Approval Date: August 30, 1990

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-841

B. Sponsor

Merck Sharp and Dohme Research Laboratories
Division of Merck & Co.
P. O. Box 2000
Rahway, N.J. 07065

C. Proprietary Name

IVOMEC Pour-On for Cattle

D. Established Name

Ivermectin

E. Dosage Form

A ready-to-use solution containing 5 mg of ivermectin per ml.

F. How Supplied

Size and Description of container

G. Dosage Regimen

1 ml per 22 lb of body weight to supply 500 mcg of ivermectin per kg.

H. Route of Administration

The formulation should be applied along the topline in a narrow strip extending from the withers to the tailhead.

I. Indication

For the treatment and control of gastrointestinal nematodes (including inhibited immature Ostertagia ostertagi); lungworms (Dictyocaulus viviparus); cattle grubs (Hypoderma spp.); sucking and biting lice; sarcoptic mange mites. The following species are included:

Gastrointestinal roundworms:

- *Ostertagia ostertagi*(adults and L4, including inhibited)
- *Haemonchus placei*(adults and L4)
- *Trichostrongylus axei*(adults and L4)
- *T. colubriformis*(adults and L4)
- *Cooperia* spp. (adults and L4)

- *Strongyloides papillosus*(adults)
- *Oesophagostomum radiatum*(adults and L4)
- *Trichuris* spp. (adults)

Lungworms:

- *Dictyocaulus viviparus* (adults and L4).

Cattle grubs (parasitic stages):

- *Hypoderma bovis*
- *H. lineatum*

Lice:

- *Linognathus vituli*
- *Haematopinus eurysternus*
- *Damalina bovis*
- *Solenopotes capillatus*

Mites:

- *Sarcoptes scabiei* var *bovis*.

Flies:

- *Hematobia irritans*(adults).

II. EFFECTIVENESS

Ivermectin is currently approved for use in cattle as an injectable formulation (NADA 128-409, approved by Final Rule in Federal Register 49:30, pp 5343-4; February 13, 1984), and as a paste formulation (NADA 137-006, approved by Final Rule in Federal Register 51:237, pp 44449; December 10, 1986). Trials conducted for approval of these two formulations provided efficacy data for a variety of both internal and external parasites of cattle. In addition to data from previously cited NADA's, efficacy studies were conducted to demonstrate the effectiveness of the pour-on formulation against the dose-limiting parasites. The aforementioned NADAs, plus the NADA that is the subject of this summary, provide acceptable efficacy data for the parasites on the labeling.

Trial 11258 was conducted to determine the effective dose to control nematodes. Cattle were randomly allocated to treatments. Necropsies for worm counts were done 14-16 days after treatment. Doses of ivermectin were 200, 500 and 1000 mcg/kg. The data show significantly ($p<0.05$) less reduction in parasite counts at 200 mcg/kg compared to higher levels for several parasites, but no significant difference between 500 and 1000 mcg/kg.

Eight trials (11076, 11258, 11383, 11384, 11498, 11506, 11759, 12543) were conducted to test the efficacy of IVOMEC Pour-On against nematodes in cattle. Animals were randomized between control and treatment group in each trial and the appropriate amount of the formulation was applied (1 ml per 22 lb). After a suitable period, depending on the parasite, the animals were necropsied for parasite recovery. The results of each trial are shown in the corresponding trial summary.

Trial 11261 was conducted to evaluate the effect of IVOMEC Pour-On on *Hypoderma* spp. in cattle. Animals with grubs in the second and third stages were randomized between control and treatment groups. The dose given was 500 mcg/kg. Animals were examined for grub emergence in the spring. Data were statistically analyzed and the results showed that there was a significant ($p<0.05$) reduction in the proportion of animals with emerging grubs in the ivermectin-treated animals.

Three trials (11260, 11267, 11503) were conducted to evaluate the effect of IVOMEC Pour-On (500 mcg/kg) against lice on cattle. Both biting and sucking lice were present. The animals were randomly assigned among control and treatment groups. The trials lasted 49 to 56 days with animals examined every 7 to 14 days throughout the trials. The lice were counted in selected areas and the data were statistically analyzed. The results showed that both biting lice and sucking lice were significantly ($p<0.05$) reduced on treated animals.

Two trials were conducted to investigate the effect of IVOMEC Pour-On on *Sarcoptes scabiei* var. *bovis* in cattle. In Trial 11202, mites were not completely controlled in all animals at 1 ml/22 lb (500 mcg/kg) due to interference with absorption of ivermectin when the formulation was applied to skin damaged by mites. Care was taken in Trial 11774 to apply the drug only to clinically healthy skin. Live mites were recovered from only on treated animals on one occasion from Day 21 to 56 after treatment.

Six trials (11616, 11704, 11943, 11944, 12100 and 12244) evaluated the efficacy of IVOMEC Pour-On in controlling extant infestations of horn flies (*Haematobia irritans*) and reducing the numbers acquired by reinfestation. The results indicate that ivermectin applied topically at 500 mcg/kg effectively controls horn flies on cattle for up to 28 days.

Sunshine:

Trials 11383 and 11498 were conducted to determine if exposing cattle treated with IVOMEC Pour-On to sunshine results in any loss of efficacy. Cattle were treated with IVOMEC Pour-On at 1 ml/22 lb and housed inside or kept outside in sunshine. Animals in each trial were randomly allocated among treatments. There was no significant ($p>0.10$) difference in the reduction of parasite burden between treated cattle housed inside and those left out or maintained in the sunshine.

Grooming:

In Trial 11503, a 56-day pasture trial, cattle were maintained in outdoor paddocks. There were five paddocks in each of two treatments with cattle and paddocks randomly assigned to treatment. One treatment group was unmedicated and the other was given IVOMEC Pour-On at 1 ml/22 lb. Louse burdens were reduced on the cattle treated with IVOMEC Pour-On as were the number of nematode parasite eggs shed.

III. TARGET ANIMAL SAFETY

A. Animal Safety:

Three trials were conducted to investigate the safety and acceptability of applying IVOMEC Pour-On to cattle.

Trial 11824 was a tolerance study to examine the effects of 2 ml/22 lb, 5 ml/22 lb and 10 ml/22 lb (2X, 5X and 10X recommended dose, respectively) on cattle and compare the effects to those in a control group. There were four randomly selected

animals per group. Animals were examined daily for 14 days after dosing. Minor signs of irritation (skin flaking) at the application sites were seen in all groups, including the vehicle control. No treatment-related effects on feed intake or body temperature were observed.

Trial 11753 was conducted to examine the effects on skin. Sixteen animals were given IVOMEC Pour-On (1 ml/22 lb) on Day 0 of the trial. Four animals were randomly selected for collection of skin samples on each of Days 7, 14, 28 and 42 after dosing. Skin sections were examined histologically. The epidermis, dermis, subcutaneous tissue and underlying muscle at the application site appeared normal at all four time periods. The histopathologic effects were minimal degrees of dermal perivascular cuffing of mononuclear cells, lymphocytes, esinophils and plasma cells. The lesions ranged from none to mild degrees of acathosis, hyperkeratosis and parakeratosis in the control and application site skin. These histologic lesions reflect mild site irritation and are biologically insignificant.

Trial 11663 was conducted to determine the effects of accidental application of the formulation to the eye of the cattle. Four randomly selected steers were assigned to each of the four treatments; saline, 1.0 ml; IVOMEC Pour-On, 0.25 ml; IVOMEC Pour-On, 0.5 ml; IVOMEC Pour-On, 1.0 ml, each instilled into the lower conjunctival fornix. The animals were observed for seven days after treatment. There was a slight increase in Ocular Lesion Scores (Draize Method) on Days 1 and 3 after dosing in the 0.5 and 1.0 groups. These subsided by Day 7. No increased lacrimation was seen nor did the animals show signs of ocular irritation or discomfort other than that at the time the formulation was given.

B. Breeding Animal Safety:

Safety in breeding animals was determined by comparison with IVOMEC Injection for cattle. Data were previously presented to show that the subcutaneous administration of ivermectin at 400 mcg/kg had no adverse effects on breeding cattle. To evaluate if topical application of ivermectin posed any risk to breeding animals, a comparative bioavailability trial was conducted. IVOMEC Injection was given to eight animals at 2 ml/110 lb (400 mcg/kg) and eight animals were given IVOMEC Pour-On at 1 ml/22 lb (500 mcg/kg). The levels of ivermectin in the plasma of the two groups of animals were compared. The groups given ivermectin topically had a significantly ($p<0.01$) lower area under the curve and a significantly ($p<0.01$) lower peak plasma level than did the group given ivermectin subcutaneously. Ivermectin given subcutaneously has well documented safety in breeding animals and the data presented here show that ivermectin applied topically will also be safe in these animals.

Trial: 11076

Name: T. A. Yazwinski, Ph.D

Location:

University of Arkansas
Fayetteville, Arkansas

Test Duration: 15 days

Treatments (Number of Animals):

Vehicle Control (6)
Ivermectin Topical, 500 mcg/kg (6).

Summary:

Parasite	**% Reduction**	**P-value**
Cooperia spp, adult	>99	.0022
Haemonchus placei, adult	100	.0022
Ostertagia spp, adult	>99	.0022
Ostertagia spp, inhibited L4	>99	.0022
Ostertagia spp, L4	>99	.0022
Strongyloides papillosus, adult	97.3	0281
Trichostrongylus axei, adult	98.8	.0022
Trichuris spp, adult	89.9	.0693

Trial: 11202

Name: D. Barth, D.V.M

Location:

MSD Sharp & Dohme G.m.b.H kathrinenhof
Merck Research Farm
Lauterbach
West Germany

Test Duration: 56 days

Treatments (Number of Animals):

Vehicle Control (6)
Ivermectin Topical, 500 mcg/kg, (6).

Summary:

% Animals Infested

Parasite - *Sarcoptes scabiei* var *bovis*	**Vehicle Control**	**Ivermectin Topical 500 mcg/kg**	**P-value**
Day -1	100	100	-
Day 7	100	33	.0152
Day 14	100	33	>.10
Day 21	100	33	.0801
Day 28	100	33	.0260
Day 35	100	17	.0260
Day 42	100	17	.0260
Day 49	100	17	.0260
Day 56	100	17	.0260

Trial: 11203

Name: D. Barth, D.V.M

Location:

MSD Sharp & Dohme G.m.b.H Kathrinenhof
Merck Research Farm
Lauterbach, West Germany

Test Duration: 35 days

Treatments (Number of animals):

- Vehicle Control, (1)
- Ivermectin Topical, 500 mcg/kg, (8)
- Ivermectin Subcutaneous, 200 mcg/kg, (8)
- Ivermectin Subcutaneous, 400 mcg/kg, (8)

Summary:

Plasma Values	**Ivermectin Topical 500 mcg/kg**	**Ivermectin Subcutaneous 200 mcg/kg**	**Ivermectin Subcutaneous 400 mcg/kg**
Area under the curve, ng/day/ml	196.2	264.1	457.4
Peak concentration, ng/ml	17.3	37.1	44.9
Time to peak	4.5	2.8	2.9

Trial: 11258

Name: R. Alva-Valdes, M.V.Z., M.S., Ph.D

Location:

Merck Research Farm
Fulton, Missouri

Test Duration: 16 days

Treatments (# of animals):

- Vehicle Control, (6)
- Ivermectin Topical, 200 mcg/kg, (6)
- Ivermectin Topical, 500 mcg/kg, (6)
- Ivermectin Topical, 1000 mcg/kg, (6).

Summary:

% Reduction

Ivermectin Topical (mcg/kg)

Parasite	**200**	**500**	**1000**
Cooperia spp, adult	92.2	100	>99
Cooperia spp, L4	73.0	100	85.4
Dictyocaulus viviparus, adult	100	100	100
Haemonchus placei, adult	100	100	100
Haemonchus spp, L4	76.2	100	100
Oesophagostomum radiatum, adult	100	100	100
Ostertagia ostertagi, adult	>99	100	100
Ostertagia ostertagi, L4	100	100	100
Trichostrongylus axei, adult	90.1	100	>99
Trichostrongylus colubriformis, adult	85.1	>99	100
Trichostrongylus spp (abomasal), L4	90.4	100	100
Trichostrongylus spp (sm. intestine), L4	74.7	100	100

P-values for Treatment Comparisons

Parasite	**Vehicle Control vs Ivermectin Groups**	**Ivermectin: 200 vs 500, 100 mcg/kg**	**Ivermectin: 500 vs 1000 mcg/kg**
Cooperia spp, adult	.0001	.0007	>.10
Cooperia spp, L4	.0421	>.10	>.10
Dictyocaulus viviparus, adult	.0001	>.10	>.10
Haemonchus placei, adult	.0001	>.10	>.10
Haemonchus spp, L4	.0076	.0980	>.10
Oesophagostomum radiatum, adult	.0001	>.10	>.10
Ostertagia ostertagi, adult	.0000	>.10	>.10
Ostertagia ostertagi, L4	.0014	>.10	>.10
Trichostrongylus axei, adult	.0000	.0002	>.10
Trichostrongylus colubriformis, adult	.0004	.0049	>.10
Trichostrongylus spp (abomasal), L4	.0040	>.10	>.10
Trichostrongylus spp (sm. intestine), L4	.0543	>.10	>.10

Trial: 11260 Name: J. E. Holste, B.S., D.V.M

Location:

Merck Research Farm
Fulton, Missouri

Test Duration: 56 days

Treatments (# of animals):

- Vehicle Control, (6)
- Ivermectin Topical, 500 mcg/kg, (6).

Summary:

Geometric Mean Count of Live Lice

Parasite- *Damalinia bovis*	**Vehicle Control**	**Ivermectin Topical 500 mcg/kg**	**P-value**
Day -1	>346.0	>334.1	-
Day 7	>176.1	0	.0022
Day 14	>256.9	0	.0022
Day 21	>118.4	0	.0022
Day 28	>162.9	0	.0022
Day 35	>102.9	0	.0022
Day 42	60.5	0	.0022
Day 49	>52.4	0	.0152
Day 56	45.4	0	.0152

Trial: 11261 Name: D. H. Wallace, D.V.M

Location:

Merck Research Farm
Fulton, Missouri

Test duration: 40 days

Treatments (# of animals):

- Vehicle Control, (6)
- Ivermectin Topical, 500 mcg/kg, (6).

Summary:

% Animals with Live Grubs

Parasite	**(range of counts) - Control**	**(range of counts) - Ivermectin**	**P-value**
Hypoderma bovis and *H. lineatum*, second and third stage larvae	100 (4-20)	17 (0-1)	.016

Trial: 11267 Name: R. Alva-Valdes, M.V.Z.,M.S.,Ph.D

Location:

Merck Research Farm
Fulton, Missouri

Test Duration: 49 days

Treatments (# of Animals):

- Vehicle Control, (6)
- Ivermectin Topical, 500 mcg/kg(6).

Summary:

Geometric Mean Count of Live Lice

Parasite - *Linognathus vituli*	**Vehicle Control**	**Ivermectin Topical 500 mcg/kg**	**P-value**
Day -1	131.8	126.8	
Day 7	98.0	0.0	0.031
Day 14	58.9	0.0	0.031
Day 21	42.7	0.0	0.031
Day 28	16.4	0.0	0.031
Day 35	5.2	0.0	0.031
Day 42	3.3	0.0	0.031
Day 49	1.8	0.0	>0.10

Trial: 11383 Name: B. M. Thomson, A.I.M.L.T

Location:

Merck Sharp & Dohme (Australia) Pty Ltd
Veterinary Research & Development Laboratory
Ingleburn, New South Wales
Australia

Test Duration: 30 days

Treatments (# of Animals):

- Vehicle Control, (6)
- Ivermectin Topical, 500 mcg/kg in shade, (6)
- Ivermectin Topical, 500 mcg/kg in sunshine, (6).

Summary:

% Reduction

Parasite	**Ivermectin Topical, 500 mcg/kg-Shade**	**Ivermectin Topical, 500 mcg/kg-Sunshine**
Cooperia spp, adult	>99	>99
Haemonchus placei, adult	100	100
Oesophagostomum radiatum, adult	100	100
Ostertagia ostertagi, adult	>99	>99

P-values for Treatment Comparisons

Parasite	**Control vs Ivermetin Topically**	**Ivermectin Topically: Shade vs. Sunshine**
Cooperia spp, adult	.0004	>.10
Haemonchus placei, adult	.0001	>.10
Oesophagostomum radiatum, adult	.0001	>.10
Ostertagia ostertagi, adult	.0001	>.10

Trial: 11384 Name: M. Thompson, A.I.M.L.T

Location:

Merck Sharp & Dohme (Australia) Pty Ltd
Veterinary Research & Development Laboratory
Ingleburn, New South Wales
Australia

Test Duration: 24 days

Treatments (# of Animals):

- Vehicle Control, (6)
- Ivermectin Topical, 500 mcg/kg, (6)

Summary:

Parasite	**% Reduction**	**P-Value**
Cooperia spp, adult	>99	.0022
Cooperia spp, L4	100	>.10
Haemonchus spp, adult	100	>.10
Oesophagostomum radiatum, adult	100	.0022
Ostertagia ostertagi, adult	100	.0022
Ostertagia ostertagi, inhibited L4	>99	.0152
Ostertagia ostertagi, L4	100	>.10
Trichostrongylus axei ,adult	100	.0022
Trichostrongylus spp, adult	100	.0606
Trichuris spp, adult	43.9	>.10

Trial: 11498 Name: J. S. Eagleston, B.V.Sc., M.V.Sc

Location:

Merck Sharp & Dohme (Australia) Pty Ltd
Veterinary Research & Development Laboratory
Ingleburn, New South Wales
Australia

Test Duration: 31 days

Treatments (# of Animals):

1. Vehicle Control, sunshine with adaptation, (6)
2. Ivermectin Topical, 500 mcg/kg - sunshine with adaptation, (6)
3. Ivermectin Topical, 500 mcg/kg - sunshine without adaptation, (6)
4. Ivermectin Topical, 500 mcg/kg - sunshine with UVabsorber, (6)
5. Ivermectin Topical, 500 mcg/kg - indoors, (6).

Summary:

Parasite	**% Reduction - 2**	**% Reduction - 3**	**% Reduction - 4**	**% Reduction - 5**
Cooperia spp, adult	85.3	73.3	95.5	88.9
Haemonchus placei, adult	100	>99	>99	100
Ostertagia ostertagi, adult	100	100	100	100
Ostertagia ostertagi, inhibited L4	100	74.2	33.3	100

Parasite	**P-values for Treatment Comparisons - 1 vs. 2, 3, 4, 5**	**P-values for Treatment Comparisons - 2 vs 3**	**P-values for Treatment Comparisons - 2 vs 4**	**P-values for Treatment Comparisons - 2 vs 5**
Cooperia spp, adult	.0010	>.10	>.10	>.10
Haemonchus placei, adult	0.0001	>.10	>.10	>.10
Ostertagia ostertagi, adult	.0000	>.10	>.10	>.10
Ostertagia ostertagi, inhibited L4	>.10	>.10	>.10	>.10

Trial: 11503 Name: R. O. Burrows, B.V.M.& S., M.R.C.V.S

Location:

Merck Sharp & Dohme (Australia) Pty, Ltd.
Veterinary Research & Development Laboratory
Ingleburn, New South Wales, Australia

Test Duration: 56 days

Treatments (# of Animals):

1. Vehicle Control, (10)
2. Ivermectin Topical, 500 mcg/kg, (10)

Summary:

Geometric Mean Count of Live Lice

Parasite - *Damalinia bovis*	**Vehicle Control**	**Ivermectin Topical -500 mcg/kg**	**P-value**
Day -7	35.9	36.3	-
Day 0	50.1	44.1	-
Day 7	46.1	0.1*	.027
Day 14	34.8	0*	.027
Day 28	35.4	0*	.011
Day 42	36.4	0*	.027
Day 56	32.1	0*	.027

*At least one animal had no lice at the count sites, but lice were found elsewhere.

Geometric Mean Count of Live Lice

Parasite - *Linognathus vituli*	**Vehicle Control**	**Ivermectin Topical - 500 mcg/kg**	**P-value**
Day -7	11.2	9.3	-
Day 0	4.7	8.9	-
Day 7	9.6	0	<.01
Day 14	8.3	0	<.01
Day 28	5.1	0	<.01
Day 42	6.2	0	<.01
Day 56	4.9	0	<.01

Trial: 11506

Name: J. S. Eagleson, B.V.Sc., M.V.Sc

Location:

Merck Sharp & Dohme (Australia) Pty Ltd
Veterinary Research & Development Laboratory
Ingleburn, New South Wales
Australia

Test Duration: 29 days

Treatments (# of Animals):

- Vehicle Control, (6)
- Ivermectin Topical, 500 mcg/kg, (6).

Summary:

Parasite	% Reduction	P-value
Cooperia spp, L4	>99	.0108
Haemonchus placei, L4	>99	.0022
Oesophagostomum radiatum, L4	100	.0022
Ostertagia ostertagi, L4	>99	.0022

Trial: 11616

Name: B. Robin, D.V.M. - Merck & Co., Inc

Location:

INRA - Le Pin au Haras
61310 Exmes, France

Test Duration: 46 days

Treatments (# of Animals):

- Vehicle Control, (12)
- Ivermectin Topical, 500 mcg/kg, (12).

Summary:

Day	Geometric Mean Count of Horn Flies - Vehicle Control	Geometric Mean Count of Horn Flies - Ivermectin Topical 500 mcg/kg
0	22.3	22.3
22	14.0	5.0
28	12.1	1.1
32	16.0	2.7
37	25.8	10.4
46	19.8	13.4

Trial: 11663 Name: J. D. Pulliam, D.V.M., M.S

Location:

Merck & Co., Inc
P. O. Box 2000
Rahway, New Jersey 07065

Test Duration: 7 days

Treatments (# of Animals): Instilled in lower conjunctival fornix of one eye

- Saline 1.0 ml, (4)
- Ivermectin Topical,0.5% solution .25 ml, (4)
- Ivermectin Topical, 0.5% solution .5 ml, (4)
- Ivermectin Topical, 0.5% solution 1.0 ml, (4).

Summary:

Instilling the topical formulation into the conjunctival fornix produced mild conjunctival vascular congestion with mild chemises. The conjunctival edema did not involve the nictitating membrane. One animal had a mild discharge during the first day. There were no effects on the cornea or iris detected by pupillary light reaction, corneal fluorescein staining or fundoscopic examination. There was a slight increase in Ocular Lesion Scores (Draize Method) on days 1 and 3 after dosing in the 0.5 ml and 1.0 ml groups. These subsided by day 7. No increased lacrimation was seen nor did the animals show signs of ocular irritation or discomfort other than at the time the formulation was given.

Trial: 11704

Name: Maxcy P. Nolan Jr., Ph.D

Location:

Cooperative Extension Service
University of Georgia
Athens, GA 30605

Test Duration: 42 days

Treatments (# of Animals):

- Vehicle Control, (34)
- Ivermectin Topical, 500 mcg/kg, (30)

Summary:

Day	Geometric Mean Count of Horn Flies - Vehicle Control	Geometric Mean Count of Horn Flies - Ivermectin Topical 500 mcg/kg
0	29.7	28.7
3	62.1	1.5
7	80.2	0.9
14	81.6	0.1
21	106.8	0.8
28	85.3	3.1
35		
42	101.1	0.3

Trial: 11753

Name: J. D. Pulliam, D.V.M., M.S

Location:

Merck & Co., Inc
P. O. Box 2000
Rahway, New Jersey 07065

Test Duration: 42 days

Treatments (# of Animals):

- Ivermectin Topical, 500 mcg/kg, necropsy Day 7, (4)
- Ivermectin Topical, 500 mcg/kg, necropsy Day 14, (4)
- Ivermectin Topical, 500 mcg/kg, necropsy Day 28, (4)
- Ivermectin Topical, 500 mcg/kg, necropsy Day 42, (4).

Summary:

Application sites remained clinically normal until necropsy (7, 14, 28 or 42 days after dosing). No treatment-related adverse reactions were observed. At necropsy the epidermis, dermis, subcutaneous tissue and underlying muscle at the application site appeared normal at all four time periods. The histopathologic effects were minimal degrees of dermal perivascular cuffing of mononuclear cells, lymphocytes, eosinophils and plasma cells. The lesions ranged from none to mild degrees of acanthosis, hyperkeratosis and parakaratosis in the control and application site skin. The peak effects were seen at 14 days after treatment when two animals had mild acanthosis and one of the two also had mild perivascular cuffing. These histologic lesions reflect mild site irritation and are biologically insignificant.

Trial: 11759

Name: M. D. Soll, B.V.Sc

Location:

Merck Sharp & Dohme (Pty) Ltd
MSD Research Centre
Hennops River, Pretoria
R.S.A

Test Duration: 17 days

Treatments (# of Animals):

- Vehicle Control, (15)
- Ivermectin Topical, 500 mcg/kg(15)

Summary:

Parasite	**% Reduction**	**P-value**
Cooperia spp, adult	80.9	.0453
Cooperia spp, L4	94.6	<.01
Haemonchus placei, adult	100	<.01
Oesophagostomum radiatum, adult	>99	<.01
Ostertagia ostertagi, adult	90.5	.0656
Trichostrongylus axei, adult	97.4	<.01
Trichostrongylus axei, L4	>99	<.01
Trichostrongylus spp, (sm. intest.) adult	44.0	>.10
Trichuris spp, adult	75.6	>.10

Trial: 11774 Name: M. D. Soll, B.V.Sc

Location:

Merck Sharp & Dohme (Pty) Ltd
MSD Research Centre
Hennops River, Pretoria
R.S.A

Test Duration: 56 days

Treatments (# of Animals):

- Untreated Control, (6)
- Ivermectin Topical, 500 mcg/kg, (6).

Summary:

Parasite - *Sarcoptes scabiei* var *bovis*	**Geometric Mean Count of Live Mites - Control**	**Geometric Mean Count of Live Mites - Ivermectin Topical 500 mcg/kg**	**Geometric Mean Count of Live Mites - P-value**
Day 0	251.4	334.1	-
Day 7	297.8	31.1	>.10
Day 14	212.7	2.2	.031
Day 21	146.4	0	.031
Day 28	145.0	0.3	.031
Day 42	164.9	0	.031
Day 56	54.9	0	.031

Trial: 11824 Name: J. D. Pulliam, D.V.M., M.S

Location:

Merck & Co., Inc
P.O. Box 2000
Rahway, New Jersey 07065

Test Duration: 14 days

Treatments (# of Animals):

1. Vehicle Control, (4)
2. Ivermectin Topical, 1000 mcg/kg, (4)
3. Ivermectin Topical, 2500 mcg/kg, (4)
4. Ivermectin Topical, 5000 mcg/kg, (4).

Summary:

Variable	Least Squares Means - Vehicle Control	Least Squares Means Ivermectin - Topically (mcg/kg) - 1000	Least Squares Means Ivermectin - Topically (mcg/kg) - 2500	Least Squares Means Ivermectin - Topically (mcg/kg) - 5000	P-Value For Treatment Comparisons - Overall Treatment	P-Value For Treatment Comparisons - 1 vs. 2, 3, 4	P-Value For Treatment Comparisons - 2 vs. 3, 4	P-Value For Treatment Comparisons - 3 vs. 4
Number of Animals	4	4	4	4	-	-	-	-
Weight (kg) Gain on Day 0	262.6	262.2	260.0	259.2	>.10	-	-	-
Weight Gain (kg) - Day 0 to 7	6.9	6.1	11.5	8.8	>.10	-	-	-
Weight Gain (kg) - Day 0 to 14	16.0	13.8	16.4	19.2	>.10	-	-	-
Daily Feed Consumption (kg) - Pretreatment	9.37	9.13	9.20	9.24	>.10	-	-	-
Daily Feed Consumption (kg) - Week 1	8.72	8.26	9.44	9.19	>.05	-	-	-
Daily Feed Consumption (kg) - Week 2	9.29	8.39	9.42	9.62	>.05	>.10	<.01	>.10
Body Temperature (deg. C) - Pretreatment	39.42	39.22	39.40	39.51	>.10	-	-	-
Body Temperature (deg. C) - Posttreatment	39.03	39.08	39.09	39.06	>.10	-	-	-

Overt signs of ivermectin toxicity, including depression, ataxia or mydriasis were not seen in these cattle dosed up to 5,000 mcg/kg (10 times proposed use level). Minor signs of application site irritation, i.e., skin flaking, were seen in all groups, including vehicle controls. No treatment-related effects on feed intake or body temperature were observed.

Trial: 11943

Name: J. L. Lancaster, Ph.D

Location:

University of Arkansas
Fayetteville, AR 72701

Test Duration: 41 days

Treatments (# of Animals):

- Vehicle Control, (20)
- Ivermectin Topical, 500 mcg/kg, (20).

Summary:

	Geometric Mean Count of Horn Flies - Vehicle Control	**Geometric Mean Count of Horn Flies - Ivermectin Topical - 500 mcg/kg**
Day -1	59.3	97.1
Day 3	n.d.	0.3
Day 7	122.1	0.7
Day 14	45.5	2.9
Day 21	109.7	11.4
Day 28	130.7	10.0
Day 35	83.8	31.4
Day 41	119.1	11.7

n.d. = not determined.

Trial: 11944 Name: J. L. Lancaster, Ph.D

Location:

University of Arkansas
Fayetteville, AR 72701

Test Duration: 43 days

Treatments (# of Animals):

- Vehicle Control, (26)
- Ivermectin Topical, 500 mcg/kg, (26).

Summary:

	Geometric Mean Count of Horn Flies - Vehicle Control	**Geometric Mean Count of Horn Flies - Ivermectin Topical - 500 mcg/kg**
Day -1/-2	439.7	809.6
Day 2/3	307.9	8.0
Day 5/6	290.9	10.6
Day 13/14	247.5	21.1
Day 19/20	452.0	76.4
Day 26/27	270.5	32.5
Day 33/34	360.5	179.8
Day 42/43	37.1	208.2

Trial: 12100 Name: H. G. Kinzer, Ph.D

Location:

Veterinary Entomology Research Laboratory
New Mexico State University
Las Cruces, New Mexico

Test Duration: 70 days

Treatments (# of Animals):

- Vehicle Control, (20)
- Ivermectin Topical, 500 mcg/kg, (20).

Treatments were switched mid season when controls were given ivermectin topically and previously treated animals received no additional treatment.

Summary:

	Geometric Mean Count of Horn Flies - Control	**Geometric Mean Count of Horn Flies - Ivermectin Topical - 500 mcg/kg**
No. Animals Counted per Treatment per Season	20	20
Early Season Treatment - Day 0	143.9	177.8
Early Season Treatment - Day 1	212.8	1.3
Early Season Treatment - Day 3	217.0	0.3
Early Season Treatment - Day 7	311.0	11.7
Early Season Treatment - Day 14	406.1	18.8
Early Season Treatment - Day 21	515.7	117.6
Early Season Treatment - Day 28	405.5	74.8
Early Season Treatment - Day 35	867.1	286.6
Early Season Treatment - Day 43	545.3	338.1
Mid- Season Treatment - Day 0	279.2	208.7
Mid- Season Treatment - Day 1	344.5	0.9
Mid- Season Treatment - Day 3	777.8	0.7
Mid- Season Treatment - Day 7	712.3	4.5
Mid- Season Treatment - Day 14	348.3	110.9
Mid- Season Treatment - Day 21	227.8	170.3
Mid- Season Treatment - Day 28	230.4	70.1
Mid- Season Treatment - Day 35	263.8	107.7
Mid- Season Treatment - Day 42	539.8	211.1
Mid- Season Treatment - Day 49	502.2	204.9
Mid- Season Treatment - Day 56	526.8	426.4
Mid- Season Treatment - Day 63	894.3	652.2
Mid- Season Treatment - Day 70	833.6	790.1

Trial: 12244

Name: R. Titchener, Ph.D

Location:

The West of Scotland Agricultural College
Auchincruive, Ayr KA6 5 HW

Test Duration: 56 days

Treatments (# of Animals):

- Vehicle Control, (15)
- Ivermectin Topical, (15).

Summary:

	Geometric Mean Count of Horn Flies - Vehicle Control	**Geometric Mean Count of Horn Flies - Ivermectin Topical - 500 mcg/kg**
Day -6	2.0	2.3
Day 3	2.7	0
Day 7	7.2	0
Day 14	19.6	0
Day 21	32.1	0
Day 28	31.7	0
Day 33	17.8	0
Day 42	11.3	0
Day 49	1.2	0
Day 56	0.5	0

Trial: 12543 Name: T.A. Yazwinski, PhD

Location:

University of Arkansas
Fayetteville, Arkansas

Test Duration: 16 days

Treatment (# of Animals):

- Vehicle Control, (8)
- Ivermectin Topical, 500 mcg/kg, (8).

Summary:

Parasite	**% Reduction**	**P-value**
Cooperia spp, adult	>99	.0002
Cooperia spp, L4	100	.0014
Dictyocaulus viviparus, adult	100	.0769
Haemonchus placei, adult	100	.0002
Haemonchus placei, L4	>99	.0002
Oesophagostomum radiatum, adult	100	.0002
Ostertagia ostertagi, adult male	100	.0002
Ostertagia spp, adult female	>99	.0002
Ostertagia spp, inhibited L4	100	.0070
Ostertagia spp, L4	100	.0256
Trichostrongylus axei, adult	>99	.0002
Trichostrongylus colubriformis, adult	100	.0256
Trichuris spp, adult	100	.0070

IV. HUMAN FOOD SAFETY

A. Drugs for Use in Food Animals:

1. Toxicity Tests:

   For a complete summary of the toxicity tests for ivermectin, please consult the FOI Summary for NADA 128-409, IVOMEC (ivermectin) 1% Injection for Cattle.

2. Safe Concentration of Total Residue:

As discussed in the FOI Summary for NADA 128-409, IVOMEC (ivermectin) Injection for Cattle, the following safe concentrations in edible tissues have been calculated from the no-observed-effect-level in the most sensitive study in the most sensitive species:

Tissue	**Safe Concentration (ppb)**
Muscle	25
Liver	50
Kidney	75
Fat	100

3. Total Residue Depletion and Metabolism Study (CA 218).

a. Investigators:

Study Director:

S.H.L. Chiu, PhD
Senior Research Fellow
Animal Drug Metabolism
Merck & Co., Inc
PO Box 2000
Rahway, NJ 07065.

Principal Biologist:

F.P. Baylis, M. S
Associated Director,
Animal Metabolism
Branchburg Farm
Merck & Co., Inc
203 River Road
Somerville, NJ 08876.

b. Animals: Twelve Angus steer approximately 8-10 months old were used.

c. Route of Administration:

Drug was applied topically along the midline of the back.

d. Time and Duration of Dose:

The animals were dosed once at the start of the experiment.

e. Radio-isotope Used:

Ivermectin, labeled with tritium in the 22,23 positions, was used.

f. Average total residue at various withdrawal times.

Tissue	**Days Post Dose - 7**		**Days Post Dose - 14**		**Days Post Dose - 28**		**Days Post Dose - 42**	
Liver	0.226	%0.102	0.126	%0.053	0.069	%0.092	0.026	%0.012
Fat	0.072	%0.033	0.052	%0.019	0.025	%0.023	0.023	%0.010
Kidney	0.021	%0.10	0.014	%0.005	0.007	%0.007	0.004	%0.002
Muscle	0.008	%0.003	0.005	%0.002	0.002	%0.002	0.002	%0.000
Muscle dosing site	0.043	%0.011	0.041	%0.014	0.019	%0.017	0.006	%0.004

* Each number is the average value % SD for three animals.

g. Summary of Metabolism Studies:

In liver, the tissue with highest residue, the averaged unaltered parent drug (H2B1a and H2B1b) accounts for about 67%, 62%, and 52% of the total radioactive residue at 7, 14, and 28 days, respectively, after dosing. In fat, the tissue with the second highest residue, the unaltered drug accounts for about 86%, 78%, 65%, and 42% of the total radioactive residue at 7, 14, 28, and 42 days after dosing.

The 14 and 28 days cattle liver were used for study of metabolites. In these samples, unaltered drug accounted for about 53% to 57% of the radioactivity. Metabolites were separated into the polar group (2% of the total radioactivity), drug like group (5% of the total radioactivity), and non-polar group (0.5 to 2% of the total radioactivity). The major polar metabolite was identified as 24-hydroxy-H2Bla. Overall, between 85 to 91% of the liver residue in the 14 and 28 days samples were identified either as the unaltered drug or as the 24-OH-H2B1a.

In fat tissue of a 28 days post dose steer, the unaltered drug and a group of non-polar metabolites accounted for 70%and 18% of the total radioactivity, respectively. The non-polar metabolites were identified as the acyl esters of 24-OH-H2B1a.

As discussed in the FOI Summary for NADA 128-409, IVOMEC (ivermectin) Injection for Cattle, these same metabolites occur in the liver and fat of cattle treated with the parenteral formulation of ivermectin.

Comparative metabolism studies indicate that the metabolism of ivermectin in cattle and rat, the toxicity test species, is qualitatively similar. In both species, the unaltered drug is the major residue. The HPLC profiles of the radioactive residue in the liver and qualitatively similar. The major metabolite in cattle and rat liver is 24-OH-H2B1a. Thus, the test species is exposed to the major drug residue components known to be present in cattle tissues.

4. Tolerance for the marker residue:

For reasons enumerated in the FOI Summary for NADA 128-409, IVOMEC (ivermectin) Injection for Cattle, liver was selected as target tissue, parent drug component H2B1a was selected as marker residue, and the tolerance for H2B1a in liver was calculated to be 15 ppb.

The residue date contained in Study CA-218 confirm that, for the topical route of administration, 15 ppb is a valid tolerance for ivermectin H2B1a as the marker residue in liver tissue of cattle.

The regulatory method of analysis has a limit of detection of 1-2 ppb and a limit of reliable measurement of 10 ppb.

5. Study establishing the withdrawal period (CA 223):

a. Investigators:

Study Director:

T.A. Wehner, PhD, Senior Research Chemist
Analytical Research
Merck & Co., Inc
PO Box 2000
Rahway, NJ 07065.

Principal Biologist:

F.P. Baylis, M.S
Associate Director,
Animal Metabolism
Branchburg Farm
Merck & Co., Inc
203 River Road
Somerville, NJ 08876.

b. Animals:

Twenty one Angus steers and 14 Angus heifers were treated with drug (500 mcg/kg) and three steers and two heifers served as control.

c. Route of Administration:

Drug was applied topically along the midline of the back.

d. Time and duration of dosing:

The animals were dosed once at the start of the experiment.

e. Summary of average marker residue concentrations:

Days Post Dose	Average Marker Residue (H2B1a) in Target Tissue (liver)
7	48 ppb % 32
14	27 ppb % 9
21	19 ppb %7.5
28	12 ppb % 7
35	8 ppb % 8
42	3 ppb % 1.3
56	0 ppb % 0.4
Control	1 ppb % 1.8

Each number is the average value % SD from three steers and two heifers.

f. Statistical method used to calculate the withdrawal period

Based on the tolerance for ivermectin of 15 ppb in cattle liver, a withdrawal time of 48 days was calculated by statistical analysis of the tolerance limit containing the 99th percentile of the population with 95% confidence.

V. REGULATORY METHOD

(a and b)

A description of the assay and a statement of the results of the method validation trial can be found in the FOI Summary for NADA 128-409, IVOMEC (ivermectin) Injection for Cattle

c. Validation:

The determinative and confirmatory methods have been validated satisfactorily by FDA and USDA laboratories. The validated regulatory analytical methods for detection of residues of ivermectin are filed in the Food Additives Manual on display in FDA's Freedom of Information Public Room, (Room 12A-30, 5600 Fishers Lane, Rockville, MD 20857).

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of section 512 of the Food, Drug and Cosmetic Act and demonstrate that ivermectin (IVOMEC® Pour-On) when administered to cattle topically at one milliliter per 22 lbs. of body weight is safe and effective for the indications stated on the product labeling.

Ivermectin is currently regulated by (a) Injection: 21CFR522.1192 for use subcutaneously in cattle, reindeer and swine, and intramuscularly in horses; (b) Oral: 21CFR520.1192 for use as a paste in horses and cattle; 21CFR520.1193 for use as tablets in dogs; 21CFR520.1194 for use as a drench in sheep, and 21 CFR520.1195 for use as a liquid in horses.

The residue data confirm that for the topical route of administration 15 ppb is the tolerance for ivermectin H2B1a as the marker residue in liver tissue of cattle. Based on the tolerance, a withdrawal time of 48 days was determined.

Under section 512 (c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 360b(c)(2)(F)(ii)], this approval qualifies for three years of marketing exclusivity because new clinical, field investigations and human food safety data were required for its approval.

The agency concludes that adequate directions for over the counter lay use have been written for the proposed conditions of topical use of ivermectin in cattle. Diagnosis of the infections can be made with a degree of certainty by the layman. The conditions described on the labeling are likely to be carried out in practice. Approved products containing ivermectin for the same claims are marketed over the counter and the agency is not aware of any reason this topical product would require the marketing status to be changed.

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