Approval Date: February 24, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 128-409

B. Sponsor

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

C. Proprietary Name

IVOMEC® Injection for Cattle and Swine

D. Established Name

ivermectin

E. Pharmacological Category

Anticoccidial, antimicrobial, antiparasitic, etc.

F. Dosage Form

IVOMEC Injection is a sterile 1% solution available in 50, 200, 500, and 1000 mL plastic containers.

G. Dispensing Status

OTC

H. Route of Administration

Subcutaneous injection

I. Indication

CATTLE: Ivomec injection is indicated for the effective treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, lice, and mange mites:

Gastrointestinal Roundworms (adults and 4th stage larvae):

- *Ostertagia ostertagi* (including inhibited O. ostertagi)
- *O. lyrata*
- *Haemonchus placei*
- *Trichostrongylus axei*
- *T. colubriformis*
- *Cooperia oncophora*
- *C. punctata*
- *C. pectinata*

- *Oesophagostomum radiatum*
- *Bunostomum phlebotomum*
- *Nematodirus helvetianus* (adults only)
- *N. spathiger* (adults only)

Lungworms (adults and fourth-stage larvae):

- *Dictyocaulus viviparus*

Cattle Grubs (parasitic stages):

- *Hypoderma bovis*
- *H. lineatum*

Sucking Lice:

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

Mites (Scabies):

- *Psoroptes ovis* (syn. *P. communis* var. *bovis*)
- *Sarcoptes scabiei* var. *bovis*

***SWINE*:**
Ivomec Injection is indicated for the effective treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, lice, and mange mites:

Gastrointestinal Roundworms:

- Large roundworm, *Ascaris suum* (adults and fourth-stage larvae)
- Red stomach worm, *Hyostrongylus rubidus* (adults and fourth stage larvae
- Nodular worm, *Oesophagostomum* spp. (adults and fourth stage larvae)
- Threadworm, *Strongyloides ransomi* (adults)

Somatic Roundworm Larvae:

- Threadworm, *Strongyloides ransomi* (somatic larvae)
- Sows must be treated at least seven days before farrowing to prevent infection in piglets.

Lungworms:
- *Metastrongylus* spp. (adults)

Lice:

- *Haematopinus suis*

Mange Mites:

- *Sarcoptes scabiei* var. *suis*

***REINDEER*:**
For the treatment and control of warbles (*Oedemagena tarandi*)

Additional indications contained in this supplemental NADA are for control of infections of *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment, and *Oesophagostomum radiatum*, *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia punctata*, and *Cooperia oncophora* for 14 days after treatment in cattle.

J. Effect of Supplement

New claims for persistent control of gastrointestinal roundworms and lungworms in cattle.

II. EFFECTIVENESS

Data demonstrating the effectiveness of IVOMEC Injection for Cattle for previously registered indications are discussed in the parent NADA 128-409 FOI Summary (approval date February 7, 1984). Data from the following dose confirmation trials demonstrate that IVOMEC Injection for Cattle given at the recommended dosage controls infections of *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment, and *Oesophagostomum radiatum*, *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia punctata,* and *Cooperia oncophora* for 14 days after treatment.

A. Dose Confirmation

1. Trial ASR 14553

(i) Type of study:

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

(ii) Investigator:

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

(iii) 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: *Ostertagia ostertagi* (1000 per day for 22 days); *Haemonchus placei* (500 per day for 15 days); *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, except that 1000 per

day were erroneously given for 2 days).

e. Dosage form: The dosage form was the approved formulation of injectable solution containing 10 mg ivermectin per mL.

f. Route of administration: Subcutaneous injection

g. Dose: 1 mL/50 kg body weight (200 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 to 51 days after treatment, 34 to 36 days after the last *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia punctata*, and *Cooperia oncophora* larvae were administered, and 27 to 29 days after the last *Ostertagia ostertagi* and *Oesophagostomum radiatum* larvae were administered.

(iv) Results

The following parasites had a minimum of six adequately infected control animals.

	Arithmetic mean		
Parasite	**Control**	**IVOMEC**	**Percent Reduction**
Ostertagia ostertagi	4214.3	0.0	100
Haemonchus placei	1345.7	54.3	96.0
Trichostrongylus axei	5491.4	14.3	99.7
Cooperia puncatata	3082.8	0.0	100
Cooperia oncophora	300.0	0.0	100
Oesoph. radiatum	121.4	1.4	98.8

(v) Statistical methods:

Nematode percentage efficacies were calculated using the following formula:

$$\% \text{ Efficacy} = \frac{\text{Mean \# of nematodes in non medicated cattle} - \text{Mean \# of nematodes in ivermectin treated cattle}}{\text{Mean \# of nematodes in non medicated cattle}} \text{X } 100$$

(vi) Conclusion:

Under the conditions of this study, IVOMEC Injection for Cattle controlled infections of *Ostertagia ostertagi* and *Oesophagostomum radiatum* for 21 days after treatment, and *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia punctata* and *Cooperia oncophora* for 14 days after treatment.

(vii) 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.

2. Trial ASR 15065

(i) Type of study:

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

(ii) Investigator:

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

(iii) General design:

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

b. Animals: Thirty (30) Holstein calves (10 per group). Animals were approximately 4 to 5 months old and weighed 157 to 234 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 Injection for Cattle subcutaneously at 1 mL/50 kg body weight. One group received a medication which is not pertinent to this document.

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 21 days) and *Dictyocaulus viviparus* (50 per day for 28 days).

e. Dosage form: The dosage form was the approved formulation of the injectable solution containing 10 mg ivermectin per mL.

f. Route of administration: Subcutaneous injection

g. Dose: 1 mL/50 kg body weight (200 mcg ivermectin/kg body weight) once.

h. Test duration: 49 to 50 days after treatment

i. Pertinent variables measured: Worm counts were determined at necropsy which was 49 to 50 days after treatment, 28 to 29 days after the last *Ostertagia ostertagi* larvae were administered, and 21 to 22 days after the last *Dictyocaulus viviparus* larvae were administered.

(iv) Results

The following parasites had a minimum of six adequately infected control animals:

Parasite	**Arithmetic mean**		**Percent Reduction**
	Control	**IVOMEC**	
Dictyocaulus viviparus	20.3	0	100
Ostertagia ostertagi	1258.0	82.0	93.5

(v) Statistical methods:

Nematode percentage efficacies were calculated using the following formula:

$$\% \text{ Efficacy} = \frac{\text{Mean \# of nematodes in non medicated cattle} - \text{Mean \# of nematodes in ivermectin treated cattle}}{\text{Mean \# of nematodes in non medicated cattle}} \text{X } 100$$

(vi) Conclusion:

Under the conditions of this study, IVOMEC Injection for Cattle controlled infections of *Ostertagia ostertagi* for 21 days after treatment and *Dictyocaulus viviparus* for 28 days after treatment.

(vii) Adverse reactions:

One animal died 22 days after treatment. The apparent cause of death was an esophageal impaction, which was not believed to be related to the experimental treatment.

3. Trial ASR 15071

(i) Type of study:

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

(ii) Investigator:

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

(iii) General design:

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

b. Animals: Thirty (30) crossbred calves (10 per group). Animals were approximately 8 to 9 months old and weighed 235 to 275 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 Injection for Cattle subcutaneously at 1 mL/50 kg body weight. One group received a medication which is not pertinent to this document.

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

e. Dosage form: The dosage form was the approved formulation of the injectable solution containing 10 mg ivermectin per mL.

f. Route of administration: Subcutaneous injection

g. Dose: 1 mL/50 kg body weight (200 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 which was 42 or 43 days after treatment and 28 or 29 days after the last larvae were administered.

(iv) Results

The following parasites had a minimum of six adequately infected control animals:

Parasite	Arithmetic mean		Percent Reduction
	Control	IVOMEC	
Haemonchus placei	1022.0	16.0	98.4
Trichostrongylus axei	1578.0	4.0	99.7
Cooperia punctata	1996.2	11.0	99.4

(v) Statistical methods:

Nematode percentage efficacies were calculated using the following formula:

$$\% \text{ Efficacy} = \frac{\text{Mean \# of nematodes in non medicated cattle} - \text{Mean \# of nematodes in ivermectin treated cattle}}{\text{Mean \# of nematodes in non medicated cattle}} \text{X } 100$$

(vi) Conclusion:

Under the conditions of this study, IVOMEC Injection for Cattle controlled infections *Haemonchus placei*, *Trichostrongylus axei* and *Cooperia punctata* for 14 days after treatment.

(vii) Adverse reactions:

One animal exhibited lameness of the left rear leg during the trial. This event was not believed to be related to the experimental treatments.

4. Trial ASR 15073

(i) Type of study:

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

(ii) Investigator:

Edward G. Johnson, D.V.M.
Johnson Research
Parma, Idaho

(iii) General design:

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

b. Animals: Thirty (30) crossbred calves (10 per group). Animals were approximately 6 to 10 months old and weighed 215 to 283 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 Injection for Cattle subcutaneously at 1 mL/50 kg body weight. One group received a medication which is not pertinent to this document.

d. Infection: Infective larvae were given to each animal daily, starting on the day after treatment, according to the following schedule: *Haemonchus placei* (500 per day for 14 days); *Trichostrongylus axei* (1000 per day for 14 days); *Cooperia punctata* (1000 per day for 14 days); *Cooperia oncophora* (1000 per day for 14 days); and *Dictyocaulus viviparus* (50 per day for 21 days).

e. Dosage form: The dosage form was the approved formulation of the injectable solution containing 10 mg ivermectin per mL.

f. Route of administration: Subcutaneous injection

g. Dose: 1 mL/50 kg body weight (200 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 which was 42 or 43 days after treatment and 28 or 29 days the last *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia punctata*, and *Cooperia oncophora* larvae were administered, and 21 or 22 days after the last *Dictyocaulus viviparus* larvae were administered.

(iv) Results

The following parasites had a minimum of six adequately infected control animals:

Parasite	Arithmetic mean		Percent Reduction
	Control	IVOMEC	
Haemonchus placei	1353.5	10.0	99.3
Trichostrongylus axei	1202.0	0.0	100
Cooperia punctata	3067.8	0.7	>99.9
Cooperia oncophora	696.0	0.7	>99.9
Dictyocaulus viviparus	32.4	0.0	100

(v) Statistical methods:

Nematode percentage efficacies were calculated using the following formula:

$$\% \text{ Efficacy} = \frac{\text{Mean \# of nematodes in non medicated cattle} - \text{Mean \# of nematodes in ivermectin treated cattle}}{\text{Mean \# of nematodes in non medicated cattle}} \text{X } 100$$

(vi) Conclusion:

Under the conditions of this study, IVOMEC Injection for Cattle controlled infections of *Dictyocaulus viviparus* for 21 days after treatment, and *Haemonchus placei*, *Trichostrongylus axei, Cooperia punctata* and *Cooperia oncophora* for 14 days after treatment.

(vii) Adverse reactions:

Signs of respiratory disease, arthritis and bloat were seen in two animals during the trial. These health problems were not believed to be related to the

experimental treatments.

5. Trial ASR 13980

(i) Type of study:

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

(ii) Investigator:

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

(iii) 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* (1000).

e. Dosage form: The dosage form was the approved formulation of the injectable solution containing 10 mg ivermectin per mL.

f. Route of administration: Subcutaneous injection

g. Dose: 1 mL/50 kg body weight (200 mcg ivermectin/kg body weight) once.

h. Test duration: 49, 50, or 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.

(iv) Results

The following parasites had a minimum of six adequately infected control animals:

Parasite	**Arithmetic mean**		**Percent Reduction**
	Control	**IVOMEC**	
Oesophagosomum radiatum	76	1.3	98

(v) Statistical methods:

Nematode percentage efficacies were calculated using the following formula:

$$\% \text{ Efficacy} = \frac{\text{Mean \# of nematodes in non medicated cattle} - \text{Mean \# of nematodes in ivermectin treated cattle}}{\text{Mean \# of nematodes in non medicated cattle}} \text{X } 100$$

(vi) Conclusion:

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

(vii) Adverse reactions:

There were no adverse reactions reported.

III. TARGET ANIMAL SAFETY

As discussed in the parent NADA 128-409 FOI Summary (approval date February 7, 1984).

IV. HUMAN FOOD SAFETY

As discussed in the parent NADA 128-409 FOI Summary (approval date February 7, 1984) and in the supplement to NADA 128-409 FOI Summary (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 injection, when used under the proposed conditions of use, is safe and effective for the control of infections of *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment, and *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 35 days following one subcutaneous injection of IVOMEC as specified in 21 CFR 522.1192.

The original approval of ivermectin injection 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 *Dictyocaulus viviparus* and *Ostertagia ostertagi* for 21 days after treatment

and *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.

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.