ostertagi, adult	8138	100
Trichostrongylus axei, adult	212	100
Trichostrongylus colubriformis, adult	2723	100

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number 0863-B-US-15-96

1. Type of Study: Dose confirmation study in cattle with induced infections of lungworm.

2. Investigator: L. L. Smith, DVM
Larry Smith Research and Development, Inc.
Lodi, WI

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose for the control of larval and adult stages of lungworm in cattle.

   b. Animals: Thirty mixed breed calves, mostly Holstein and dairy-beef crosses, weighing between 108 and 167 kg, were randomly assigned to one of three treatment groups based on body weight.

   c. Housing: Animals were maintained in pens by treatment group in three separate pens. The pens were attached to a modified open front barn for shelter. Cattle were exposed to ambient weather conditions during the study and the total snowfall during the experimental period was 20.4 inches.

   d. Infection: Each animal was experimentally infected with approximately 3,000 lungworm third-stage larvae on Day 0.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied to cattle, once on Day 5 or Day 28 postinfection, at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

      One group of cattle was treated on Day 5 postinfection to evaluate efficacy against fourth-stage lungworm and one group was treated on Day 28 postinfection to evaluate efficacy against the adult stage.

   h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight. Control animals were treated on Day 28 postinfection.

   i. Test Duration: Necropsy of all animals was on Day 42 postinfection.

   j. Pertinent Parameters Measured: Lungworms were collected at necropsy and subsequently counted by stage.

4. Results: Efficacy data are given in the following table.

Nematode species and stage	Arithmetic Mean in Control Cattle	% Efficacy of Moxidectin Pour-on
Dictyocaulus viviparus, adult	17	100
Dictyocaulus viviparus, L_4	17	100

5. Adverse Reactions: No adverse reactions to treatment were observed.

Persistent Efficacy - Endoparasites

Three pivotal studies were conducted in the United States to evaluate the persistent activity of moxidectin 0.5% pour-on in preventing infection of treated cattle with third-stage larvae of *Ostertagia ostertagi* and *Dictyocaulus viviparus*. The studies had similar designs and consisted of cattle in each treatment group receiving a single challenge of third-stage larvae of both nematode species, on a specific posttreatment day. Inoculum were administered on Days 21, 28, 35 or 42 posttreatment. These studies demonstrated that moxidectin 0.5% pour-on has effective persistent activity for 28 days against *Ostertagia ostertagi* and 42 days against *Dictyocaulus viviparus*.

Individual Persistent Efficacy Studies

Study Number 0863-B-US-5-95

1. Type of Study: Dose confirmation study in cattle with induced gastrointestinal roundworm and lungworm infections.

2. Investigator: L. R. Cruthers, Ph.D.
   Professional Laboratory and Research Services, Inc.
   Corapeake, NC

3. General Design:

   a. Purpose: This study was designed to determine the period of time following treatment in which gastrointestinal roundworm and lungworm infections are controlled in cattle.

   b. Animals: Forty mixed beef breed heifer calves, weighing between 146 and 208 kg, were randomly assigned to one of five treatment groups (8 per group) based on body weight. Cattle had been treated with an approved anthelmintic at the time of purchase and all cattle were negative for the presence of nematode eggs and lungworm larvae in feces at the start of the study.

   c. Housing: Animals were maintained in individual outdoor pens and exposed to ambient weather conditions during the posttreatment period.

   d. Infection: On Day 0, each calf was infected with an inoculum containing approximately 25,000 *Ostertagia* and 1,500 *Dictyocaulus viviparus* third-stage larvae.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

There were four different groups of cattle treated with moxidectin pour-on. A different group was treated at 42, 35, 28 and 21 days prior to the experimental larval challenge on Day 0

h. Controls: Untreated control animals were used.

i. Test Duration: Necropsy was on Days 22 or 23 postinfection.

j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table. The lungworm infection only established in one control calf; therefore, it was not possible to the evaluate persistent efficacy of moxidectin against this nematode in this study.

Nematode species and stage	Treatment Group[a]	Arithmetic Mean	% Efficacy of Moxidectin
Ostertagia ostertagi	Controls	1287.5	
adult males	Day -21	80.0	93.8
	Day -28	22.5	98.3
	Day -35	430.0	66.6
	Day -42	1582.5	0
Ostertagia spp.	Controls	1502.5	
adult females[b]	Day -21	117.5	92.2
	Day -28	50.0	96.7
	Day -35	600.0	60.1
	Day -42	1887.5	0

[a]Day is day of treatment with moxidectin pour-on relative to larval infection.
[b]*O. lyrata* males were found in 3 control and 4 animals in the Day 42 group.

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number 0863-B-US-6-95

1. Type of Study: Dose confirmation study in cattle with induced gastrointestinal roundworm and lungworm infections.

2. Investigators:

E.G. Johnson, DVM
Johnson Research
Parma, ID

G.L. Zimmerman, DVM, Ph.D.
Zimmerman Research
Livingston, MT

3. General Design:

   a. Purpose: This study was designed to determine the period of time following treatment in which gastrointestinal roundworm and lungworm infections are controlled in cattle.

   b. Animals: Forty Holstein steer calves, weighing between 133 and 198 kg, were randomly assigned to one of five treatment groups (8 per group) based on body weight. Cattle were treated with an approved anthelmintic at the time of purchase. All cattle were negative for nematode eggs and lungworm larvae in feces at the start of the study.

   c. Housing: Animals were maintained in individual pens on concrete floors in a barn during the posttreatment period.

   d. Infection: On Day 0, each calf was infected with an inoculum containing approximately 25,000 *Ostertagia* and 1,500 *Dictyocaulus viviparus* third-stage larvae.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

      There were four different groups of cattle treated with moxidectin pour-on. A different group was treated at 42, 35, 28 and 21 days prior to the experimental larval challenge on Day 0

   h. Controls: Untreated control animals were used.

   i. Test Duration: Necropsy was on Day 21 or 22 postinfection.

   j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

Nematode species and stage	Treatment Group[a]	Arithmetic Mean	% Efficacy of Moxidectin Pour-on
Ostertagia ostertagi, adult	Controls	8597.5	
	Day -21	0	100
	Day -28	0	100
	Day -35	2.5	>99.9
	Day -42	25.0	99.4
Dictyocaulus viviparus, adult	Controls	42.3	
	Day -21	0	100
	Day -28	0	100
	Day -35	0	100
	Day -42	0	100

[a]Day is day of treatment with moxidectin pour-on relative to larval infection.

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number 0863-B-US-8-96

1. Type of Study: Dose confirmation study in cattle with induced gastrointestinal roundworm and lungworm infections.

2. Investigator: S. Ranjan, B.V.Sc., Ph.D.
Fort Dodge Animal Health
Princeton, NJ

3. General Design:

    a. Purpose: This study was designed to demonstrate therapeutic efficacy against established larval infections and to determine the period of time following treatment in which gastrointestinal roundworm and lungworm infections are controlled in cattle.

    b. Animals: Forty Holstein calves (20 steers and 20 heifers), weighing between 100 and 154 kg were used. For each sex, calves were ranked by body weight and randomly assigned to one of five treatment groups (4 steers and 4 heifers per group). Cattle had been treated with an approved anthelmintic at the time of purchase and all cattle were negative for the presence of nematode eggs and lungworm larvae in feces at the start of the study.

    c. Housing: Animals were maintained in pens on a concrete floor by treatment group by sex (4 animals per pen) in an open front barn.

    d. Infection: On Day 0, each calf was infected with an inoculum containing approximately 25,000 *Ostertagia* and 1,500 *Dictyocaulus viviparus* third-stage larvae.

    e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

    f. Route of Administration: Topically along the back from the withers to the tailhead.

    g. Doses: Moxidectin 0.5% pour-on was applied once at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

    There were five different groups of cattle treated with moxidectin pour-on. A different group was treated at 42, 35, 28 and 21 days prior to the experimental larval challenge on Day 0 and one group was treated five days postinfection to demonstrate therapeutic efficacy against established larval infections.

    h. Controls: Untreated control animals were used.

    i. Test Duration: Necropsy was on Day 28 to 30 postinfection.

    j. Pertinent Parameters Measured: Nematodes collected at necropsy were subsequently counted and identified.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table.

Nematode species and stage	Treatment Group[a]	Arithmetic Mean	% Efficacy of Moxidectin Pour-on
Ostertagia ostertagi, males	Controls	2602.0	
	Day 5	0	100
	Day -21	12.2	99.5
	Day -28	39.0	98.5
	Day -35	399.5	84.7
	Day -42	1131.1	56.5
Dictyocaulus viviparus, adults	Controls	69.0	
	Day 5	0	100
	Day -21	0	100
	Day -28	0	100
	Day -35	0	100
	Day -42	0	100

[a]Day is day of treatment with moxidectin pour-on relative to larval infection.

5. Adverse Reactions: No adverse reactions to treatment were observed.

B. Ectoparasite Claims

1. Dose Determination Studies - Mange Mites

Two pivotal experiments (B-91-21 and B-92-15) were conducted to determine the effective dose against experimentally-induced *Psoroptes ovis* infestations on cattle. In B-91-21, cattle were treated with moxidectin 0.5% pour-on at 0.5, 0.75, or 1.0 mg moxidectin/kg body weight. In B-92-15, cattle were treated with moxidectin 0.5% pour-on at 0.25, 0.50 or 0.75 mg moxidectin/kg body weight. In both studies care was taken to avoid application to the mange lesions. A previous study had demonstrated that the efficacy of the product was decreased if scabs in the pour-on site were not avoided during application. In both studies, weekly mite counts were done on all animals for eight weeks posttreatment. The conclusion derived from these trials was that 0.5 mg moxidectin/kg body weight is the optimal dose of moxidectin pour-on for the control of psoroptic mange.

A dose determination study (B-93-9) was conducted with calves experimentally infested with *Chorioptes bovis* and treated with moxidectin 0.5% pour-on at either 0.25, 0.50 or 0.75 mg moxidectin/kg body weight. This study demonstrated that moxidectin at 0.50 mg/kg body weight is recommended for the control of *Chorioptes bovis* infestations in cattle.

Individual Dose Determination Studies

Study Number B-91-21

1. Type of Study: Dose determination study in cattle with induced infestations of *Psoroptes ovis*.

2. Investigator: B. C. Clymer, Ph.D.
   CAVL, Inc. and CRC
   Amarillo, TX

3. General Design:

   a. Purpose: This study was designed to evaluate the dose required for effective control of *Psoroptes ovis* infestations in cattle.

   b. Animals: Thirty-two mixed English breed heifers, weighing between 150 and 246 kg, were randomly assigned to treatment groups (eight/group) based on pretreatment mite counts.

c. Housing: All animals were housed in individual stanchions from Day -26 to Day 0 in order to establish the infestations. Following treatment cattle were maintained in outdoor pens by treatment group (eight animals/pen) and exposed to ambient weather conditions.

d. Infestation: Cattle were experimentally infested with mites.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 1, 1.5 or 2 mL/10 kg body weight providing 0.5, 0.75 or 1.0 mg moxidectin/kg body weight, respectively.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 2 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Skin scrapings for mite counts were done through Day 56 posttreatment.

j. Pertinent Parameters Measured: Number of live mites found in skin scrapings were counted pretreatment (Day -1) and at eight weekly intervals posttreatment.

4. Results: All 0.5 and 0.75 mg moxidectin/kg animals were negative for mites by Day 42 and 28, respectively. One animal at 1.0 mg moxidectin/kg remained positive throughout the study.

	Arithmetic mean in	% Reduction of *Psoroptes ovis* mites by moxidectin pour-on (mg/kg)		
Day	control cattle	0.5	0.75	1.0
7	171.1	94.7	97.4	96.6
14	180.0	99.4	99.8	97.5
21	76.4	99.5	99.7	87.2
28	48.9	95.1	100	94.6
35	15.2	96.7	100	87.7
42	7.0	100	100	87.5
49	4.1	100	100	87.9
56	4.1	100	100	84.8

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number B-92-15

1. Type of Study: Dose determination study in cattle with induced infestations of *Psoroptes ovis*.

2. Investigator: H. G. Kinzer, Ph.D.
   New Mexico State University
   Las Cruces, NM

3. General Design:

   a. Purpose: This study was designed to evaluate the dose required for effective control of *Psoroptes ovis* infestations in cattle.

   b. Animals: Twenty-four Hereford cross calves, weighing between 223 and 298 kg, were randomly assigned to treatment groups (six/group) based on pretreatment mite counts.

   c. Housing: All animals were housed indoors in individual stanchions within pens.

   d. Infestation: Cattle were experimentally infested with mites.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, 1.0 or 1.5 mL/10 kg body weight providing 0.25, 0.5 or 0.75 mg moxidectin/kg body weight, respectively.

   h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1.5 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

   i. Test Duration: Skin scrapings for mite counts were done through Day 56 posttreatment

   j. Pertinent Parameters Measured: Number of live mites and mite eggs were counted pretreatment (Day -1) and at eight weekly posttreatment intervals posttreatment.

4. Results: Efficacy data are summarized in the following table.

Day	Arithmetic Mean in Control Cattle	% Reduction of *Psoroptes ovis* mites by moxidectin pour-on (mg/kg) 0.25	0.5	0.75
7	519.7	64.7	98.3	97.3
14	793.5	80.4	99.2	90.7
21	772.7	98.2	99.8	99.7
28	340.0	98.6	99.8	99.3
35	521.2	97.1	100	99.8
42	704.6	98.3	100	>99.9
49	81.8	97.8	100	100
56	140.0	95.1	100	100

Day	Arithmetic Mean in Control Cattle	% Reduction of *Psoroptes ovis* eggs by moxidectin pour-on (mg/kg) 0.25	0.5	0.75
7	32.2	76.7	92.8	77.7
14	33.0	55.1	98.5	84.8
21	40.7	93.8	98.8	99.2
28	26.7	98.1	98.8	100
35	19.7	100	100	100
42	26.2	98.1	100	100
49	9.0	100	100	100
56	10.6	89.0	100	100

5. Adverse Reactions: No adverse reactions to treatment were observed. One control animal was removed from the study after week 5 due to life-threatening scabies burden.

Study Number B-93-9

1. Type of Study: Dose determination study in cattle with induced infestations of *Chorioptes bovis*.

2. Investigator: L.L. Smith, D.V.M.
   Larry Smith Research and Development Inc.
   Lodi, WI

3. General Design:

   a. Purpose: This study was designed to evaluate the dose required for effective control of *Chorioptes bovis* infestations in cattle.

b. Animals: Twenty-eight female beef-cross calves, weighing between 167 and 311 kg, were randomly assigned to treatment groups (seven/group) based on pretreatment mite counts.

c. Housing: All animals were housed indoors in individual stanchions.

d. Infestation: Cattle were experimentally infested with mites.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, 1.0 or 1.5 mL/10 kg body weight providing 0.25, 0.5 or 0.75 mg moxidectin/kg body weight, respectively.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1.5 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Skin scrapings for mite and mite egg counts were done through Day 56 posttreatment.

j. Pertinent Parameters Measured: Number of live mites and mite eggs were counted pretreatment (Day -1) and at eight weekly posttreatment intervals.

4. Results: At termination of the study, all control cattle were positive for mites while a total of three mites were found on two animals in the group treated with moxidectin pour-on at 0.5 mg/kg body weight.

	Arithmetic Mean in	% Reduction of *Chorioptes bovis* mites by moxidectin pour-on (mg/kg)		
Day	Control Cattle	0.25	0.5	0.75
7	233.3	0	57.4	57.0
14	223.4	55.5	99.4	92.9
21	59.4	0	98.3	92.1
28	195.1	21.3	97.6	100
35	96.0	23.4	100	100
42	234.4	38.0	100	100
49	254.0	43.1	100	100
56	261.7	44.8	99.8	100

Day	Arithmetic Mean in Control Cattle	% Reduction of *Chorioptes bovis* eggs by moxidectin pour-on (mg/kg)		
		0.25	0.5	0.75
7	2.5	100	80.0	100
14	19.8	100	100	100
21	20.4	95.1	98.4	100
28	1.2	100	85.7	100
35	4.4	93.5	100	100
42	15.7	100	100	100
49	13.5	100	100	100
56	8.3	100	100	100

5. Adverse Reactions: No adverse reactions to treatment were observed.

Lice Dose Determination Study

A dose determination study was conducted in Wyoming (Experiment B-90-36), in which naturally infested cattle were treated with moxidectin at 0.25, 0.50, and 0.75 mg/kg body weight. Cattle were infested with the sucking lice, *Solenopotes capillatus* and *Linognathus vituli*, and the biting louse, *Bovicola (Damalinia) bovis*. Lice counts were done at weekly intervals for eight weeks posttreatment. All three doses of moxidectin 0.5% pour-on were effective in reducing the numbers of adult and nymphal stages of lice. At trial termination (Day 56 posttreatment), all cattle treated with moxidectin pour-on were free of adult and nymphal stages of all three species of lice with the exception of cattle treated with 0.25 mg moxidectin/kg body weight. The majority of the animals (five of eight) in the 0.25 mg moxidectin/kg group were positive for adult *S. capillatus* while three of eight animals were positive for nymphs. Based on the proportion of lice-free animals at the trial termination, the minimum fully effective dose against adult *S. capillatus* was 0.5 mg moxidectin/kg body weight.

Study Number B-90-36

1. Type of Study: Dose determination study in cattle with naturally-acquired lice infestations.

2. Investigator: J.E. Lloyd, Ph.D.
   University of Wyoming
   Laramie, WY

3. General Design:

   a. Purpose: This study was designed to evaluate the dose required for effective control of lice infestations in cattle.

b. Animals: Thirty-two Hereford and Hereford X Angus cross beef cattle, weighing between 157 and 331 kg, were randomly assigned to treatment groups (eight/group) based on pretreatment counts of total adult and nymphal *Solenopotes capillatus*.

c. Housing: Following treatment cattle were maintained in outdoor pens by treatment group (eight animals/pen) and exposed to ambient weather conditions.

d. Infestation: All cattle had naturally-acquired lice infestations.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5, 1.0 or 1.5 mL/10 kg body weight providing 0.25, 0.5 or 0.75 mg moxidectin/kg body weight, respectively.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1.5 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Lice counts were conducted for 56 days

j. Pertinent Parameters Measured: Lice were counted weekly at eight predilection sites on each animal for eight weeks posttreatment.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following tables.

Lice Counts and % Reduction of adult and nymphal *Bovicola bovis* by moxidectin pour-on

DAY	Moxidectin mg/kg bw (percent efficacy)			
	0	0.25	0.5	0.75
0	53	59	44	78
7	54	1 (98%)	0 (100%)	0 (100%)
14	43	0 (100%)	0 (100%)	0 (100%)
21	49	0 (100%)	0 (100%)	0 (100%)
28	38	0 (100%)	0 (100%)	0 (100%)
35	32	0 (100%)	0 (100%)	0 (100%)
42	30	0 (100%)	0 (100%)	0 (100%)
49	22	0 (100%)	0 (100%)	0 (100%)
56	13	0 (100%)	0 (100%)	0 (100%)

Lice Counts and % Reduction of adult and nymphal *Solenopotes capillatus* by moxidectin pour-on

DAY	Moxidectin mg/kg bw (percent efficacy)			
	0	0.25	0.5	0.75
0	52	44	40	68
7	40	7 (82%)	1 (97%)	0 (100%)
14	66	2 (97%)	0.2 (>99%)	0 (100%)
21	66	2 (97%)	0 (100%)	0 (100%)
28	60	1 (98%)	0 (100%)	0 (100%)
35	57	0.3 (>99%)	0 (100%)	0 (100%)
42	54	1 (98%)	0.1 (>99%)	0 (100%)
49	52	1 (98%)	0.3 (>99%)	0 (100%)
56	61	2 (98%)	0 (100%)	0 (100%)

Lice Counts and % Reduction of adult and nymphal *Linognathus vituli* by moxidectin pour-on

DAY	Moxidectin mg/kg bw (percent efficacy)			
	0	0.25	0.5	0.75
0	74	31	55	36
7	64	0 (100%)	0 (100%)	0 (100%)
14	65	0 (100%)	0 (100%)	0 (100%)
21	37	0 (100%)	0 (100%)	0 (100%)
28	40	0 (100%)	0 (100%)	0 (100%)
35	26	0 (100%)	0 (100%)	0 (100%)
42	22	0 (100%)	0 (100%)	0 (100%)
49	27	0 (100%)	0 (100%)	0 (100%)
56	21	0 (100%)	0 (100%)	0 (100%)

5. Adverse Reactions: No adverse reactions to treatment were observed. One animal in the 0.5 mg/kg treatment group died due to *Clostridium novyi* infection which was not related to moxidectin treatment.

2. Dose Confirmation Studies - Mange Mites

Study Number 0863-B-US-14-96

1. Type of Study: Dose confirmation study in cattle with naturally-acquired infestations of *Chorioptes bovis*.

2. Investigator: L.L. Smith, D.V.M.
Larry Smith Research and Development, Inc.
Lodi, WI

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose required for control of *Chorioptes bovis* infestations in cattle.

b. Animals: Twenty mature mixed breed dairy cows, weighing between 381 and 675 kg, were randomly assigned to treatment groups (ten/group) based on pretreatment mite counts.

c. Housing: All cows were housed indoors in individual stanchions.

d. Infestation: Cattle were purchased from local farms from which they had naturally-acquired the mite infestations.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to cows at 1 mL/10 kg body weight providing 0.5 moxidectin/kg body weight.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to cows at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Skin scrapings for mite and egg counts were done through Day 56 posttreatment.

j. Pertinent Parameters Measured: Number of live mites and mite eggs were counted pretreatment (Day -1) and at eight weekly posttreatment intervals posttreatment.

4. Results: The Day 0 count was 468.0 for the control group and 478.8 for the treated group. All control cattle were positive for mites and mite eggs throughout the study. Two moxidectin treated animals were positive for mites and one was positive for mite eggs at study termination (Day 56 posttreatment).

Day	Arithmetic mean number of mites in control cattle	% Reduction of *Chorioptes bovis* mites by moxidectin pour-on
7	388.5	85.5
14	493.4	87.3
21	831.8	89.1
28	1167.0	95.2
35	753.5	97.2
42	826.6	96.2
49	799.4	97.3
56	726.3	98.0

5. Adverse Reactions: No adverse reactions to treatment were observed. One control animal was removed from the study after the week 6 counts as the result of a uterine torsion. This condition was not study related.

Dose Confirmation Studies - Lice and Cattle Grubs

Two study types were used to confirm the efficacy of the 0.5 mg moxidectin/kg dose against both sucking and biting lice. One study type (B-93-4) was designed only to evaluate efficacy against lice (*Linognathus vituli*, *Solenopotes capillatus*, *Haematopinus eurysternus*, and *Bovicola bovis*). The second study type (B-91-24) used cattle which were infested with both lice (*Haematopinus eurysternus* and *Bovicola bovis*) and cattle grubs allowing efficacy evaluation against both parasite types concurrently. These studies evaluated efficacy against lice using naturally infested cattle treated with 0.5 mg moxidectin/kg versus cattle treated with pour-on vehicle. The dose determination study (B-90-36) serves as the second dose confirmation study for *Linognathus vituli* and *Solenopotes capillatus*. It was conclusively demonstrated that moxidectin 0.5% pour-on at the proposed recommended dose of 0.5 mg moxidectin/kg body weight provided excellent control of both adult and nymphal stages of the sucking lice, *Linognathus vituli*, *Solenopotes capillatus*, and *Haematopinus eurysternus*, and the biting louse, *Bovicola (Damalinia) bovis.*

Efficacy against migrating larval stages of the northern cattle grub, *Hypoderma bovis*, was evaluated in two pivotal studies (B-91-24 and B-91-20). These studies contained a combined total of 60 control animals of which 49 were infested with *H. bovis* larvae and a combined total of 59 treated animals of which only one animal was positive (a total of three 3rd instars emerged).

Two pivotal studies (B-91-20 and B-91-19) were conducted with cattle naturally-infested, and one pivotal study (B-92-5) was conducted with cattle with experimentally-infested with migrating larval stages of the common cattle grub, *Hypoderma lineatum*. Study number B-91-19 is reported as a clinical field trial in this FOI summary. These studies contained a combined total of 97 control animals of which 77 were infested with *H. lineatum* larvae and a combined total of 179 treated animals of which no animals were positive for *H. lineatum* larvae.

These trials demonstrated that the proposed recommended dose for moxidectin 0.5% pour-on of 0.5 mg moxidectin/kg body weight was safe and highly effective against migrating larval stages of both *H. bovis* and *H. lineatum*.

Individual Dose Confirmation Studies

Study Number B-93-4

1. Type of Study: Dose confirmation study in cattle with naturally-acquired lice infestations.

2. Investigator: J. E. Lloyd, Ph.D.
   University of Wyoming
   Laramie, WY

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose required for control of lice infestations in cattle.

   b. Animals: Twenty-four mixed breed beef cattle, weighing between 187 and 287 kg, were randomly assigned to treatment groups (eight/group) based on pretreatment counts of total adult and nymphal *Solenopotes capillatus*.

   c. Housing: Following treatment cattle were maintained in outdoor pens by treatment group (eight animals/pen) and exposed to ambient weather conditions.

   d. Infestation: All cattle had naturally-acquired lice infestations.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 0.5 or 1 mL/10 kg body weight providing 0.25 or 0.5 mg moxidectin/kg body weight.

   h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

   i. Test Duration: Lice counts conducted for 55 days

   j. Pertinent Parameters Measured: Lice were counted from eight predilection sites on each individual animal at weekly intervals for eight weeks posttreatment.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following tables.

Lice Counts and % Reduction of adult and nymphal lice on cattle by moxidectin pour-on applied at 0.25 or 0.5 mg moxidectin /kg

Bovicola bovis

Group	Day -2	Day 6	Day 13	Day 27	Day 55
Control	53	26	23	36	31
Moxidectin	74	0	0	0	0
0.25 mg/kg		100%	100%	100%	100%
Moxidectin	67	0	0	0	0
0.5 mg/kg		100%	100%	100%	100%

Linognathus vituli

Group	Day -2	Day 6	Day 13	Day 27	Day 55
Control	68	77	69	63	15
Moxidectin	53	0	0	0	0
0.25 mg/kg		100%	100%	100%	100%
Moxidectin	46	0	0	0	0
0.5 mg/kg		100%	100%	100%	100%

Solenopotes capillatus

Group	Day -2	Day 6	Day 13	Day 27	Day 55
Control	12	11	12	12	6
Moxidectin	18	3.5	1.3	1.5	0.5
0.25 mg/kg		68%	89%	88%	92%
Moxidectin	18	0	0	0	0
0.5 mg/kg		100%	100%	100%	100%

Haematopinus eurysternus

Group	Day -2	Day 6	Day 13	Day 27	Day 55
Control	26	35	43	81	164
Moxidectin	28	0	6.5	0	0
0.25 mg/kg		100%	85%	100%	100%
Moxidectin	6	0	0	0	0
0.5 mg/kg		100%	100%	100%	100%

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number B-91-24

1. Type of Study: Dose confirmation study in cattle with naturally-acquired lice and grub infestations.

2. Investigator: L. L. Smith, D.V.M.
Larry Smith Research and Development, Inc.
Lodi, WI

3. General Design:

    a. Purpose: This study was designed to confirm the effective dose required for control of lice and grub infestations in cattle.

    b. Animals: Forty beef breeds and beef-cross breeds, weighing between 158 and 332 kg, were randomly assigned to treatment groups (twenty/group) based on pretreatment counts of *Haematopinus eurysternus*.

    c. Housing: Following treatment cattle were maintained in a loose-pen barn with outdoor pens by treatment group (twenty animals/pen) and exposed to ambient weather conditions.

    d. Infestation: All cattle had naturally-acquired lice and grub infestations.

    e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

    f. Route of Administration: Topically along the back from the withers to the tailhead.

    g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

    h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

    i. Test Duration: Lice counts for 56 days and warble counts throughout an 85 day period.

    j. Pertinent Parameters Measured: Lice were counted from eight predilection sites on each individual animal at weekly intervals for eight weeks posttreatment. Warbles were counted and grubs identified at weekly intervals from Day 21 to Day 85 posttreatment.

4. Results: Efficacy data for parasites present in a minimum of six control animals are given in the following table. Efficacy was demonstrated against adult and nymphal stages of both lice species present. A total of nine of the 20 control animals were infested with the cattle grub, *Hypoderma bovis*. The infested cattle had an average of 8.7 grubs while no grubs were found in any of the treated animals at any time during the study.

Lice Counts and % Reduction of adult and nymphal *Haematopinus eurysternus and Bovicola bovis* by moxidectin pour-on applied at 0.5 mg moxidectin /kg

Bovicola bovis

Group	Pretx	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56
Control	107	142	153	148	147	161	399	258	275
Moxidectin 0.5 mg/kg	112	0	0	0	0	0.2	0.3	0	0.5
		100%	100%	100%	100%	>99%	>99%	100%	>99%

Haematopinus eurysternus

Group	Pretx	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56
Control	967	839	875	783	677	743	746	721	467
Moxidectin 0.5 mg/kg	1050	0	0	0	0	0	0	0.3	0.2
		100%	100%	100%	100%	100%	100%	>99%	>99%

% Reduction of *Hypoderma bovis* by moxidectin pour-on applied at 0.5 mg moxidectin /kg

Day	Arithmetic mean number of grubs		% Efficacy
	Control Group	Moxidectin Group	
21	1.4	0	100
28	2.1	0	100
35	2.8	0	100
42	3.0	0	100
49	3.1	0	100
56	3.1	0	100
63	2.8	0	100
70	2.4	0	100
77	1.2	0	100
85	0.9	0	100

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number B-91-20

1. Type of Study: Dose confirmation study in cattle with naturally-acquired lice and grub infestations.

2. Investigator: J.E. Lloyd, Ph.D.
University of Wyoming
Laramie, WY

3. General Design:

    a. Purpose: This study was designed to evaluate the dose required for effective control of cattle grub infestations in cattle.

    b. Animals: Eighty crossbred beef steers, weighing between 160 and 273 kg, were randomly assigned to treatment groups (40 animals/group) based on pretreatment body weights.

    c. Housing: Following treatment cattle were maintained in outdoor pens by treatment group (eight animals/pen) and exposed to ambient weather conditions.

    d. Infestation: All cattle had naturally-acquired grub infestations.

    e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

    f. Route of Administration: Topically along the back from the withers to the tailhead.

    g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

    h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

    i. Test Duration: Grub counts throughout a 191 day experimental period.

    j. Pertinent Parameters Measured: Cattle were manually palpated for warbles for approximately six months while grubs were emerging in the back of cattle. Third instar larvae were identified to species using a fiber optic light while encysted in the backs of animals.

4. Results: All 40 control animals were positive for both *Hypoderma bovis* and *Hypoderma lineatum*. A total of three, third instar *H. bovis* were found in one of the moxidectin pour-on treated animals.

% Reduction of *Hypoderma bovis* by moxidectin pour-on applied at 0.5 mg moxidectin /kg

Day	Arithmetic mean number of grubs		% Efficacy
	Control Group	Moxidectin Group	
114	5.7	0.03	99.6
121	8.6	0.05	99.4
128	8.3	0.05	99.4
135	6.3	0.03	99.6
142	5.8	0.03	99.5
149	5.3	0	100
156	3.5	0.03	99.2
163	2.0	0.03	98.7
170	0.9	0	100
177	0.4	0	100

% Reduction of *Hypoderma lineatum* by moxidectin pour-on applied at 0.5 mg moxidectin /kg

Day	Arithmetic mean number of grubs		% Efficacy
	Control Group	Moxidectin Group	
79	0.1	0	100
86	2.3	0	100
93	5.5	0	100
100	7.6	0	100
107	8.1	0	100
114	3.1	0	100
121	0.9	0	100
128	0.3	0	100

5. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number B-92-5

1. Type of Study: Dose confirmation study in cattle with experimentally-induced grub infestations.

2. Investigators: J. A. Miller, Ph.D. and P. J. Scholl, Ph.D.
   USDA-ARS
   US Livestock Insects Research Laboratory
   Kerrville, TX

3. General Design:

   a. Purpose: This study was designed to confirm the efficacy and safety, relative to treatment timing, of moxidectin pour-on for grub infestations in cattle.

   b. Animals: Thirty-two Hereford and Hereford cross calves, weighing between 125 and 225 kg were used. Animals were randomly assigned to four treatment groups (eight animals/group) on the basis of KELISA values, indicative of exposure to *Hypoderma lineatum* larvae, and fecal nematode egg counts.

   c. Housing: Animals were stanchioned during the controlled infestations and for observation during a 21 day period following treatment. The cattle were maintained on common pasture when not stanchioned.

   d. Infestations: Each animal was experimentally-infested with 50 infective *Hypoderma lineatum* larvae over an approximate one month period (Feb. 17 to Mar. 21). Following this procedure, cattle grazed pastures where they acquired natural nematode infections.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once in June to calves at 0.5 mL/10 kg body weight providing 0.25 mg moxidectin/kg body weight.

      Moxidectin 0.5% pour-on was applied once in June to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

Moxidectin 0.5% pour-on was applied once in August to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

Treatment date - June treatment was considered appropriate treatment timing and August was considered late season treatment based on the life cycle of the common cattle grub. The late season treatment occurred when larvae were expected to be migrating through the esophageal tissues.

h. Controls: Pour-on vehicle (no moxidectin) applied on both treatment dates to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Warble counts at various times throughout a 221 day test period.

j. Pertinent Parameters Measured: Cattle were manually palpated for warbles starting October 8, and continuing until all animals were negative for warbles for two consecutive weeks (Feb 5).

4. Results: Seven out of eight control animals were infested with *Hypoderma lineatum*. No warbles were palpated in any treated animal during the test period. Efficacy compared to peak control values is as follows:

Efficacy of moxidectin pour-on (mg/kg) against *H. lineatum*

Value	Control	0.25	0.5	0.5 (late)
Mean peak warble count	33.1	0	0	0
Range	0 - 62	0	0	0
% reduction		100	100	100

5. Adverse Reactions: No adverse reactions to treatment were observed with either normal or late season treatment.

Horn Fly Dose Confirmation Studies

The efficacy of the recommended dose of moxidectin pour-on in reducing adult horn fly populations on treated cattle was confirmed in two studies. One study, conducted under confined conditions, clearly demonstrated the activity of the product against horn flies. A second study demonstrated efficacy in a cow-calf herd maintained under field conditions.

Study Number B-92-16

1. Type of Study: Dose confirmation study against *Haematobia irritans* (horn fly) under confined conditions.

2. Investigator: B. C. Clymer, Ph.D.
   CAVL, Inc. and CRC
   Amarillo, TX

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose for control of horn flies on cattle under confined conditions.

   b. Animals: This study used 12 Hereford steers, weighing between 247 and 304 kg. It was determined which six animals produced feces with the highest pupation following seeding with horn fly eggs (principals) and these animals were randomly assigned to the control or treated groups. The remaining six animals (alternates) were also randomly assigned to the control or treated groups. All principal and alternate animals were treated on Day 0. Alternate animals were available to replace a principal animal if necessary for health reasons.

   c. Housing: Each principal animal was kept in a stanchion within an individual environmentally controlled room. Alternate animals were housed by treatment group in outdoor pens which were partially covered with a roof.

   d. Infestation: Pupae and adult flies from a fly colony were added to environmentally controlled rooms to establish the fly populations. Additional pupae were added to the rooms every two to three days to repopulate the rooms with flies.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to cattle at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to cattle at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: 63 days posttreatment.

j. Pertinent Parameters Measured: Horn flies on each animal were counted twice a week until Day 63. Total fecal collections were done and effects on pupation and horn fly emergence were evaluated.

4. Results: On Day 0 the control group mean horn fly count was 1029.9 and the treated group mean was 1463.6. Moxidectin pour-on effectively reduced adult horn fly counts during the posttreatment period. Moxidectin treatment did not affect pupation or adult fly emergence in this study.

% Reduction of *Haematobia irritans* on steers treated with moxidectin pour-on applied at 0.5 mg moxidectin /kg

Day	Arithmetic mean number of flies		% Efficacy
	Control Group	Moxidectin Group	
4	1166.7	133.3	88.6
7	1050.0	44.0	95.8
11	650.0	34.3	94.7
14	833.3	12.0	98.6
18	313.3	25.7	91.8
21	333.3	28.3	91.5
25	510.0	7.7	98.5
28	426.7	37.3	91.2
32	450.0	11.7	97.4
35	406.7	10.0	97.5
39	600.0	37.3	93.8
42	683.3	23.3	96.6
46	440.0	49.3	88.8
49	483.3	18.7	96.1
53	466.7	14.0	97.0
56	416.7	28.7	93.1
60	366.7	47.3	87.1
63	316.7	43.7	86.2

5. Adverse Reactions: No adverse reactions to treatment were observed. Two control animals were replaced during the study due to bloat.

Study Number B-93-17

1. Type of Study: Dose confirmation study using cattle with naturally-acquired *Haematobia irritans* (horn fly) infestations.

2. Investigator: H. J. Meyer, Ph.D.
North Dakota State University
Fargo, ND

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose for control of horn flies on cattle under field conditions.

   b. Animals: This study used 44 Gelbvieh and Angus breed beef cows, weighing between 481 and 686 kg. All cows were nursing a calf ranging in weight from 102 to 230 kg. The cow-calf pairs were assigned to one of two pastures (22 per pasture) based on cow age, calf sex, calf age, and sire of the calf. One pasture was randomly assigned to the treated group and one pasture to the control group.

   c. Housing: The two groups of cow-calf pairs were maintained on two centrally-located adjacent pastures at the Central Grasslands Research Station in Streeter, ND.

   d. Infestation: Cattle were naturally infested with horn flies.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   f. Route of Administration: Topically along the back from the withers to the tailhead.

   g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to cows and calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight. Calves were treated to avoid the possible creation of a reservoir for horn flies within the treated herd. Horn fly counts on calves were not taken or used in the evaluation.

   h. Controls: Pour-on vehicle (no moxidectin) was applied once to cows at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight. Calves were treated at the same dose rate as their dams which was necessary to maintain the blinding of the study personnel as to treatment identity.

i. Test Duration: 42 days posttreatment.

j. Pertinent Parameters Measured: Horn flies on one entire side of each animal were counted pretreatment and at weekly intervals for six weeks posttreatment.

4. Results: Moxidectin pour-on effectively reduced fly counts for at least seven days posttreatment. At 14 days posttreatment there was no difference between the groups and there was also a noticeable drop in the fly population in the control herd. This drop may have been due to the influence of the treated herd, in an adjacent pasture, on fly populations affecting both the treated and control pastures.

% Reduction of *Haematobia irritans* on cows treated with moxidectin pour-on applied at 0.5 mg moxidectin /kg

Day	Arithmetic mean number of flies		% Efficacy
	Control Group	Moxidectin Group	
7	347.1	19.2	94.5
14	60.5	59.9	
15	86.9	168.6	
21	116.6	85.0	
28	103.7	101.1	
35	66.5	79.4	
42	30.3	22.1	

5. Adverse Reactions: No adverse reactions to treatment were observed.

C. Clinical Field Studies

Six field studies were conducted at various locations throughout the United States. Five of these studies (four pasture studies and one feedlot) evaluated the efficacy and safety of the final commercial formulation of moxidectin 0.5% pour-on using cattle with naturally acquired nematode infections. An additional study was conducted to evaluate efficacy and safety using cattle naturally infested with the common cattle grub, *Hypoderma lineatum*.

Field Efficacy Against Endoparasites - Pasture Studies

1. Type of Study: Four pivotal field clinical studies (Study Numbers 0863-B-US-9-96, 0863-B-US-11-96, 0863-B-US-12-96, 0863-B-US-13-96) were conducted under pasture management conditions using cattle with naturally-acquired nematode infections.

2. Investigators:

0863-B-US-9-96
C. R. Reinemeyer, D.V.M., Ph.D.
University of Tennessee
Knoxville, TN

0863-B-US-11-96
G. H. Meyers, Ph.D.
Gil Meyers, Ph.D., Inc.
Magnolia, KY

0863-B-US-12-96
J. C. Williams, Ph.D.
Louisiana State University
Baton Rouge, LA

0863-B-US-13-96
T. A. Yazwinski, Ph.D.
University of Arkansas
Fayettesville, AR

3. General Design:

   a. Purpose: These studies were designed to confirm the effectiveness and safety of the recommended dose of moxidectin pour-on when used under pasture conditions for the control of endoparasites in cattle.

   b. Animals: At each study site approximately 100 animals were treated with moxidectin 0.5% pour-on and approximately 50 animals were treated with pour-on vehicle. As a result of the unequal numbers of treated and control cattle it was necessary to divide them into three groups of fifty animals each in order to blind the study personnel. Cattle were assigned to one of the three groups on the basis of two pretreatment fecal egg counts. Fifty blocks of three animals each were created and a random number was assigned to each animal. The random numbers were used to assign cattle to one of three groups (control and two treated groups).

Summary information for cattle treated with moxidectin 0.5% pour-on at each study site.

Study Number	Number of Control Cattle	Number of Treated Cattle	Breed
0863-B-US-9-96	50	100	mixed beef
0863-B-US-11-96	47	96	mixed beef, Holstein, mixed Holstein
0863-B-US-12-96	50	100	Angus & Brangus
0863-B-US-13-96	50	100	mixed beef

c. Housing: All cattle were maintained on pasture throughout the studies. In two studies (0863-B-US-12-96 and 0863-B-US-13-96), cattle were maintained on three separate pastures by treatment group. In one study (0863-B-US-9-96), as the result of local management practices, cattle were divided into separate pastures by sex without regard for treatment group assignment. In the final study, cattle from two nearby farms were used, steers and heifers on both farms were mixed with no treatment group separation.

d. Infection: Cattle had naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to cattle at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to cattle at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Final fecal egg counts at 21 days posttreatment

j. Pertinent Parameters Measured: Individual animal fecal samples were examined pretreatment and posttreatment using a flotation procedure in all four studies.

4. Results: The results of fecal nematode egg count reductions are summarized in the following table.

Arithmetic means of fecal strongylate egg counts (EPG) in vehicle treated control and moxidectin 0.5% pour-on treated cattle and percent efficacy of moxidectin 0.5% pour-on.

Study Number		Arithmetic Means		Percent
(Site)	Day	Control	Moxidectin	Efficacy
0863-B-US-9-96	-11	86.1	85.1	
(Tennessee)	-8	87.3	85.2	
	14	85.5	5.3	93.8
	21	90.9	9.8	89.2
0863-B-US-11-96	-14	23.2	22.0	
(Kentucky)	-7	33.5	31.9	
	14	14.7	0.5	96.5
	21	32.4	1.1	96.7
0863-B-US-12-96	-12	688.1	700.5	
(Louisiana)	-7	819.9	826.4	
	14	658.8	4.3	99.4
	21	710.8	20.2	97.2
0863-B-US-13-96	-12	359.1	379.9	
(Arkansas)	-7	410.6	390.5	
	14	447.2	18.0	96.0
	21	342.4	18.6	94.6

5. Adverse Reactions: No adverse reactions to treatment or pour-on site reactions were observed in any animal at any of the four study sites.

Field Efficacy Against Endoparasites - Feedlot Study

Study Number B-93-13

1. Type of Study: This was a pivotal field clinical study conducted under feedlot management conditions using cattle with naturally-acquired nematode infections.

2. Investigator: J. N. Davidson, D.V.M., M.P.V.M
Health Management Services
Tulare, CA

3. General Design:

    a. Purpose: This study was designed to confirm the effectiveness and safety of the recommended dose of moxidectin pour-on when used under field conditions for the control of endoparasites in cattle.

    b. Animals: This study used a total of 100 crossbred beef steers and heifers, weighing between 138 and 297 kg at trial initiation. Animals were randomly assigned to the moxidectin treated or control group (50 animals/group) based on total EPG counts.

    c. Housing: Following treatment cattle were maintained in outdoor pens by treatment group and exposed to ambient weather conditions.

    d. Infection: Cattle had naturally-acquired nematode infections.

    e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

    f. Route of Administration: Topically along the back from the withers to the tailhead.

    g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to cattle at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

    h. Controls: Pour-on vehicle (no moxidectin) was applied once to cattle at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

    i. Test Duration: Final fecal samples for EPG counts were taken at 56 days posttreatment.

    j. Pertinent Parameters Measured: Individual animal fecal samples were examined pretreatment and posttreatment using a modified McMaster procedure.

4. Results: The results of fecal nematode egg count reductions are summarized in the following table.

Arithmetic means of fecal trichostrongyle egg counts (EPG) in vehicle treated control and moxidectin 0.5% pour-on treated cattle and percent efficacy of moxidectin 0.5% pour-on.

	Arithmetic Means		Percent
Day	Control	Moxidectin	Efficacy
-7	668	690	
-3	680	654	
7	374	16	95.7
14	168	14	91.7
28	250	6	97.6
56	218	2	99.1

5. Adverse Reactions: No adverse reactions to treatment or pour-on site reactions were observed in any animal.

Field Efficacy Against Cattle Grubs

Study Number B-91-19

1. Type of Study: Field Clinical study in cattle with naturally-acquired grub infestations.

2. Investigator: J. B. Campbell, Ph.D.
University of Nebraska
North Platte, NE

3. General Design:

   a. Purpose: This study was designed to confirm the effective dose for control of cattle grubs under field conditions in cattle.

   b. Animals: This study used 175 four-way crossbred heifers, weighing between 115 and 255 kg, that were randomly allocated to either the control group (50 animals) or the treated group (125 animals).

   c. Housing: All cattle were maintained on pasture at a commercial ranch in Dunning, NE on which cattle had a history of grub infestations. After treatment and until Day 60 posttreatment, control and moxidectin treated cattle were grazed in two separate pastures. From Day 60 to trial termination, all cattle were combined and maintained on a common pasture.

d. Infestation: Cattle had naturally-acquired cattle grub infestations.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on was applied once on Day 0 to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

h. Controls: Pour-on vehicle (no moxidectin) was applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: Treatment took place in October and warbles were counted the following February and March (152 days posttreatment).

j. Pertinent Parameters Measured: Warbles were palpated and grubs collected for identification at 120 and 152 days posttreatment.

4. Results: On Day 120 posttreatment, 30 of the control animals were positive for grubs and nine control animals were positive on Day 152. All grubs collected for identification were determined to be the common cattle grub, *Hypoderma lineatum*. No grubs were palpated in any of the moxidectin pour-on treated cattle on either examination day.

% Reduction of *Hypoderma lineatum* by moxidectin pour-on applied at 0.5 mg moxidectin /kg

Day	Arithmetic mean number of grubs		% Efficacy
	Control Group	Moxidectin Group	
120	7.1 (range 0 - 37)	0	100
152	0.7 (range 0 - 9)	0	100

5. Adverse Reactions: No adverse reactions to treatment were observed. One control animal died of pneumonia prior to the Day 120 palpation.

D. Effect of Weather on Efficacy

A total 29 pivotal efficacy studies are summarized in this document, of which in 19 studies the cattle were maintained outdoors exposed to ambient weather conditions during the posttreatment period. These studies were conducted during all seasons of the year in variety of geographical locations. Cattle were exposed from weather conditions ranging from bright sunshine to cold snowy conditions. As a result, the efficacy of moxidectin 0.5% pour-on was demonstrated a spectrum of real world weather conditions. Two pivotal studies were conducted to specifically determine the potential effect of rainfall on the efficacy of moxidectin pour-on. In both studies rain was applied at a rate of 2 inches per hour. This rate was considered "worst-case", because it is equivalent to the mean maximum hourly rainfall in the United States (based on a U.S. Department of Interior Geological Survey). Both studies demonstrated that under the worst predicted U.S. rain conditions no effect on product efficacy would be expected.

Study Number B-92-13

1. Type of Study: Dose confirmation of efficacy against nematodes and the influence of rainfall on efficacy.

2. Investigator: B. C. Clymer, Ph.D.
   CAVL, Inc. and CRC
   Amarillo, TX

3. General Design:

   a. Purpose: This study was designed to evaluate the potential effect of rainfall on the efficacy of moxidectin pour-on against gastrointestinal roundworms as determined by fecal egg counts.

   b. Animals: Forty-eight mixed beef breed heifers, weighing between 179 and 250 kg, were randomly assigned to one of six treatment groups (eight animals/group) based on the average of the Day -3 and Day -2 fecal egg counts.

   c. Housing: Following treatment cattle were maintained in outdoor pens by treatment group. Each pen had a roofed area in which animals could be confined if rain was imminent to avoid confounding the effect of simulated rain with natural rain. At all other times cattle were outdoors exposed to ambient weather conditions.

   d. Infection: All cattle had naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on applied once to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

The following five groups were treated with moxidectin pour-on and exposed to simulated rain for 30 minutes at a rate of 2 inches/hour:

- Moxidectin pour-on treatment and no rain exposure
- Moxidectin pour-on treatment and rain exposure prior to treatment
- Moxidectin pour-on treatment and rain exposure 2 hours posttreatment
- Moxidectin pour-on treatment and rain exposure 6 hours posttreatment
- Moxidectin pour-on treatment and rain exposure 24 hours posttreatment

h. Controls: Pour-on vehicle (no moxidectin) applied once to calves at 1 mL/10 kg body weight providing 0 mg moxidectin/kg body weight.

i. Test Duration: EPG evaluation for 21 days posttreatment.

j. Pertinent Parameters Measured: Individual animal fecal samples were examined pretreatment and posttreatment using a flotation procedure.

4. Results: Application of moxidectin pour-on at the recommended dose to wet cattle or to cattle exposed to heavy rainfall (2 inches/hour) at 2 to 24 hours posttreatment did not impair efficacy as determined by fecal output of nematode eggs. All moxidectin treatment reductions were different ($P<0.05$) from the untreated control animals. On Day 7, there was no effect of simulated rain either pre- or posttreatment. On Days 14 and 21, simulated rain prior to treatment, and at 2 and 24 posttreatment, was not different from the positive controls (treatment and no exposure to rain); however, the reduction of the group treated 6 hours posttreatment was less than the positive controls. This result was heavily skewed by the EPG count of one animal and is of questionable biological significance since rain at shorter and longer time intervals relative to treatment did not affect efficacy.

Treatment	Arithmetic Means Day 7	Day 14	Day 21	% Reduction of EPG's Day 7	Day 14	Day 21
Controls	144.78[a]	94.92[a]	114.35[a]			
Treatment and no rain	0.02[b]	0.02[b]	0.22[b]	>99.9	>99.9	99.8
Rain prior to treatment	0.35[b]	1.12[b,c]	5.05[b,c]	99.8	98.8	95.6
Rain 2 h posttreatment	0.35[b]	0.12[b]	2.00[b,c]	99.8	99.9	98.2
Rain 6 h posttreatment	3.02[b]	17.62[c]	27.05[c]	97.9	81.4	76.3
Rain 24 h posttreatment	0.15[b]	0.20[b]	0.68[b]	99.9	99.8	99.4

[a,b,c] Means in the same column with different superscripts differ at P<0.05.

e. Adverse Reactions: No adverse reactions to treatment were observed.

Study Number 0863-B-US-4-95

1. Type of Study: Evaluation of the wash-off potential of moxidectin from cattle treated with moxidectin 0.5% pour-on and exposed to simulated rain.

2. Investigator: William Barton, Ph.D.
   CAVL, Inc.
   Amarillo, TX

3. General Design:

   a. Purpose: This study was designed to quantify the amount of moxidectin which would be expected to wash-off from treated cattle following a heavy rain event (2 inches/hour).

   b. Animals: Six mixed beef breed heifers, weighing between 196 and 236 kg, were randomly assigned to one of three treatment groups (two animals/group).

   c. Housing: Following treatment, each animal was confined indoors in an individual pen. Cattle were held indoors to avoid any confounding effect of existing weather conditions on the simulated rain aspect of the study. Cattle were released to outdoor pens when the simulated rain was completed.

   d. Infection: Not applicable, efficacy was not evaluated in this study.

   e. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

f. Route of Administration: Topically along the back from the withers to the tailhead.

g. Doses: Moxidectin 0.5% pour-on applied once to calves at 1 mL/10 kg body weight providing 0.5 mg moxidectin/kg body weight.

There were three groups treated with moxidectin pour-on and exposed to simulated rain at one, two or six hours after treatment. Each animal was individually placed in an apparatus that was lined with stainless steel and allowed for total collection of the water applied to the animals. Rain was applied for 30 minutes at a rate of 2 inches/hour. When the simulated rain was completed and the animal removed, the apparatus was rinsed with methanol to remove any residual moxidectin which may have been bound to the walls of the apparatus.

h. Controls: None, one animal was placed in the apparatus and rinse samples were collected for analytical purposes. These samples were not used for statistical purposes.

i. Test Duration: All samples were collected on the day of treatment.

j. Pertinent Parameters Measured: The water and methanol rinses for each animal were assayed for moxidectin content.

4. Results: As a percentage of the moxidectin dose applied, the amount of moxidectin which washed-off at one, two and six hours posttreatment was 0.6, 0.71, and 1.49%. These values were not different from each other as determined with a protected LSD procedure. The mean amount of moxidectin which washed-off of all animals regardless of timing of rain was 0.93%. Under conditions of heavy rain (2 inches/hour), approximately 1% of the applied dose would be predicted to be washed-off. This minor amount will not affect the efficacy of the product.

5. Adverse Reactions: No adverse reactions to treatment were observed.

V. TARGET ANIMAL SAFETY

Specific nonclinical laboratory experiments were carried out in accordance with the applicable Good Laboratory Practices (GLP) regulations (i.e., 21 CFR Part 58) in the target species to address the following potential safety-in-use considerations: toxic syndrome as defined by the results of a drug tolerance test, margin of safety as delineated by a toxicity study with consecutive-day treatment at up to five times the recommended level, ocular exposure and three separate trials designed to evaluate reproductive safety in breeding bulls and estral and pregnant cows. All studies were performed with the final moxidectin pour-on formulation which was evenly applied in accordance with label directions.

A. Drug Tolerance Test - Study Number B-93-7

1. Type of Study: The drug tolerance test is designed to determine the dose level of an animal drug product which will elicit a toxic syndrome and provide the basis for recognition of a drug reaction attributable to product use in the target species.

2. Investigator: W. B. Epperson, D.V.M.
   Cyanamid Agricultural Research Center
   Princeton, NJ

3. General Design:

   a. Purpose: This study was designed to evaluate the clinical and pathological effects of application of moxidectin 0.5% pour-on at dose rates of 5X the recommended dose (2.5 mg moxidectin/kg body weight) for five consecutive days, 10X the recommended dose (5.0 mg moxidectin/kg body weight) for two consecutive days, or 25X the recommended dose (12.5 mg moxidectin/kg body weight) in a single application.

   b. Animals: Eight Angus crossbred steers (4) and heifers (4), approximately 12 months of age, and weighing 257 to 284 kg were allotted to four treatment groups (one male, one female per group).

   c. Control: Vehicle

   d. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   e. Route of Administration: Topically along the back from the withers to the tailhead.

f. Doses: Pour-on vehicle (no moxidectin) - 5 mL/10 kg body weight (providing 0 mg moxidectin/kg body weight) applied daily for five consecutive days.

5X dose of moxidectin 0.5% pour-on - 5 mL/10 kg body weight (providing 2.5 mg moxidectin/kg body weight) applied daily for five consecutive days.

10X dose of moxidectin 0.5% pour-on - 10 mL/10 kg body weight (providing 5 mg moxidectin/kg body weight) applied daily on two consecutive days.

A single application of a 25X dose of moxidectin 0.5% pour-on - 25 mL/10 kg body weight (providing 12.5 mg moxidectin/kg body weight).

g. Test Duration: 19 days

h. Pertinent Measurements/Observations: Physical examinations were conducted on Day -1 (day before treatment) and on the day of sacrifice. Body weight was measured on the day of allotment to treatment groups, on Experimental Day 1 which was the first day treatment was administered, and on the day of sacrifice. Venous blood samples, urine and feces were collected on Day -1 pre-treatment and Days 1, 2, 3, 4, 7, and 14 after treatment for hematology, clinical chemistry, urinalysis and fecal analysis. Health observations were made once hourly in the four hours after treatment on each treatment day. Thereafter, health observations were recorded twice daily and unforeseen circumstances were recorded once daily. Amounts of feed offered and consumed were recorded throughout the experiment. Necropsies were performed on Day 12, (7 days posttreatment) or Day 19 (14 days posttreatment) and all animals were evaluated for macroscopic pathology. All tissues from all treatment groups were examined microscopically.

4. Results:

a. Clinical Observations: Run-off (loss of product to the ground) was observed in the immediate post-application period in the test animals which received the 10X and 25X doses. Transient, mild salivation was observed in the two animals receiving the 5X dose level following the first treatment. The hypersalivation dissipated within one hour of treatment. A slight increase in salivation was again seen in one of the 5X-treatment animals following the Day 3 application.

The excessive salivation once more subsided to normal levels within one hour posttreatment. No test animals showed any other clinical signs attributable to pour-on treatment in the 7- to 14-day posttreatment observation period. No signs of irritation at the treatment site were noted at any observation throughout the study.

b. Feed and Water Consumption: Feed intakes were considered to be within normal variation for all animals in the study.

c. Body Weight: All calves in all groups gained weight over the time from treatment to necropsy.

d. Hematology/Serum Chemistry: Blood samples obtained from test animals at critical points throughout the study revealed no significant serum chemistry or hematology abnormalities.

e. Urinalysis: No test article-related effects were observed.

f. Fecal Examination: No test article-related effects were observed.

g. Gross and Histopathologic Observations: Euthanasia and postmortem examinations were performed on one animal per group on Day 7 following the last treatment. The remaining test animals were necropsied on Day 14 following the last treatment. No gross lesions suggestive of treatment-related toxicity were observed at necropsy. Similarly, microscopic evaluation of 41 different tissues (representative of all major organ systems) obtained at necropsy revealed no histopathologic changes indicative of a toxic drug effect.

5. Statistical Analysis: None

6. Conclusion: Application of moxidectin 0.5% pour-on solution at 5X the recommended dose for 5 consecutive days, 10X for 2 consecutive days and 25X for one day did not produce any significant adverse clinical or pathological effects.

B. Toxicity Test (1X, 3X, 5X Study) - Study Number B-93-6

1. Type of Study: The objective of the target animal toxicity study is to determine the safety of the drug product to the target animal and the signs and predictable effects (if any) of product-related toxicity.

2. Investigator: W. B. Epperson, D.V.M.
Cyanamid Agricultural Research Center
Princeton, NJ

3. General Design:

   a. Purpose: The purpose of this study was to evaluate the clinical and pathological effects of application of moxidectin 0.5% pour-on at 0.5, 1.0, and 2.5 mg moxidectin/kg body weight (1X, 3X, and 5X, respectively) along with a control (0 mg/kg body weight) for three consecutive days in cattle.

   b. Animals: Sixteen Angus crossbred steers (8) and heifers (8) weighing between 266 and 296 kg at treatment and 10-12 months of age were randomly assigned to four treatment groups (2 males and 2 females).

   c. Control: Vehicle

   d. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   e. Route of Administration: Topically along the back from the withers to the tailhead.

   f. Doses: Pour-on vehicle (no moxidectin) - 5 mL/10 kg body weight (providing 0 mg moxidectin/kg body weight) applied daily for three consecutive days.

      1X dose of moxidectin 0.5% pour-on - 1 mL/10 kg body weight (providing 0.5 mg moxidectin/kg body weight) applied daily for three consecutive days.

      3X dose of moxidectin 0.5% pour-on - 3 mL/10 kg body weight (providing 1.5 mg moxidectin/kg body weight) applied daily for three consecutive days.

      5X dose of moxidectin 0.5% pour-on - 5 mL/10 kg body weight (providing 2.5 mg moxidectin/kg body weight) applied daily for three consecutive days.

   g. Test Duration: 25 days

   h. Pertinent Measurements/Observations: Physical examinations were conducted on Day -1 (day before treatment) and on the day of sacrifice. Body weight was measured on the day of allotment to treatment groups, on Experimental Day 1 which was the first day treatment was administered, and on Day 22. Venous blood samples, urine (free catch) and feces were collected on Day -1 pretreatment and Day 22 after treatment for hematology, clinical chemistry, urinalysis and fecal analysis.

Health observations were made once hourly for four hours after treatment on each treatment day. Thereafter, health observations were recorded twice daily and unforeseen circumstances were recorded once daily. Amounts of feed offered and consumed were recorded throughout the experiment. Necropsies were performed on Day 23 to Day 25 and all animals were evaluated for macroscopic pathology. All tissues from all treatment groups were examined microscopically.

4. Results:

   a. Clinical Observations: Four animals (one in the 5X, one in the 3X and two in the vehicle group) showed very mild signs of increased salivation after the first treatment. Salivation started after treatment administered and continued through one hour posttreatment. On the second and third days of treatment only one animal in the vehicle group exhibited excess salivation. Twice daily observations indicated no noticeable adverse effects in the posttreatment period.

   b. Feed and Water Consumption: There was no difference in feed intake between treated groups over the treatment and posttreatment period.

   c. Body Weight: Average weight gains were similar for all groups. Statistical analysis of body weight gain revealed no significant differences between treatment groups.

   d. Hematology/Serum Chemistry: A comparison of pre- and posttreatment hematology, and clinical chemistry values indicated no biologically significant changes.

   e. Urinalysis: No test article-related effects were observed.

   f. Fecal Examination: No test article-related effects were observed.

   g. Gross and Histopathologic Observations: Euthanasia and necropsy were performed on all animals between 20 and 22 days following the last treatment. No gross lesions suggestive of treatment-related toxicity were observed at necropsy. Similarly, microscopic evaluation of 41 different tissues (representative of all major organ systems) obtained from the high-dose and placebo treatment groups at necropsy revealed no histopathologic changes indicative of a toxic drug effect.

5. Statistical Analysis: Results of hematology, clinical chemistry variables, feed intake and body weight gain of cattle were examined by analysis of variance (ANOVA) and analysis of covariance (ANCOVA).

6. Conclusion: Application of moxidectin 0.5% pour-on solution at 1X, 3X and 5X the recommended dose for three consecutive days did not produce any significant adverse clinical or pathological effects.

C. Ocular Safety - Study Number B-93-8

1. Type of Study: The study was performed to evaluate the irritant effects of direct exposure of the bovine eye to moxidectin pour-on.

2. Investigator: W. B. Epperson, D.V.M.
   Cyanamid Agricultural Research Center
   Princeton, NJ

3. General Design:

   a. Purpose: The purpose of this study was to evaluate the effect of accidental application of moxidectin 0.5% pour-on into the eyes of cattle.

   b. Animals: Four Angus crossbred steers weighing approximately 280 kg and between 10 and 12 months of age were used.

   c. Control: Sterile saline

   d. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

   e. Route of Administration: Intraocular instillation directly into the lower fornix of the eye.

   f. Doses: Three test animals were exposed to direct intraocular instillation of different volumes (0.25, 0.5 and 1 mL) of the moxidectin pour-on solution. The fourth animal served as a sham-treated control and was administered a similar 1 mL sterile saline treatment.

   g. Test Duration: 7 days

h. Pertinent Measurements/Observations: Ocular exams were performed on Day -1 (day before treatment) and Day 0 (day of treatment) prior to treatment and one hour posttreatment. Ocular exams were conducted daily until Day 6. Fluoroscein staining was performed as part of all ocular exams with the exception of the two exams performed on Day 0. A physical exam was conducted Day -1, and on Day 7, the final day of the study. The animals were observed twice daily, starting on Day -7 and ending on Day 7.

4. Results: Results of ocular and physical exams before treatment indicated that all animals were normal. In all cases the moxidectin pour-on was quickly removed from the eye by tearing and it resided in the periocular region below the eye by one hour posttreatment. No ocular abnormalities, aside from discharge, were noted at one hour posttreatment. There was no evidence of ocular inflammation caused by any of the treatments at any of the posttreatment examinations.

5. Statistical Analysis: None

6. Conclusion: A single application of up to a 5X dose of moxidectin 0.5% pour-on placed in the bovine eye did not create an adverse ocular reaction.

D. Breeding Bull Safety - Study Number B-92-24

1. Type of Study: Reproductive safety study in bulls.

2. Investigator: Robert G. Mortimer, M.S., D.V.M.
Colorado State University Agricultural Campus
Fort Collins, CO

3. General Design:

a. Purpose: To assess the effects of moxidectin at 3X the recommended dose on seminal quality and breeding performance of bulls.

b. Animals: Twelve sexually mature, virgin Hereford bulls, 20 to 25 months of age, were randomly divided into two treatment groups, with ten bulls in the moxidectin treatment group and two bulls in the control group. A total of 120 heifers, approximately 1 to 2 years old and weighing 302 to 497 kg were used for the breeding phase.

c. Control: Vehicle

d. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

e. Route of Administration: Topically along the back from the withers to the tailhead.

f. Doses: Ten bulls were treated with a 3X dose of moxidectin pour-on [3 mL/10 kg body weight (1.5 mg moxidectin/kg body weight)] which was applied in accordance with label directions. The two remaining bulls received a similar placebo treatment (vehicle) containing no moxidectin.

g. Pertinent Measurements/Observations: Breeding soundness exams (BSE) were conducted in accordance with the 1992 Society of Theriogenologists guideline. Two consecutive ejaculates of semen per day were collected and evaluated on Days -5, -3, and -1 pretreatment and Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112 and 119 posttreatment. Semen volume and concentration were also determined for each BSE day. Each bull was pastured with ten prostaglandin synchronized (dinoprost tromethamine administered twice 13 days apart) heifers for a 60-day breeding period. Libido assessments were made throughout the initial week of the breeding period. Pregnancy status of each heifer was determined 45 days following the end of the breeding period.

4. Results: Results of scrotal circumference, percent progressive mortality, sperm count per ejaculate, percent normal morphology, and sperm abnormalities are summarized in the table below. There were no significant differences in these parameters between the control and moxidectin-treated groups.

Response Variable	Group LS Mean/Mean for Control Bulls	Group LS Mean/Mean for Moxidectin-Treated Bulls
Scrotal Circumference (cm)	37.32[a]	37.08[a]
*Progressive Motile (%)	70.88[a]	69.08[a]
Sperm per Ejaculate (10^6)	4499.87	3860.11
Sperm per Ejaculate (log transformed count)	3.6532[a]	3.5866[a]
Morphology, Normal (%)	88.22[a]	88.17[a]
SPERM ABNORMALITY:		
Head (%)	3.31[a]	5.21[a]
*Midpiece (%)	0.11[a]	0.18[a]
Distal Midpiece Reflex (%)	5.41[a]	3.88[a]
*Tail (%)	0.02[a]	0.18[a]
Proximal Droplet (%)	0.95[a]	1.16[a]
*Distal Droplet (%)	1.00[a]	0.50[a]
*Other (%)	0.86[a]	0.10[a]
*Other Cells	0.00[a]	0.00[a]

*Covariate was not significant alpha=0.05

[a]LS Mean/Mean within a row with the same superscript did not differ at alpha=0.10.

There was no adverse effect on libido and ability to inseminate and impregnate females. The overall conception rates for the moxidectin group was 97% and 100% for the control group. There was no significant difference in the pregnancy rate between the treated and control animals. The proportion of bulls with 100% conception rate for the controls was not significantly different from that for the moxidectin-treated group, as analyzed by a Chi-square test at alpha=0.1.

5. Statistical Analysis: Weighted averages of two ejaculates per day were calculated from percent motility, sperm per ejaculate, percent normal sperm and percent individual sperm cell abnormalities, and a single measure of scrotal circumference was used for statistical analyses. Statistical analysis of covariance was applied to determine the treatment effect, with the pretreatment value as a covariate. A two-sided Student's t-test was used to compare the mean pretreatment values for different response variables in the control and the treated groups at alpha=0.10. The proportion of cows confirmed pregnant and the proportion of bulls making 100% of the assigned cows pregnant were compared between the control and the treated groups by Chi-square test at alpha=0.10.

6. Conclusion: A single topical application of moxidectin 0.5% pour-on at 1.5 mg/kg body weight (3X the recommended dose) on bulls did not have an adverse effect on scrotal circumference, serum quality, libido, and breeding performance.

E. Estral Cow Safety - Study Number B-92-22

1. Type of Study: Reproductive safety study in cows before, during, and after estrus and during early gestation.

2. Investigator: D. Owen Rae, D.V.M., M.P.V.M.
University of Florida Beef Research Unit
Gainesville, FL

3. General Design:

   a. Purpose: The objective of this study was to assess the effects of moxidectin at 3X the recommended dose on folliculogenesis, ovulation, postovulation, pregnancy, and calving rate in estrous cycling cows.

   b. Animals: One hundred and eighty two pastured Angus and crossbred beef cows, averaging 3 years of age were maintained under similar conditions. Cows were randomly assigned to five groups of 28 cows and three groups of 14 cows.

c. Control: Vehicle or no treatment

d. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

e. Route of Administration: Topically along the back of the withers to the tailhead.

f. Doses: After each cow was synchronized for estrous with a norgestomet implant and a norgestomet/estradial valerate injection, the test animals in the 28-cow groups were treated at least once with 3X dose levels of moxidectin pour-on [3 mL/10 kg body weight (1.5 mg moxidectin/kg body weight)] at one of five timepoints calculated to correspond with critical phases of the estrous cycle [folliculogenesis (Day -26 and Day -2), ovulation (Day 0) and 7, 14, 28 days post ovulation]. Two of the 14-cow groups were administered identical volumes of the formulation without moxidectin at multiple points during their estrous cycle consistent with the timing of the 28-cow group treatments. The last 14-cow group received no treatment.

g. Test Duration: 18 months

h. Pertinent Measurements/Observations: All cows were artificially inseminated on Day 0. Any cows returning to estrus after the AI breeding were bred naturally. At Day 48 or 51 (following the AI breeding), each cow was assessed rectally for pregnancy status, days pregnant, and body condition score. Cows determined to be pregnant to the Day 0 insemination were used in the determination of first service conception rate. Cows that calved within 290 days of the first service were used in the determination of the first service calving rate. All cows that calved were used to determine the total calving rate for all cows in the study. Only the cows calving as the result of the first breeding were used for the generation of the calving data (i.e., calf birth and 60 day weights, gross calf abnormalities, and health of the calf at birth and at the 60 day weighing). The primary parameters were first service pregnancy rate, first service calving rate, and calf normality (health, weight, growth to 60 days, and lack of congenital abnormalities). Adverse reactions to treatment, cow body weight, body condition score, and the total pregnancy and calving rates for all cows in the study were secondary parameters.

4. Results: The average pregnancy rate after the first insemination ranged from 46.4% to 64.3%. The total pregnancy rate based on palpation and calving information ranged from 89.3% to 100%. However, there were no significant differences in these pregnancy rates among the 8 treatment groups. No adverse reactions to moxidectin treatment were observed at the application site or in the general condition of the cows on treatment day and for the duration of the trial. The following table summarizes the number of cows per group, pregnancy and calving rates for the first service conception and total pregnancy and calving rates for all cows in the study.

Group	No. Cows in Group	Time of Treatment	# Cows Pregnant 1st service	Preg Rate 1st Service	Total Preg Rate	No. Cows Calving 1st Service	Calving Rate 1st Service
1	28	Moxidectin Day -26, and 2	16	57.1%	96.4%	16	57.1%
2	28	Moxidectin Day 0	15	53.6%	89.3%	14	50.0%
3	28	Moxidectin Day 7	16	57.1%	89.3%	15	53.6%
4	28	Moxidectin Day 14	13	46.4%	96.4%	13	46.4%
5	28	Moxidectin Day 28	13	46.4%	92.9%	13	46.4%
6	14	Vehicle Days -26, -2, 7, 28	7	50.0%	92.9%	7	50.0%
7	14	Vehicle Days 0, 7, 14	9	64.3%	100%	9	64.3%
8	14	No treatment	9	64.3%	100%	9	64.3%

The average calf weights at birth were relatively uniform (27.8 to 31.9 kg) and were not significantly different from each other. The majority of calves were healthy at birth except one stillbirth in each of Groups 2, 3, and 8. Another calf in Group 3 was born alive, but was weak and low in birth weight (12.7 kg). The calf was raised as an orphan due to poor maternal traits of the cow. No significant differences were observed in calf health among the eight treatment groups.

At the 60 day weighing, calves from the first service conceptions had an average weight range from 84.8 kg to 90.9 kg. There were no significant differences among the eight treatment groups. All calves were healthy at the 60 day weighing.

5. Statistical Analysis: Pregnancy rates and calving rates were analyzed by a Chi-square test. Calf weights were analyzed by a one-way analysis of variance with treatment groups compared using the least significant difference procedure. All comparisons were performed at the 0.10 level.

6. Conclusion: Cows treated with moxidectin 0.5 pour-on topically at 3 times the recommended dose (1.5 mg moxidectin/kg body weight) at folliculogenesis, ovulation, or postovulation on Days 7, 14, or 28, were not adversely affected in terms of conception, pregnancy maintenance, and the development, growth, or health of the fetus or calf.

F. Pregnant Cow Safety - Study Number B-93-1

1. Type of Study: Reproductive safety study in cows during early, mid, and late gestation.

2. Investigator: Larry R. Cruthers, Ph.D.
Professional Laboratory and Research Services
Corapeake, NC

3. General Design:

   a. Purpose: The purpose of this study was to determine the effects of moxidectin 0.5% pour-on at 3X (1.5 mg moxidectin/kg body weight) the recommended dose (0.5 mg moxidectin/kg body weight) on the general health, gestation characteristics, calf weights, calf deformities, and number of live calf births in three different groups of pregnant cows treated during early, mid or late gestation.

   b. Animals: One hundred and eighty mixed-breed beef cows of average age between 5 and 6 years that had produced at least one live calf previously were bred by natural service. Upon confirmation of pregnancy, the cows were assigned to four groups, I, II, III, and IV with 45 cows per group. The control group, I, consisted of three subgroups, Ia, Ib, and Ic, with 15 cows per subgroup and were treated with carrier vehicle during the first (Ia), second (Ib), and third (Ic) trimester of gestation. Each subgroup was paired with their respective treatment groups (II, III, and IV) and treated with carrier vehicle at the same time the moxidectin pour-on was applied to groups II, III, and IV. Most of the cows were nursing calves at the time of breeding.

   c. Control: Vehicle

   d. Dosage Form: Moxidectin 0.5% pour-on, 5 mg/mL

e. Route of Administration: Topically along the back of the withers to the tailhead.

f. Doses: Cows in the first three groups were treated with 3X dose levels of moxidectin pour-on [3 mL/10 kg body weight (1.5 mg moxidectin/kg body weight)] in accordance with label directions on three separate occasions during either early - (Group I - treated on days 55, 80 and 105 of gestation), mid- (Group II - treated on days 130, 155, and 180 of gestation) or late-gestation (Group III - treated on days 205, 230, and 255 of gestation). The fourth group was divided into three 15-cow control subgroups which were each treated with identical volumes of a placebo formulation concurrently with either Group I, II, or III.

g. Test Duration: 1 year

h. Pertinent Measurements/Observations: Calving rate, calf birth weight, 60-day weight, and average daily gain of calves were the parameters of interest.

4. Results: There was no significant difference in the number of healthy calves born to cows in any of the four treated groups or the health of the calves. The following table shows the number of calves born for each treatment group.

Treatment Group	Group ID	# of Cows	# of Cows w/o Calves (%)	# of Live Calves (%)*	# of Dead Calves (%)
Early Gestation					
Vehicle control	Ia	15	2 (13.3%)	13 (86.7%)	0
Moxidectin	II	45	3 (6.7%)	38 (84.4%)	4** (8.9%)
Mid Gestation					
Vehicle Control	1b	15	2 (13.3%)	13 (86.7%)	0
Moxidectin	III	45	2 (4.4%)	40 (88.9%)	3 (6.7%)
Late Gestation					
Vehicle Control	Ic	15	0	15 (100%)	0
Moxidectin	IV	44***	3 (6.8%)	40 (90.9%)	1 (2.3%)

*Three additional calves were born and orphaned. They were not included in the analysis due to uncertainty over their dams and treatment groups.

**One calf in this group was born alive and died within 2 hours. For statistical purposes, the calf was handled as a dead calf.

***One cow in this group died before treatment and was not replaced.

There were no statistically significant treatment effects on live births, dead births, or cows not producing a calf. Of the 179 cows participating in the trial, 170 cows produced a calf, of which 8 calves did not survive. Five of these calves were dystocias and assistance was necessary to complete the birth. No gross abnormalities were observed in any of the dead calves, with the exception of one calf in Group III that had an atrial septal defect that was not of enough significance to cause death. There were no abnormalities noted in any of the calves at the observations made at less than 48 hours postpartum or at examination at approximately 60 days. The following table summarizes the calf data. The three orphaned calves are not included in the table or the analysis.

Treatment Group	Group ID	Weight 1 (lb)	Weight 2 (lb)	ADG (lb/day)
Early Gestation				
Vehicle	Ia	74.6[a]	180.7[a]	1.77[a]
Moxidectin	II	74.3[a]	187.6[a]	1.90[a]
Mid Gestation				
Vehicle	Ib	73.7[a]	188.3[a]	1.87[a]
Moxidectin	III	77.1[a]	194.3[a]	1.94[a]
Late Gestation				
Vehicle	Ic	69.4[a]	192.1[a]	1.85[a]
Moxidectin	IV	75.8[b]	192.8[a]	1.93[a]

[a,b]Means of control and treated groups for a common variable and the same gestation phase with different superscripts differ at P<0.10.

5. Statistical Analysis: Each of the moxidectin treated groups of cows were compared to their respective controls. Cow weights and body condition scores were tested for statistical significance using a one-way analysis of variance at the 10% level. The effect of treatment on live births produced from cows in the various treatment groups were analyzed by first coding each birth as 1 for a dead birth; 2 for a live birth; or 0 for no birth. These data were analyzed using Fisher's Exact Test for a 2X3 contingency table (2 treatments and 3 categories) and also a Chi-square test at the 10% level. Calf weights, both at less than or equal to 2 days of age (weight 1) and at approximately 60 days of age (weight 2) , as well as average daily gain over this time period, were analyzed using ANOVA with treatment, calf sex, and treatment X calf sex as sources of variation.

6. Conclusion: This trial demonstrated that moxidectin 0.5% pour-on was safe when administered to pregnant beef cows at 3X the recommended dose on three occasions during early, mid, or late gestation. There were no negative effects of treatment on the number of live calves born, the health of the calves, their weights during the first 48 hours postpartum and at approximately 60 days of age, or their average daily gain over this time period.

G. Safety in Youngest Age Tested - Study Number 0863-B-US-10-96

1. Type of Study: The objective of the study was to evaluate the safety of the product in newborn calves.

2. Investigator: Larry R. Cruthers, Ph.D.
   Professional Laboratory and Research Services, Inc.
   Corapeake, NC

3. General Design:

   a. Purpose: The study was designed to evaluate the clinical effects of moxidectin 0.5% pour-on in newborn calves treated at the recommended dose level (0.5 mg/kg body weight) or 3X the recommended dose level (1.5 mg/kg body weight) and concurrently nursing from dams treated at the recommended dose level.

   b. Animals: Thirty-one cross-bred beef calves, weighing between 22.7 and 47.6 kg, and their dams were randomly assigned to one of three treatment groups. The study was designed to have ten animals per treatment group; however, the dam of one calf treated with the recommended dose level did not allow its calf to nurse. This calf was removed from the study on Day 8 and a replacement calf was subsequently added to this treatment group.

   c. Controls: vehicle

   d. Dosage Form: moxidectin 0.5% pour-on, 5 mg/mL

   e. Route of Administration: Topically along the back from the withers to the tailhead

   f. Doses: pour-on vehicle (no moxidectin) - applied to calves at 3 mL/10 kg body weight (providing 0 mg moxidectin/kg body weight) and their dams at 1 mL/10 kg body weight (providing 0 mg moxidectin/kg body weight) in a single application within 12 hours of parturition.

      1X dose moxidectin 0.5% pour-on - applied to calves at 1 mL/10 kg body weight (providing 0.5 mg moxidectin/kg body weight) and their dams at 1 mL/10 kg body weight (providing 0.5 mg moxidectin/kg body weight) in a single application within 12 hours of parturition.

3X dose moxidectin 0.5% pour-on - applied to calves at 3 mL/10 kg body weight (providing 1.5 mg moxidectin/kg body weight) and their dams at 1 mL/10 kg body weight (providing 0.5 mg moxidectin/kg body weight) in a single application within 12 hours of parturition.

g. Test Duration: 14 days

h. Pertinent Parameters Measured: Health observations of the calves and cows were made twice daily, once in the morning and once in the afternoon, for 14 days posttreatment. Blood was sampled from calves pretreatment and on Days 2 and 7 posttreatment for analysis of serum iron. Ocular examinations were performed on calves on Days 1, 2 and 3 posttreatment.

4. Results:

a. Clinical Observations: Twice daily observations over a two-week posttreatment period indicated no noticeable adverse reactions in any of the calves or cows that were attributed to treatment with moxidectin.

b. Ocular Examinations: No treatment-related abnormalities were observed in calves on Days 1, 2 or 3 posttreatment.

c. Serum Iron Analyses: All pretreatment and Day 2 posttreatment serum iron values were within the normal range for calves. The average Day 7 serum iron values were elevated and outside of the normal range (57 to 162 µg/dL) for calves in the control and the two treated groups. There were no significant differences in serum iron between control and treated calves either pretreatment or on Days 2 and 7 posttreatment.

5. Statistical Analysis: None

6. Conclusions: Moxidectin 0.5% pour-on applied at 1X and 3X the recommended dose level to newborn calves (<12 hours old) who were nursing dams concurrently treated with the recommended dose level, did not produce any adverse clinical effects, ocular signs or serum iron concentrations.

VI. HUMAN FOOD SAFETY

A. Toxicology

Genotoxicity Studies

Moxidectin was tested in a battery of four different short-term genetic toxicity experiments. These studies included a bacterial/microsome mutagenicity (Ames) test, a mammalian cell CHO/HGPRT mutagenicity assay, an *in vivo* chromosomal aberration test and an unscheduled DNA synthesis assay. The moxidectin test article used in all four of these tests had a purity of 88.5%. Specific information pertaining to the conduct and outcome of these four genotoxicity studies is briefly summarized below.

1. Bacterial/Microsome Mutagenicity Assay (Ames Test)

   a. Identification: Study performed by K. A. Traul and staff at American Cyanamid's Princeton, New Jersey testing facility. Experimental period: July 5, 1989 to March 22, 1990. Cyanamid Genetic Toxicology Study No.: 89-02-01.

   b. Procedure: The microbial/microsome mutagenicity plate incorporation assay was used to determine the ability of the test article (moxidectin) at concentrations ranging from 54 to 2000 µg/plate with and without added metabolic activation in the form of Aroclor-induced rat liver S-9 to cause genetic damage (either base-pair substitution or frame shift mutation) in the following six bacterial tester strains: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538 and *E. coli* WP-2uvrA-. Five dose levels were used with three replicates per dose point. The high dose level was limited by the solubility of moxidectin in the test system. The assay was done twice to confirm the results.

   c. Findings: Moxidectin was not mutagenic at dose levels up to and including 2000 µg/plate in any of the six bacterial tester strains.

2. Mammalian Cell CHO/HGPRT Mutagenicity Test

   a. Identification: Study performed by K. A. Traul and staff at American Cyanamid's Princeton, New Jersey testing facility. Experimental period: July 27, 1989 to April 9, 1990. Cyanamid Genetic Toxicology Study No.: 89-05-002.

   b. Procedure: The mammalian cell mutagenicity assay was used to determine the ability of the test article (moxidectin) at concentrations ranging

from 5 to 10 µg/ml with and without added metabolic activation in the form of Aroclor-induced rat liver S-9 to cause genetic damage (mutations) at the HGPRT locus of the Chinese hamster ovary (CHO) K_1BH_4 cells present in the test system. Five dose levels were used with two replicates per dose point. The assay was done twice to confirm the results.

c. Findings: The results of the CHO/HGPRT Mutagenicity Test were inconclusive and unresolved.

3. *In Vivo* Chromosome Aberration Assay in Rat Bone Marrow Cells

a. Identification: Study performed by R. K. Sharma and staff at American Cyanamid's Princeton, New Jersey testing facility. Experimental period: October 27, 1989 to April 10, 1990. Cyanamid Genetic Toxicology Study No.: 89-14-002.

b. Procedure: Male and female Sprague-Dawley rats were given a single oral administration of either 15, 30 or 60 mg moxidectin/kg body weight by gavage and euthanized either 12, 24 or 48 hours post treatment for the collection of bone marrow. The test animals were treated with intraperitoneal injections of colchicine two-three hours prior to sacrifice to arrest dividing cells at metaphase. The bone marrow cells were analyzed microscopically for evidence of chromosomal aberrations.

c. Findings: The results of the *In Vivo* Chromosome Aberration Assay in Rat Bone Marrow Cells were inconclusive and unresolved.

4. Unscheduled DNA Synthesis in Primary Hepatocytes

a. Identification: Study performed by R. D. Curren and staff at testing facilities operated by Microbiological Associates, Inc. in Rockville, Maryland. Experimental period: December 12, 1989 to October 18, 1990. MBA Study No.: T9090.380025.

b. Procedure: Five doses of moxidectin were tested. Test plates seeded with 5 x 10^5 rat hepatocytes/plate were treated with 0.1 to 5 µg/ml of moxidectin (doses ≥ 10 µg/ml were not analyzed for UDS due to excessive toxicity). All plates received ^{3}H-thymidine at a concentration of 10 µC/ml. Positive and negative controls were run concurrently. After 18-20 hours the plates were processed and slides prepared for microscopic evaluation. Evaluation for UDS was determined by a standardized procedure involving quantification of increases in mean net nuclear count.

c. Findings: Rat hepatocyte cell cultures exposed to moxidectin concentrations of up to 5 µg/ml for 18-20 hours showed no significant increase in unscheduled DNA synthesis.

Repeated-Dose Toxicity Studies

Two dietary toxicity studies were conducted in which moxidectin was fed continuously to laboratory rats and dogs for three months. In both experiments, moxidectin test article with a purity of 81.3% was incorporated in the test animal diet at constant concentrations measured in parts per million (ppm) of moxidectin. Diets were formulated to correct for purity. The dose levels (expressed in mg/kg body weight/day) were calculated from food consumption and body weight data collected as part of each experiment. Specific information regarding the conduct and outcome of these two feeding studies is briefly summarized below.

1. 13-Week Rat Continuous Feeding Study

a. Identification: Study performed by J. E. Fischer and staff at American Cyanamid's Princeton, New Jersey testing facility. Experimental period: April 29, 1988 to August 5, 1988. Cyanamid Toxicology Report No.: AX89-1.

b. Design: Twenty Sprague-Dawley [Crl:CD(SD)BR] rats/sex/group were fed diets with either 0, 25, 50, 100 or 150 ppm concentrations of moxidectin for 13 weeks.

c. Findings: Slight depression in body weight gain in all 100 ppm test animals, increased kidney and adrenal gland weights in 100 ppm females and slight increase in hypersensitivity to touch during first two weeks of experimental period for all 100 and 150 ppm test animals. No signs of toxicity were noted in the 50 and 25 ppm treatment groups.

d. Conclusion: The NOEL for this study was 50 ppm (~3.9 mg/kg body weight/day).

2. 91-Day Dietary Toxicity Study in Dogs

a. Identification: Study performed by G. E. Schulze and staff at testing facilities operated by Hazelton Laboratories America, Inc. in Vienna, Virginia. Experimental period: January 26, 1989 to April 28, 1989. HLA Study No. 362-198.

b. Design: Four purebred Beagle dogs/sex/group were continuously fed diets with either 0, 10, 30 or 60 ppm concentrations of moxidectin for 91 days.

c. Findings: A dose response increase in incidence of lacrimation was observed in treated dogs. At 60 ppm, lacrimation was associated with salivation, tremors, and ataxia. Tremors were also observed in one low-dose male during weeks 1-3 and 13. Statistically significant reductions in food intake and body weight gains were reported in both male and female dogs in the 30 and 60 ppm treatment groups.

d. Conclusion: Based on the dose-response increase in incidence of lacrimation in treated animals and the occurrence of tremors in low-dose males, a NOEL could not be established for this study.

Reproductive Toxicity Studies

The effects of continuous treatment with various levels of moxidectin on fertility and reproductive performance were evaluated in a three generation (two-litter) study carried out in laboratory rats. The moxidectin test article with a purity of 88.6% was incorporated in the test animal diet at constant concentrations measured in parts per million (ppm) of moxidectin. Diets were formulated to correct for purity. The four treatment levels were selected on the basis of a pilot study. The dose levels (expressed in mg/kg body weight/day) were calculated from food consumption and body weight data collected as part of the experiment. This reproductive toxicity experiment is summarized below.

1. Three Generation (Two-Litter) Rat Reproduction Study

a. Identification: Study performed by R. E. Schroeder and staff at testing facilities operated by Bio/dynamics, Inc. in East Millstone, New Jersey. Treatment period: October 11, 1989 to July 16, 1991. Bio/dynamics Project No.: 89-3496.

b. Design: Twenty-five Sprague Dawley [Crl:CD(SD)COBS] rats/sex/group were continuously fed diets with either 0, 1, 2, 5 or 10 ppm concentrations of moxidectin beginning at 10 weeks prior to mating and extending to terminal sacrifice. As diagrammed below, males and female from each treatment group were mated to produce two successive litters. Offspring from the second litter were randomly selected, given the same level of moxidectin their parents had received and mated to also produce two successive second generation litters.

Reproductive Progression Used in Study

$$\text{Initial Parents } (P_1)^{a} \rightarrow \begin{cases} 1^{st} \text{ Litters } (F_{1a}) \\ 2^{nd} \text{ Litters } (F_{1b}) \rightarrow [F_1]^{ab} \rightarrow \begin{cases} 1^{st} \text{ Litters } (F_{2a}) \\ 2^{nd} \text{ Litters } (F_{2b}) \rightarrow [F_2]^{ab} \rightarrow \begin{cases} 1^{st} \text{ Litters } (F_{3a}) \\ 2^{nd} \text{ Litters } (F_{3b}) \end{cases} \end{cases} \end{cases}$$

[a]Treatment periods: P_1 generation males (October 11, 1989 to April 26, 1990) and females (October 11, 1989 to May 11, 1990); F_1 generation males (May 16 to November 21, 1990) and females (May 16 to December 12, 1990); F_2 generation males (December 19, 1990 to June 26, 1991) and females (December 19, 1990 to July 16, 1991).

[b]F_1 parents selected randomly from second P_1 litter (F_{1b}) of corresponding treatment group; F_2 parents selected randomly from second F_1 litter (F_{2b}) of corresponding treatment group.

c. Findings: Reduced body weights in the 10 ppm treatment group were observed in the F_1 (statistically significant) and F_2 (not statistically significant) parental males. In the 10 ppm treatment group, decreased pup survival was observed in F_{1a} pups during the entire lactation period, in F_{2a} pups mainly between Days 0-4 of lactation and in F_{3a} pups between Days 4-21 of lactation. The decreased pup survival resulted in increased percentages of litters with pup mortality in the 10 ppm F_{1a}, F_{2a} and F_{3a} litters during the same respective times during the lactation period. The 1, 2 and 5 ppm dose level resulted in no treatment-related effects in the P_1, F_1 and F_2 parents, reproductive performance, litter characteristics or the rat pups.

d. Conclusion: The NOEL for this study was 5 ppm (~0.4 mg/kg body weight/day).

Developmental Toxicity Studies

The teratogenic potential of moxidectin was evaluated in two experiments involving rodent and non-rodent laboratory animal species (rat and rabbit). In both studies, the moxidectin was administered by gavage as part of a corn oil solution which was formulated to correct for the 88.5% (rat) and 85.3% (rabbit) purity of the test material.

Specific information regarding the conduct and outcome of these two teratology studies is briefly summarized below.

1. Oral Developmental Toxicity Study in Rats

a. Identification: Study performed by A. M. Hoberman and staff at testing facilities operated by Argus Research Laboratories, Inc. in Horsham, Pennsylvania. Treatment period: January 2-17, 1989. Argus Project No.: 101-006.

b. Design: Between 23 and 25 pregnant Sprague Dawley [Crl:CD(SD)BR] rats/group were administered either 0, 2.5, 5, 10 or 12 mg/kg body weight/day dose levels of moxidectin in a corn oil solution by gavage on Days 6 through 15 of their gestation period. Cesarean delivery of each dam's litter was accomplished on Day 20 of gestation.

c. Findings: Statistically significant reductions in food consumption were recorded in both the 10 and 12 mg/kg/day treatment groups with consequent decreased maternal body weights in these test animals. Increases in the incidence of fetal alteration (cleft palate) were noted in the 10 mg/kg/day (not statistically significant) and 12 mg/kg/day (statistically significant) treatment groups. Malformations were only seen at maternally toxic levels. No treatment-related effects were noted in the dams or offspring in the 2.5 and 5 mg/kg body weight/day treatment groups.

d. Conclusions: The maternal and developmental NOEL for this study was 5 mg/kg body weight/day. Moxidectin is neither a selective developmental toxicant nor a teratogen in rats.

2. Oral Developmental Toxicity Study in Rabbits

a. Identification: Study performed by E. A. Lochry and staff at testing facilities operated by Argus Research Laboratories, Inc. in Perkasie, Pennsylvania. Treatment period: July 31, 1989 to August 12, 1989 Argus Project No.: 101-007.

b. Design: Between 14 and 18 pregnant New Zealand White [Hra:(NZW)SPF] rabbits/group were administered either 0, 1, 5, or 10 mg/kg body weight/day dose levels of moxidectin in a corn oil solution by gavage on Days 7 through 19 of their gestation period. Cesarean delivery of each dam's litter was accomplished on Day 29 of gestation.

c. Findings: Statistically significant increases in the incidence of abnormal feces (dried, soft or liquid) and decreases in maternal food consumption and weight gain were reported in both the 5 and 10 mg/kg/day treatment groups with consequent decreased maternal body weights in these test animals. The 10 mg/kg/day group had

smaller litter size and higher percentage of dead or resorbed conceptuses per litter than the other groups. No gross lesions, soft tissue, or skeletal abnormalities that could be related to treatment were found in the fetuses.

d. Conclusions: The maternal and developmental NOEL for this study were 1 mg/kg body weight/day and 5 mg/kg body weight/day, respectively. Moxidectin is neither a selective developmental toxicant nor a teratogen in rabbits.

Chronic Toxicity and Carcinogenicity Studies

Chronic dietary toxicity studies were conducted in laboratory mice, rats and dogs. In each experiment the test article was incorporated in the test animal diet at constant concentrations measured in parts per million (ppm) of moxidectin and fed continuously for one year to dogs and for two years to the mice and rats. Diets were formulated to correct for the 88.5% (dog) and 81.5% (mouse and rat) purity of the test article. The dose levels (expressed in mg/kg body weight/day) were calculated from food consumption and body weight data collected as part of each experiment. Study descriptions and conclusions determined from the data collected in these three experiments are summarized below.

1. One-Year Dietary Toxicity Study in Dogs

a. Identification: Study performed by G. E. Schulze and staff at testing facilities operated by Hazelton Washington, Inc. in Vienna, Virginia. Experimental period: July 17, 1989 to July 19, 1990. HLA Study No. 362-200.

b. Design: Six purebred Beagle dogs/sex/group were continuously fed diets with either 0, 10, 20, or 45 ppm concentrations of moxidectin for one year.

c. Findings: Although not statistically significant, the average body weights for both males and females in the 45 ppm treatment group were reduced. Decreases in mean ovary, heart, liver and kidney weights for the 45 ppm females were also noted. No treatment-related effects were seen in the 10 and 20 ppm test animals.

d. Conclusion: The NOEL for this study was 20 ppm (~0.5 mg/kg body weight/day).

2. Two-Year Dietary Chronic Toxicity and Oncogenicity Study in Mice

a. Identification: Study performed by E. I. Goldenthal and staff at testing facilities operated by the International Research and Development Corporation in Mattawan, Michigan. Experimental period: December 15, 1989 to December 17, 1991. IRDC Project No. 141-031.

b. Design: Sixty-five Charles River CD-1 mice/sex/group were continuously fed diets with either 0, 15, 30, or 60/50 ppm concentrations of moxidectin for two years. The high-dose dietary level was reduced from 60 ppm to 50 ppm after the first eight weeks of the study due to a significant number of deaths in the high-dose male and female test animals.

c. Findings: A significant treatment-related increased mortality in female 50 ppm test animals was observed toward the end of the experiment. No treatment-related effects were observed in the 15 and 30 ppm test animals. No evidence of carcinogenicity was noted in this study.

d. Conclusion: The NOEL for this study was 30 ppm (~5.0 mg/kg body weight/day).

3. Two-Year Dietary Chronic Toxicity and Oncogenicity Study in Rats

a. Identification: Study performed by T. Zoetis and staff at testing facilities operated by Hazelton Washington, Inc. located in Vienna, Virginia. Experimental period: January 11, 1990 to January 17, 1992. HWA Study No.: 362-202.

b. Design: Sixty-five Sprague-Dawley [Crl:CD(SD)BR]rats/sex/group were continuously fed diets with either 0, 15, 60, or 120/100 ppm concentrations of moxidectin for two years. The high-dose dietary level was reduced from 120 ppm to 100 ppm due to increased mortality, abnormal clinical signs, and depressed body weight gains in the high-dose female test animals in the first eight weeks of the study.

c. Findings: There were no treatment-related effects at any dose level during the study, except for those associated with the deaths which occurred in the high-dose (120 ppm) female treatment group during the first eight weeks of the experiment. No evidence of carcinogenicity was noted in this study.

d. Conclusion: The NOEL for this study was 100 ppm (~6.0 mg/kg body weight/day).

B. Safe Concentration of Residues

The lowest NOEL in the most sensitive species obtained in the battery of toxicity studies previously described in Section VI A is 0.4 mg/kg bw/day. This NOEL was determined in the three generation (two litter) rat reproduction study. In the absence of any structural relationship to any known carcinogen and the experimentally demonstrated lack of reproductive or oncogenic effects, the appropriate safety factor to be applied to this long-term study NOEL is 100. Applying this 100-fold safety factor to the 0.4 mg/kg bw/day NOEL results in a calculated acceptable daily intake (ADI) of up to 0.004 mg moxidectin/kg body weight/day. The calculation to achieve this value is presented below:

ADI = 0.4 mg moxidectin/kg/day (NOEL) ÷ 100 (safety factor) = 0.004 mg moxidectin/kg/day

The safe concentration of moxidectin residues in each of the four major edible tissues of cattle (muscle, liver, kidney and fat) is determined by using the ADI (in micrograms/kg body weight/day), the weight in kg of an average adult (60 kg) and the estimated amount of each edible tissue consumed per day in grams using the following relationship:

Safe Concentration (ppm) = ADI (µg/kg/day) x 60 kg ÷ edible tissue consumption value (g/day)

The consumption values employed in these calculations are taken from Section IV (B) of the Center for Veterinary Medicine's "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals" (revised July 1994). The safe concentration of moxidectin residue for each edible cattle tissue and the associated consumption value used in its calculation are listed below.

Edible Beef Tissue	Daily Consumption (grams)	Safe Concentration (ppm)
Muscle	300	0.8
Liver	100	2.4
Kidney	50	4.8
Fat	50	4.8

C. Total Residue and Metabolism

The levels of total drug-related residues of moxidectin in the edible tissues of cattle were determined in a series of three residue studies conducted using [^{14}C]-labeled moxidectin administered either by subcutaneous injection or topical application. For comparison, similar experimentation was also carried out in laboratory rats. These studies are summarized below.

1. Total Residue and Metabolism in Cattle

1.1 Absorption, Distribution, Excretion and Biotransformation of [^{14}C]-Moxidectin Administered by Injection to Steers

a. Identification: Study conducted by J. A. Zulalian, Ph.D., and staff at American Cyanamid's Princeton, New Jersey testing facility. Experimental period: May 23, 1990 to July 31, 1990. Report No.: PD-M 28-34.

b. Design: Three Hereford steers with an average weight of 224 kg were given a single subcutaneous administration of an injectable formulation providing 0.2 mg [^{14}C]-labeled moxidectin/kg body weight. Total urine and feces were collected daily from these treated steers. A fourth Hereford steer weighing 225 kg which served as a control received a single subcutaneous injection of a comparable volume of the same formulation containing no [^{14}C]-labeled moxidectin. The control steer was sacrificed six days following treatment and the treated steers were sequentially sacrificed on 7, 14 and 28 days posttreatment. Samples of 25 different tissues and body fluids were harvested for analysis. Total [^{14}C] residues were determined in all tissue, feces and urine samples to evaluate the absorption, distribution and excretion of the radioactivity. Selected samples were also used to assess the biotransformation of moxidectin. Additional *in vitro*

metabolism studies using steer liver microsomes and Aroclor-1254 S9 rat liver homogenates were performed to confirm the identification of the metabolites derived in the *in vivo* steer study.

c. Findings: Total radioactivity recovered in all collected samples accounted for 73%, 71% and 77% of the administered dose at 7, 14 and 28 days posttreatment, respectively. The primary route of excretion was through the feces accounting for 32%, 41% and 58% of the administered dose at each respective sequential sacrifice time point. A maximum of 3% of the radioactivity was recovered in the urine. Total residue levels in all tissues declined steadily throughout the 28-day time period demonstrating the absence of bioaccumulation and were 10 to 40 times higher in fat than in the other major edible tissues (muscle, kidney and liver). The extractability of the total [^{14}C] was greater than 90% in all edible tissues and feces indicating the absence of significant bound residues. Qualitatively similar profiles of moxidectin and seven metabolites were detected in all tissues at the three sacrifice times. Moxidectin was the major component accounting for between 75% and 90% of the radioactivity in fat. Only two metabolites (C-29/C-30 hydroxymethyl and C-14 hydroxymethyl) contributed more than 5% of the total residual radioactivity in any tissue at any sampling point. The remaining minor metabolites were all mono- and di-hydroxylation products of moxidectin.

d. Conclusions: The primary route of excretion is via feces. Because residue levels in fat are 10-40 times higher than other edible tissues, fat is the appropriate target tissue for residue monitoring purposes. The steady decline of total residue levels over time shows the absence of bioaccumulation and the greater than 90% extractability of total [^{14}C] confirms the absence of significant bound residues. The parent molecule, which generally accounts for 80% of the total residue in fat, is the major residue, establishing unaltered moxidectin as the marker residue. Hydroxylation is the principal route of biotransformation in cattle.

1.2 Biotransformation of [^{14}C]-Moxidectin in Steers When Applied Topically As A Pour-On

a. Identification: Study conducted by S.-S Wu, Ph.D., and staff at American Cyanamid's Princeton, New Jersey testing facility.

Experimental period: April 23, 1992 to August 31, 1992. Report No.: PD-M 29-43.

b. Design: Six Hereford steers with an average weight of 159 kg were given a single application along the backline of a pour-on formulation providing 0.5 mg [^{14}C]-labeled moxidectin/kg body weight. Two additional Hereford steers with an average weight of 156 kg which served as controls and were similarly treated with a comparable volume of the same formulation containing no [^{14}C]-labeled moxidectin. Total urine and feces were collected daily from the treated steers. Groups of one control and three treated steers were sacrificed 2 and 14 days following treatment. Samples of loin muscle, liver, kidney, back fat and omental fat were taken for analysis. Total [^{14}C] residues in these tissues and the excreta were determined by radioassay (limit of detection; 2 ppb). Residues in tissues and feces were extracted and characterized by high performance liquid chromatography.

c. Findings: Total [^{14}C] residues in the tissues from the steers sacrificed two days after treatment were 7-10 ppb in omental fat; <2-7 ppb in back fat; 2-4 ppb in liver and <2 ppb in kidney and muscle Due to these extremely low residue levels, no characterization of these residues was possible. The 14-day posttreatment residues levels were 33-259 ppb in omental fat; 12-129 ppb in back fat; 5-26 ppb in liver, 3-18 ppb in kidney and <2-3 ppb in muscle. Extractability of total [^{14}C] residues was greater than 86% in tissues 90% in feces. The radioactive profiles were qualitatively similar for all tissues. Unaltered moxidectin was the only significant component in both omental and back fat accounting for >75% of the residue. No single metabolite contributed more than 5% of the total residue in fat. A minimum of five metabolites was detected in the other tissues. Of these, the same two monohydroxylated derivatives of the parent compound identified in the previous [^{14}C] injectable study predominated. Feces was the principal route of excretion.

d. Conclusions: The distribution, excretion and biotransformation of moxidectin in steers is similar when administered by injection or applied topically as a pour-on. These data confirm that moxidectin in fat is approximately 80% of the total residue in fat after injectable and pour-on treatment.

1.3 Residue Profile in the Fat of Heifers and Steers Treated By Subcutaneous Injection with [^{14}C]-Moxidectin.

a. Identification: In-life experimentation conducted by Charles Heird, Ph.D., and staff at Southwest Bio-Labs, Inc., Las Cruces, New Mexico. Analytical component performed by S.-S. Wu and staff at American Cyanamid's Princeton, New Jersey testing facility. Experimental period: November 12, 1996 to March 24, 1997. Report No.: MET 97-006.

b. Design: Twelve English crossbred cattle (four steers and eight heifers) with an average weight of 226 kg were given a single subcutaneous administration of an injectable formulation providing 0.2 mg [^{14}C]-labeled moxidectin/kg body weight. An additional English crossbred steer and heifer with an average weight of 225 kg served as untreated controls. The treated cattle were randomly assigned to four groups consisting of one steer and two heifers. These groups were sequentially sacrificed 3, 7, 14 and 28 days after treatment and omental and back fat as well as injection site tissues were collected for analysis. The magnitude of [^{14}C] residues (TRR) was measured by radioassay (limit of quantitation: 5 ppb). The [^{14}C]-moxidectin-derived residue profile and the ratio of parent compound to TRR in fat was determined by high performance liquid chromatography.

c. Findings: Extractability of radiolabeled residues in all omental and back fat samples was 99-100%. Unaltered moxidectin was identified as the major residue accounting for 84% (steers) and 83% (heifers) of the TRR in the omental fat and 80% (steers) and 81% (heifers) of the TRR in the back fat. Overall, moxidectin accounted for 82% of the total residue in fat. The two monohydroxylated moxidectin metabolites (C-29/C-30 hydroxymethyl and C-14 hydroxymethyl) identified in previous studies were observed at levels <10% of the TRR.

d. Conclusions: Unaltered moxidectin represents approximately 82% of the TRR in the omental and back fat of both male and female cattle. The metabolite profiles seen in both steers and heifers are also qualitatively and quantitatively very similar.

2. Comparative Metabolism in Rats

1.1 Absorption, Distribution, Excretion of [^{14}C]-Moxidectin in Rats

a. Identification: Study conducted by S.-S. Wu, Ph.D., and staff at American Cyanamid's Princeton, New Jersey testing facility. Experimental period: May 15, 1990 to July 8, 1991. Report No.: PD-M 28-33.

b. Design: Two groups of five male and five female Sprague-Dawley CD albino rats [Crl:CD(SD)] were given a single low or high oral administration containing 1.5 or 12 mg [^{14}C]-labeled moxidectin/kg body weight, respectively. Urine and feces were collected for seven days following treatment, then the test animals were sacrificed and tissues/organs/body fluids were harvested for analysis along with the urine and feces for determination of mass balance. A third treatment group consisting of 15 male and 15 female CD(SD) albino rats were administered the 1.5 mg [^{14}C]-labeled moxidectin/kg body weight dose level orally for seven consecutive days. Evenly distributed subgroups were sequentially sacrificed a 6, 24, 72, 120 and 168 hours posttreatment and liver, kidney, muscle and fat tissues were collected to determine the nature and depletion of the [^{14}C] residues.

c. Findings: In both the high- and low-dose groups feces was the primary route of excretion accounting for between 59.7-91.3% of the administered radioactivity in all rats over the seven-day test period. Contrastingly, less than 2% of the radioactivity was found in the urine during the seven-day period. Of all the tissues analyzed, the highest residue levels were found in fat. Extractability of residues from tissues and feces was between 85-99% demonstrating the absence of bound residues. Metabolite characterization showed unaltered moxidectin was the only significant residue in both tissues and feces. The minor metabolites consisted of the two monohydroxylated moxidectin derivatives seen in cattle and a third hydroxylated metabolite only identified in the rat. This metabolite profile indicates the principal route of moxidectin metabolism in the rat is hydroxylation.

d. Conclusions: The metabolism of moxidectin by cattle and rats is qualitatively very similar. In both species moxidectin is excreted primarily in feces with only limited amounts voided in the urine. Due to the highly lipophilic nature of the drug, the proclivity for substantially greater moxidectin residues in fat relative to the other major tissue types is also seen in both species. The primary component of these residues in each

species is the parent compound accounting for between 75% to 90% of the total residues in the fat of both cattle and rats. The metabolic profiles in both species are also very comparable. In both cattle and rats the primary route of metabolism is hydroxylation. The two monohydroxylated derivatives of the parent compound identified as metabolites in cattle are also found in rats. The only species difference is the presence of a third hydroxylated metabolite which was only identified in rats. These similarities confirm the suitability of utilizing the rat in toxicity studies to evaluate the human food safety of moxidectin.

D. Selection of Marker Residue and Target Tissue

As demonstrated in the previously summarized [^{14}C]-moxidectin metabolism studies in cattle, the predominant residue found in fat of moxidectin-treated cattle is the unaltered parent compound (80% of the total residue) making moxidectin the appropriate marker residue to be used in tissue residue depletion experimentation. Due to the highly lipophilic nature of moxidectin, the highest levels of total drug-related residues and slowest residue depletion are found in fat, establishing fat as the appropriate target tissue.

E. Cold Tissue Residue Depletion in Cattle

Depletion of the marker residue in fat and muscle was demonstrated in an experiment specifically designed to evaluate the period of peak residues resulting from treatment with the recommended dose level of the final moxidectin 0.5% pour-on formulation under weather conditions conducive to optimum uptake of the drug, characterize application site residue levels and assess the depletion of tissue residue concentrations over five posttreatment intervals.

a. Identification: Study performed by L. S. de Montigny, DVM, and staff at American Cyanamid's Princeton, New Jersey testing facility. Experimental period: August 1, 1996 to February 13, 1997. Study No.: 0863-B-US-7-96.

b. Design: Thirty-three Angus and Angus crossbred cattle (17 heifers and 16 steers) weighing an average of 335 kg were randomly assigned to five, six-animal treated groups with equal sex distribution and an untreated control group (two heifers and one steer). The treated groups received a single topical application of the final 0.5% pour-on formulation at the recommended dose level of 0.5 mg moxidectin/kg body weight. All cattle comprising a treated group were sacrificed at either 3, 7, 10, 14 or 21 days posttreatment and samples of fat and muscle adjacent to (back fat, loin muscle) or

remote from (omental fat and leg muscle) the application site were taken for residue analysis. Two control animals (one heifer and one steer) were sacrificed at the initial time point while the remaining control heifer was sacrifice at the final time point. Identical tissues were harvested for analysis from the control animals. Treatment coincided with the seasonal period when the highest ambient temperatures and humidity level are typically experienced at the testing facility.

c. Findings: The mean moxidectin (marker residue) concentrations at the five sacrifice times in back and omental fat and loin and leg muscle following treatment with the recommended level of the final moxidectin 0.5% pour-on formulation are summarized below:

Moxidectin Residue Levels[a]

Sacrifice Time (days posttreatment)	Back Fat (ppb)[b]	Omental Fat (ppb)[b]	Loin Muscle (ppb)[b]	Leg Muscle (ppb)[b]
3	56±32	90±76[c]	<10	<10
7	63±18	71±27	<10	<10
10	63±69	65±69	<10	<10
14	28±20[c]	49±26[c]	<10	<10
21	25±16[c]	31±17	<10	<10

[a]Values listed in table are the mean of tissues types taken from six animals (three males and three females) at each sacrifice point plus or minus (±) one standard deviation.

[b]Validated limit of quantitation (LOQ) of HPLC method of analysis is 10 ppb (μg/kg).

[c]One animal had a residue of <10 ppb (LOQ of method); a value of 9 was used to calculate the mean.

d. Conclusions: The data reported in this cold residue depletion study show that concentrations of moxidectin in the target tissue peak at three to seven days posttreatment. Residue levels are not higher in the tissues adjacent to the application site (back fat, loin muscle) when compared to tissues remote from the site of application (omental fat, leg muscle). No significant differences exist in the moxidectin residue depletion profile observed in male and female cattle. Because parent moxidectin is 80% of the total residue, the

total residue in the fat samples given in the table above can be calculated by dividing the observed values by 0.8.

F. Assignment of Zero Tissue Withdrawal Period

Because total residue concentrations of moxidectin (marker residue) in both omental and back fat are more than ten-fold below the safe concentration of 4.8 ppm during the period of peak residues, no withdrawal period is required for the edible tissues of cattle treated per label directions with Cydectin moxidectin 0.5% Pour-On for Cattle.

G. Regulatory Methods and Tolerances

Due to the fact that no posttreatment withdrawal time is necessary for the edible tissue of cattle treated with the approved level of 0.5 mg/kg body weight of Cydectin moxidectin 0.5% Pour-On for Cattle, no official regulatory method is required. Sponsor-validated research methods for moxidectin in fat and milk are on file with the Center for Veterinary Medicine.

However, because FSIS/USDA will, in its monitoring program, assay muscle and liver samples of cattle with a multiresidue method capable of detecting and measuring moxidectin, FDA has established tolerances of 50 ppb and 200 ppb for parent moxidectin in muscle and liver, respectively, of cattle. These tolerances were based on data from a study in which FSIS/USDA used its multiresidue method to measure incurred moxidectin residue in samples taken at 3 days after treatment (the time of peak residues). Moxidectin was observed to range from 6.1 to 24.4 ppb in muscle and 33.6 to 101.9 ppb in liver. When these tolerances are used for monitoring, the total residue in edible tissues will be below the calculated safe concentrations, thus ensuring the safe use of moxidectin pour-on.

H. User Safety Statement

Animals used to evaluate the safety to humans involved in handling and administering moxidectin 0.5% Pour-On for Cattle, and the subsequent handling of treated cattle has demonstrated the product is mildly irritating to the eyes and skin and does not cause skin sensitization after repeated exposure. The routine inhalation of vapors associated with normal product use do not pose a significant health risk. This pour-on product is not to be used for medicinal purposes by humans. If accidental ingestion or contact with eyes or skin occurs, users should follow the first aid steps stated on the label. If any symptoms attributable to exposure to the product persist, consultation with a physician is recommended. The product label will instruct users who experience adverse reactions to report these using the 1-800 number provided on the product label.

VII. AGENCY CONCLUSIONS

The data submitted in support of this original NADA satisfy the requirements of section 512 of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that CYDECTIN® (moxidectin) Pour-On for Cattle is safe and effective for treatment and control of infections and infestations due to internal and external parasites of cattle, when administered topically at a dose of 500 µg/kg bodyweight.

An Acceptable Daily Intake (ADI) of 0.004 mg/kg/day in tissues has been established. Because total residue concentrations of moxidectin (marker residue) in both omental (abdominal) and back fat (target tissue) are more than ten-fold below the safe concentration of 4.8 ppm during the period of peak residues, no withdrawal period is required for the edible tissues of cattle treated according to label directions. Since no withdrawal time is necessary, no official regulatory method is required. Sponsor-validated research methods for moxidectin in fat and milk are on file with the Center for Veterinary Medicine.

However, because FSIS/USDA will, in its monitoring program, assay muscle and liver samples of cattle with a multiresidue method capable of detecting and measuring moxidectin, FDA has established tolerances of 50 ppb and 200 ppb for parent moxidectin in muscle and liver, respectively, of cattle. These tolerances were based on data from a study in which FSIS/USDA used its multiresidue method to measure incurred moxidectin residue in samples taken at 3 days after treatment (the time of peak residues). Moxidectin was observed to range from 6.1 to 24.4 ppb in muscle and 33.6 to 101.9 ppb in liver. When these tolerances are used for monitoring, the total residue in edible tissues will be below the calculated safe concentrations, thus ensuring the safe use of moxidectin pour-on.

The data submitted for CYDECTIN® (moxidectin) Pour-On for Cattle support the marketing of the product as an over-the-counter new animal drug. Adequate directions for use have been written for the layman, and the conditions for use prescribed on the label are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall have over-the-counter marketing status.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have 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 at the Dockets Management Branch (HFV-305), Park Building (Room 1-23), 12420 Parklawn Dr., Rockville, Maryland 20855.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application 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 the application and conducted or sponsored by the applicant. CYDECTIN® (moxidectin) Pour-On for Cattle is under U.S. patent number 4,916,154, which expires on April 10, 2007.

VIII. APPROVED PRODUCT LABELING

Facsimile bottle labeling, insert, and box container for the 2.5 liter size containers.

cc:
Courtesy Copy for the Sponsor
HFV-199, N-141099 A-0000, orig
HFV-2, Special Mailing List
HFV-15, FOI Staff
HFV-102, GADQC Reserve Copy
HFV-153, Green Book (HFernandez)
HFA-305, Dockets Management Branch
HFR-MA350, NWK-DO
Reviewer-Typist/ Messenheimer/11-24-97
ec: CVM Records\ONADE\\N141099\A0000foi.sum