Approval Date: June 5, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-841

B. Sponsor

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

C. Proprietary Name

Ivomec Pour-On® for Cattle

D. Established Name

ivermectin

E. Dosage Form, Route of Administration, and Dosage

As discussed in the parent NADA 140-841 FOI summary (approval date December 4, 1990).

F. Indication

Previously approved indications are as discussed in the parent NADA 140-841 FOI summary (approval date December 4, 1990). Additional indications contained in this supplemental NADA are for control of infections of *Ostertagia ostertagi, Haemonchus placei, Trichostrongylus axei, Oesophagostomum radiatum, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment.

G. Effect of Supplement

New claims for persistent control of gastrointestinal roundworms

II. EFFECTIVENESS

Data demonstrating the effectiveness of IVOMEC Pour-On for Cattle for previously approved indications are discussed in the parent NADA 140-841 FOI summary (approval date December 4, 1990). Data from the following dose confirmation trials demonstrate that IVOMEC Pour-On for Cattle given at the recommended dosage controls infections of *Ostertagia ostertagi, Haemonchus placei, Trichostrongylus axei, Oesophagostomum radiatum, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment.

A. Dose Confirmation

Trial ASR 14346

1. Type of study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms.

2. Investigator:

   Larry R. Cruthers, M.S., Ph.D.
   PLRS Laboratories, Inc.
   Corapeake, North Carolina

3. General design:

   a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

   b. Animals: Twenty (20) beef crossbred calves (10 per group). Animals were approximately 6 to 8 months old and weighed 182 to 266 kg at the start of the study. Animals were free of patent infections at the time of treatment.

   c. Controls: Negative controls received the vehicle for IVOMEC Pour-On.

   d. Infection: Infective larvae were given to each animal daily, starting on the day after treatment, according to the following schedule: *Ostertagia ostertagi* (1000 per day for 14 days); *Haemonchus placei* (500 per day for 14 days); *Trichostrongylus axei* (1000 per day for 14 days); and *Cooperia oncophora* (500 per day for 14 days).

   e. Dosage form: The dosage form was a solution containing 5 mg ivermectin per ml.

   f. Route of administration: Topical

   g. Dose: 1 ml/10 kg body weight (500 mcg ivermectin/kg body weight) once.

   h. Test duration: 41 or 42 days after treatment

   i. Pertinent variables measures: Worm counts were determined at necropsy

4. Results: The following parasites had a minimum of six adequately infected control animals and > or equal to 90% efficacy was demonstrated against them, the level required to justify a claim.

Parasite	Arithmetic mean		
	Control	**IVOMEC Pour-On**	**Percent reduction**
Ostertagia ostertagi	492.0	0.0	100
Haemonchus placei	340.0	2.0	99.4
Trichostrongylus axei	704.0	4.0	99.4
Cooperia oncophora	680.0	6.0	99.1

5. Statistical methods:

   Nematode percentage efficacies were calculated using the following formula:

   [Arithmetic mean number of nematodes in non-medicated cattle) - (Arithmetic mean number of nematodes in ivermectin-treated cattle)] ÷ (Arithmetic mean number of nematodes in non-medicated cattle) x 100 = Percentage Efficacy

6. Conclusion:

   Under the conditions of this study, IVOMEC Pour-On for Cattle controlled infections of *Ostertagia ostertagi, Haemonchus placei, Trichostrongylus axei*, and *Cooperia oncophora* for 14 days after treatment.

7. Adverse reactions:

   There were no adverse reactions during the study.

Trial ASR 14553

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

2. Investigator:

   Bruce N. Kunkle, D.V.M., M.S., Ph.D.
   Merck & Co., Inc.
   Fulton, Missouri

3. General design:

   a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

   b. Animals: Twenty-eight (28) crossbred calves (7 per group). Animals were approximately 6 months old and weighed 152 to 221 kg at the start of the study. All animals were treated with another anthelmintic during the acclimation period to eliminate any existing infections.

c. Controls: Negative controls received no treatment. Two groups received medications which are not pertinent to this document.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: *Trichostrongylus axei* (1000 per day for 15 days); *Cooperia punctata* (500 per day for 15 days); *Cooperia oncophora* (500 per day for 15 days); and *Oesophagostomum radiatum* (100 per day for 22 days).

e. Dosage form: The dosage form was a solution containing 5 mg ivermectin per ml.

f. Route of administration: Topical

g. Dose: 1 ml/10 kg body weight (500 mcg ivermectin/kg body weight) once.

h. Test duration: 49 to 51 days after treatment

i. Pertinent variables measured: Worm counts were determined at necropsy.

4. Results: The following parasites had a minimum of six adequately infected control animals and > or equal to 90% efficacy was demonstrated against them, the level required to justify a claim.

	Arithmetic mean		
Parasite	**Control**	**IVOMEC Pour-On**	**Percent reduction**
Trichostrongylus axei	5491.4	2.9	>99.9
Oesophagostomum radiatum	121.4	0	100.0
Cooperia punctata	3082.8	2.9	>99.9
Cooperia oncophora	300.0	2.9	99.0

5. Statistical methods:

Nematode percentage efficacies were calculated using the following formula:

[Arithmetic mean number of nematodes in non-medicated cattle) - (Arithmetic mean number of nematodes in ivermectin-treated cattle)] ÷ (Arithmetic mean number of nematodes in non-medicated cattle) x 100 = Percentage Efficacy

6. Conclusion:

Under the conditions of this study, IVOMEC Pour-On for Cattle controlled infections of *Trichostrongylus axei, Cooperia punctata* and *Cooperia oncophora* for 14 days after treatment and *Oesophagostomum radiatum* for 22 days after treatment.

7. Adverse reactions:

Some animals had loose stools during the trial and one animal vomited. These health problems were not believed to be related to the experimental treatments.

Trial ASR 15185

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

2. Investigator:

   Charles H. Courtney, D.V.M., Ph.D.
   University of Florida
   Gainesville, Florida

3. General design:

   a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

   b. Animals: Twenty (20) Angus cross calves (10 per group). Animals were approximately 8 to 10 months old and weighed 208 to 260 kg at the start of the study. Animals were free of patent infections at the time of treatment.

   c. Controls: Negative controls received the vehicle for IVOMEC Pour-On.

   d. Infection: Infective larvae were given to each animal daily, starting on the day after treatment, according to the following schedule: *Ostertagia ostertagi* (1000 per day for 14 days); *Haemonchus* spp. (500 per day for 14 days); *Trichostrongylus axei* (1000 per day for 14 days); and *Cooperia* spp. (500 per day for 14 days).

   e. Dosage form: The dosage form was a solution containing 5 mg ivermectin per ml.

   f. Route of administration: Topical

   g. Dose: 1 ml/10 kg body weight (500 mcg ivermectin/kg body weight) once.

   h. Test duration: 42 or 43 days after treatment

   i. Pertinent variables measured: Worm counts were determined at necropsy.

4. Results: The following parasites had a minimum of six adequately infected control animals and > or equal to 90% efficacy was demonstrated against them, the level required to justify a claim.

Parasite	Arithmetic mean		
	Control	**IVOMEC Pour-On**	**Percent reduction**
Ostertagia ostertagi	496.0	0.2	>99.9
Haemonchus placei	227.6	0.0	100
Trichostrongylus axei	1268.1	0.0	100
Cooperia punctata	389.1	0.0	100
Cooperia oncophora	223.4	0.0	100

5. Statistical methods:

   Nematode percentage efficacies were calculated using the following formula:

   [Arithmetic mean number of nematodes in non-medicated cattle) - (Arithmetic mean number of nematodes in ivermectin-treated cattle)] ÷ (Arithmetic mean number of nematodes in non-medicated cattle) x 100 = Percentage Efficacy

6. Conclusion:

   Under the conditions of this study, IVOMEC Pour-On for Cattle controlled infections of *Ostertagia ostertagi, Haemonchus placei, Trichostrongylus axei, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment.

7. Adverse reactions:

   One animal hit its nose against a fence resulting in a bloody nose. This event was not believed to be related to the experimental treatments.

Trial ASR 13980

1. Type of study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms and lungworms.

2. Investigator:

   R.E. Plue, D.V.M.
   Springdale, Arkansas

3. General design:

   a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

   b. Animals: Thirty-five (35) Holstein calves (7 per group). Animals were approximately 6 to 8 months old and weighed 142.9 to 207.3 kg at the start of the study. Animals were free of patent infections at the time of treatment.

c. Controls: Negative controls were untreated. Three groups received a medication or were treated at a time not pertinent to this document.

d. Infection: Infective larvae were given to each calf 14 days after treatment, according to the following schedule: *Oesophagostomum radiatum* (1,000).

e. Dosage form: The dosage form was a solution containing 5 mg ivermectin per ml.

f. Route of administration: Topical

g. Dose: 1 ml/10 kg body weight (500 mcg ivermectin/kg body weight) once.

h. Test duration: 49 to 51 days after treatment

i. Pertinent variables measured: Worm counts were determined at necropsy which was 49, 50, or 51 days after treatment and 35, 36, or 37 days after the last larvae were administered.

4. Results - The following parasite had a minimum of six adequately infected control animals and at 14 days from treatment to infection demonstrated > or equal to 90% efficacy, the level required to justify a claim:

	Arithmetic mean		
Parasite	**Control**	**IVOMEC Pour-On**	**Percent reduction**
Oesophagostomum radiatum	76	2.8	96

5. Statistical methods:

   Nematode percentage efficacies were calculated using the following formula:

   [Arithmetic mean number of nematodes in non-medicated cattle) - (Arithmetic mean number of nematodes in ivermectin-treated cattle)] ÷ (Arithmetic mean number of nematodes in non-medicated cattle) x 100 = Percentage Efficacy

6. Conclusion:

   Under the conditions of this study, IVOMEC Injection for Cattle controlled infections of *Oesophagostomum radiatum* for 14 days after treatment.

7. Adverse reactions:

   There were no adverse reactions reported.

III. ANIMAL SAFETY

As discussed in the parent NADA 140-841 FOI summary (approval date December 4, 1990).

IV. HUMAN SAFETY

As discussed in the parent NADA 140-841 FOI summary (approval date December 4, 1990) and in the supplement to NADA 128-409 FOI summary (IVOMEC Injection for Cattle; approval date September 12, 1994).

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of section 512 of the Act and demonstrate that ivermectin topical formulation, when used under the proposed conditions of use, is safe and effective for the control of infections of *Ostertagia ostertagi, Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment.

For cattle the tolerance of residues are specified in 21 CFR 556.344. A tolerance for the marker residue (22, 23-dihydro-avermectin B1a) of ivermectin is 100 ppb in the liver (target tissue). The withdrawal time is 48 days following one topical application of IVOMEC Pour-On® for Cattle as specified in 21 CFR 524.1193.

The original approval of ivermectin topical formulation was as an over-the-counter drug. Adequate directions for use have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall retain over-the-counter marketing status.

Under the Center's supplemental approval policy 21 CFR 514.106(b)(2), this is a Category II change. The approval of this change did not require a reevaluation of the safety or effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval 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. The three years of marketing exclusivity applies only to the new claim for the control of *Ostertagia ostertagi, Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment in cattle for which the supplemental application was approved.

VI. ATTACHMENTS

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.