I. GENERAL INFORMATION

A. File Number

NADA 140-854

B. Sponsor

Syntex Animal Health, Inc.
3401 Hillview Avenue
Palo Alto, CA 94304

C. Proprietary Name

Synanthic®

D. Established Name

oxfendazole

E. Dosage Form

Suspension 22.5% (225 mg/ml)
Suspension 9.06% (90.6 mg/ml)

F. Dosage Regimen

4.5 mg oxfendazole/kg body weight (2.05 mg/lb).

G. Route of Administration

Suspension 22.5% (225 mg/ml): intraruminally, using the rumen injector, or orally, using appropriate dosing equipment.
Suspension 9.06% (90.6 mg/ml): oral administration only using appropriate dosing equipment.

H. Species/Class

Cattle

I. Indication

Oxfendazole is indicated for the treatment and control of:

Lungworms (*Dictyocaulus viviparus*):

- Adults, L-4. Stomach worms:
- Barberpole worms (*Haemonchus contortus* and *H. placei*): Adults.
- Brown stomach worms (*Ostertagia ostertagi*): Adults, L-4, and inhibited L-4 larvae.
- Small stomach worms (*Trichostrongylus axei*): Adults.

Intestinal worms:

- Hookworms (*Bunostomum phlebotomum*): Adults.
- Small intestinal worm (*Cooperia* spp.): Adults, L-4.
- Tapeworms (*Moniezia benedeni*): Adults.
- Nodular worms (*Oesophagostomum radiatum*): Adults.

II. EFFECTIVENESS

Oxfendazole was identified in the laboratories of Syntex Research, Palo Alto, California, as having broad spectrum anthelmintic properties against larval and adult forms of gastrointestinal cestodes and nematodes in various animal species. The drug was therefore evaluated for efficacy in cattle both within the United States and internationally.

In the United States, pivotal studies using the intraruminal method of delivery included dose-titration studies, dose-confirmation studies, and clinical field trials in five different geographical areas. Doses of 2.25 to 6.75 mg oxfendazole/kg of body weight were used in the dose-titration studies, while a dose of 4.5 mg/kg was used for the dose-confirmation and field trial studies. Oxfendazole was supplied to the investigators as a 22.5% suspension which was administered either intraruminally or orally. For oral administration only, the drug was supplied to investigators as a 9.06% suspension. The drug was evaluated for efficacy in controlled critical trials where groups of naturally infected animals were treated with the compound, sacrificed approximately 14 days later, and the remaining parasitic burdens compared to those of control animals. These dose titration and dose-confirmation studies were conducted by Dr. M. Sharp, Vernon, Texas; Drs. J. A. Hawkins and C. Ed Couvillion, Mississippi State University, Mississippi State, Mississippi; Dr. J. E. Miller, Louisiana State University, Baton Rouge, Louisiana.

Internationally, a series of pivotal studies were conducted by Dr. J. Berger, the Wellcome Foundation Ltd., Kwanyanga, South Africa, in animals artificially infected with various nematodes. One study involved animals naturally infected with tapeworms (*Moniezia benedeni*). These studies were conducted using the 9.06% oxfendazole suspension (See Table: Efficacy of Oxfendazole in Controlled Critical Studies Against Various Parasites At 4.5 mg/kg).

Each claim for a larval or adult form of a helminth species is supported by adequate and well controlled studies.

The efficacy was calculated as follows:

$$\frac{(Number\ of\ parasites\ in\ control\ animals - Number\ of\ parasites\ in\ treated\ animals)}{(Number\ of\ parasites\ in\ control\ animals\ \times 100)} = \%\ Removal$$

The data were then analyzed statistically by parametric and nonparametric methods. The results of these analyses support the claim that, in cattle, oxfendazole is highly effective anthelmintic with a wide range of activity at a dose of 4.5 mg/kg of body weight.

EFFICACY OF OXFENDAZOLE IN CONTROLLED CRITICAL STUDIES AGAINST VARIOUS PARASITES AT 4.5 MG/KG

Pivotal Studies

Parasite	**(% Efficacy) Range**	**Investigator**
Haemonchus contortus	100	H, S
Haemonchus placei, Adults	99.9 - 100	M, B, G
Ostertagia ostertagi Inhibited larvae	24 - 83.5	S, H, M, G
Ostertagia ostertagi L-4	70 - 98	B, S
Ostertagia ostertagi Adults	99.2 - 100	S, H, M, B, G
Trichostrongylus axei Adults	99 - 100	S, H, M, G
Cooperia spp. L-4, Adults	99 - 100	M, H, S, B, G
Bunostomum phlebotomum Adults	100	M, B
Oesophagostomum radiatum Adults	100	M, H, S, B, G
Dictyocaulus viviparus L-4	100	B
Dictyocaulus viviparus Adults	96.7 - 100	H, S, B
Moniezia benedeni Adults	100	B

Pivotal Investigators/Number of studies conducted:
S = Dr. M. Sharp, Vernon, TX (USA)/1
H = Dr. J. Hawkins/Dr. C. Ed Couvillion, Mississippi State, MS (USA)/1
M = Dr. J. Miller, Baton Rouge, LA (USA)/1
B = Dr. J. Berger, Wellcome, South Africa/6
G = Dr. J. Guinan, Wellcome, Australia/1

EFFICACY OF OXFENDAZOLE AGAINST VARIOUS PARASITES AT 4.5 MG/KG CORROBORATIVE STUDIES

Parasite	**(% Efficacy) Range**	**Investigator**
H. placei	100	C
Haemonchus spp.	100	D
O. ostertagi Adult	99.3-100	D,A,E,C,K
O. ostertagi L4	100	D,E
O. ostertagi Inhibited larvae	94.8-99.5	A,E,K
T. axei	99.6-100	A,C,K
Cooperia spp.	99.9-100	D,A,C,K
O. radiatum	99.5	C
D. viviparus Adult	100	A,D,W,P
D. viviparus L-4	87.5-100	D,W

Corroborative Investigators/Number of studies conducted:
P = H. Pfeiffer, Veterinary Medical University, Vienna, Austria/1
D = N. E. Downey, the Agricultural Institute, Dublin, Ireland/1
E = D. C. Elliot, Ministry of Agriculture, and Fisheries, New Zealand/1
W = N. H. Wynne-Jones, ICI Tasman Vaccine Ltd., Upper Hutt, New Zealand/1
A = J. Armour, Glasgow University, Scotland/2
C = C. Curr, Wellcome, Australia/1
K = T. Kistner, Corvallis, Oregon (USA)/1

Dose Titration Study (pivotal), James E. Miller, D.V.M., Louisiana State University, Baton Rouge, LA - Study IAS 1134-613.1 Forty calves were randomly assigned to 4 groups containing 10 animals each and were dosed with oxfendazole as follows: Group 1, 6.75 mg/kg; Group 2, 4.50 mg/kg; Group 3, 2.25 mg/kg and Group 4, untreated controls. Approximately two weeks after treatment, all animals were sacrificed and nematodes were collected. Oxfendazole was 98% or more efficacious against mature adults of all species. No adverse reactions were recorded during the study. Efficacy was as follows:

Median Percent Efficacy

Parasite	**2.25 mg/kg**	**4.5 mg/kg**	**6.75 mg/kg**
T. axei	98	99	100
H. placei	100	100	100
Cooperia spp. Adults	98	99	100
O. ostertagi Adults	98	100	100
O. ostertagi Late 4th stage	30	0	60
O. ostertagi Early 4th stage	0	24	92
B. phlebotomum	100	100	100
O. radiatum	100	100	100

Dose Titration Study (pivotal), James A. Hawkins, D.V.M., Ph.D., C. Ed Couvillion, D.V.M., Ph.D., Mississippi State University, Mississippi State, MS - Study IAS 1134-613.1 Forty calves of mixed sexes, obtained from a single farm in Mississippi, were selected. Ten animals were randomly assigned to each of four treatment groups. Three groups of animals were dosed intraruminally with oxfendazole as follows: Group 1, 6.75 mg/kg; Group 2, 4.50 mg/kg; and Group 3, 2.25 mg/kg. The control animals in Group 4 were not treated. No adverse reactions were reported during the course of the study. The animals were necropsied seven days after treatment. Efficacy was as follows:

Median Percent Efficacy

Parasite	**2.25 mg/kg**	**4.5 mg/kg**	**6.75 mg/kg**
T. axei	100	99.9	100
H. contortus	100	100	100
Cooperia spp.	99.4	100	99.6
D. viviparus	100	100	100
O. radiatum	100	100	100
O. ostertagi Adults	94.4	99.6	99.5
O. ostertagi Inhibited 4th stage	32.2	79.2	89.3

Means connected by the same line are not significantly different.

Dose Confirmation Study (pivotal), M.L. Sharp, D.V.M., Vernon, TX - Study IAS 1134-606 Twenty calves of mixed sexes were obtained from suppliers in south Texas. Equal numbers of animals were randomly assigned to treatment groups. Group 1 animals were treated with 4.5 mg/kg of oxfendazole while the control animals in Group 2 were untreated. Treatments were administered by intraruminal injection using the 22.5% suspension. There were no adverse reactions reported during the course of the study. All animals were necropsied seven days after treatment. Oxfendazole was 100% efficacious in removing the adults stage of the following species: *O. ostertagi, Haemonchus*spp., *T. axei, O. radiatum, Cooperia*spp.,

and *D. viviparus*. Although they were not totally eliminated, the L4 stages of *O. ostertagi* were significantly reduced. The percent efficacy for the Developing L4 was 70% (p=.01) and for the Early L4 the efficacy was 83.5% (p=.02)

Critical Study (pivotal), J. Berger, Wellcome, South Africa - Study IAS 1067-C189

In a trial in which 18 artificially infected calves were used, the efficacy of a dose rate of 4.5 mg/kg of oxfendazole was assessed against the fourth larval stage of *Cooperia*spp. and the adult stage of *D. viviparus*. Efficacies of 99.7% and 96.7% respectively were recorded.

Critical Study (pivotal), J. Berger, Wellcome, South Africa - Study IAS 1067-C249

In a trial in which 19 artificially infected calves were used, the efficacy of a dose rate of 4.5 mg/kg of oxfendazole was assessed against the fourth larval stage of *D. viviparus*and the adults stage of *B. phlebotomum*. Efficacies of 95.4% and 100%, respectively, were recorded.

Critical Study (pivotal), J. Berger, Wellcome, South Africa - Study IAS 1067-C277

In a trial in which 31 artificially infected calves were used, the efficacy of a dose rate of 4.5 mg/kg of oxfendazole was assessed against the fourth larval and the adult stages of *O. ostertagi.* Efficacy of 98.0% was recorded.

Critical Study (pivotal), J. Berger, Wellcome, South Africa - Study IAS 1067-C279

In a trial in which 21 artificially infected calves were used, the efficacy of a dose rate of 4.5 mg/kg of oxfendazole was assessed against the adult stages of *H. placei, Cooperia*spp. and *O. radiatum*and against adult *D. viviparus*. Efficacies of 99.9%, 99.9%, 100%, and 100%, respectively, were recorded.

Critical Study (pivotal), J. Berger, Wellcome, South Africa - Study IAS 1067-C290

In a critical trial using calves naturally infected with *M. benedeni*, 11 of 12 treated calves were totally cleared of tapeworms following a dose of 4.5 mg/kg micronized oxfendazole. The remaining calf carried a single scolex without strobila.

Critical Study (pivotal), J.J. Guinan et al, Wellcome, Australia - Study IAS 1103-C354

Geometric Mean % Efficiency

Parasite	**OFZ 9.06% PO**	**OFZ Batch 2 22.5% IR**	**OFZ Batch 3 22.5% IR**
O. ostertagi Adults	100	99.7	99.9
O. ostertagi Inhibited L4	89.8	83.5	74.3
T. axei	99.9	99.8	99.9
H. placei	100	100	100
Cooperia spp.	100	99.8	99.9
O. radiatum	100	100	100

*PO = Suspension, oral; IR = Suspension, injected intraruminally
In this study, both suspensions of oxfendazole were found to be 100% ovicidal by 24 hours post-treatment.

Dose Titration Study (corroborative), T.P. Kistner, Oregon State University, Corvallis, OR - Study IAS 1067-X819

Oxfendazole (OFZ) suspension was administered orally to pregnant cows at doses of 2.5 and 5.0 mg/kg of body weight. All cows were heavily infected with inhibited L-4 of *O. ostertagi*. At 2.5 mg/kg (n=11), OFZ was 81.6% efficacious against inhibited L-4 stages of ostertagiasis. At 5.0 mg/kg (n=10), OFZ was 94.8% effective against the inhibited L-4 of ostertagiasis. Efficacy against *T. axei*adults was 100%.
Numerous corroborative, controlled critical studies have been conducted in other countries (See Table: Efficacy Of Oxfendazole Against Various Parasites At 4.5 Mg/Kg Corroborative Studies):

Critical Study (corroborative), H. Pfeiffer, Veterinary Medical University, Vienna, Austria - Study IAS 1067-C692

A single 4.5 mg/kg dose of oxfendazole was effective in removing adult *D. viviparus*.

Critical Study (corroborative), N. E. Downey, The Agricultural Institute, Dublin, Ireland - Study IAS 1067-X817

The anthelmintic activity of oxfendazole was tested in calves at dosages of 2.5 and 5.0 mg/kg. At 2.5 and 5.0 mg/kg, oxfendazole showed 100% efficacy against adult *O. ostertagi*, fourth stage *Ostertagia*spp., adult *Haemonchus*spp., adult *Cooperia*spp., adult and fourth stage *D. viviparus*. Against adult *C. oncophora*, efficacy was 99.8 and 100% at doses of 2.5 and 5.0 mg respectively.

Critical Study (corroborative), D. C. Elliot, Ministry of Agriculture, and Fisheries, New Zealand - Study IAS 1067-C099

This study was designed to determine the efficacy of oxfendazole against inhibited fourth stage larvae of *O. ostertagi*when administered orally to cattle at a rate of 4.5

mg/kg of body weight. Seven treated steers were compared to seven control steers seven days after treatment. The efficacies for early L-4, L-4, and adults were 92.6, 96.8, and 99.7% respectively.

Critical Study (corroborative), N.H. Wynne-Jones, ICI Tasman Vaccine Ltd., Upper Hutt, New Zealand - Study IAS 1067-X818

Twelve Fresian calves harboring naturally acquired infections of *D. viviparus*were used in a control project to test the efficacy of oxfendazole at 2.5 mg/kg. The 2.5 mg/kg dose rate was 100% effective against all stages of *D. viviparus*.

Critical Study (corroborative), J. Armour, Glasgow University, Scotland - Study IAS 1067-C033

Oxfendazole at the dose rate of 4.53 mg/kg was 100% effective in removing adult and immature stages of *D. viviparus*in yearling calves. The absence of larvae in the faeces of the treated animals is a positive factor in the control of bovine husk.

Critical Study (corroborative), J. Armour, Glasgow University, Scotland - Study IAS 1067-C114

An overall efficacy of 99.5% against adults and inhibited larvae of *O. ostertagi*with total elimination (100%) of the other abomasal parasite *T. axei*is excellent. In addition a 100% reduction of the intestinal nematode *C. oncophora*shows this to be an extremely effective anthelmintic for use in the treatment of bovine parasitic gastroenteritis.

Critical Study (corroborative), C. Curr, Wellcome, Australia - Study IAS 1067-C062

Weaner cattle, carrying naturally acquired burdens of gastrointestinal nematodes, were treated with oxfendazole at a dose of 4.53 mg/kg. Complete clearance of adult *H. placei*, and immature *Cooperia*spp. was effected; and against adult *O. ostertagi*, *T. axei*, *Cooperia*spp. and *O. radiatum*efficacies of 99.9%, 99.6%, 99.9% and 99.5%, respectively were recorded.

Clinical Field Trials

The effectiveness of oxfendazole has been evaluated in clinical field trials. These trials were conducted by Julian H. Edwards, D.V.M., Scotland Neck, NC; Ross A. Hendry, D.V.M., Brandenton, FL; Edward O. Kearley, D.V.M., Ceres, CA; Larry E. Mehr, D.V.M., Memphis, TN; and Daryl G. Meyer, D.V.M., Gothenburg, NE.

Each of five investigators selected approximately 100 cattle for field trials to evaluate the anthelmintic efficacy of intraruminally-administered oxfendazole. Group 1 animals were treated with a 22.5% oxfendazole suspension by intraruminal injection, at a dose rate of 4.5 mg per kg of live body weight. Group 2 animals were untreated controls. Fecal samples were collected prior to treatment for EPG (eggs per gram) determination and again approximately 7 to 11 days post-treatment. There were no adverse reactions recorded during the course of the trials.

In four of the five trials, oxfendazole treatment was effective in reducing the fecal egg counts ($p<.001$); the median reduction ranged from 92% to 100%. In the remaining trial, the median reduction for oxfendazole was 100% while the median reduction for

the controls was 0%. However, the oxfendazole advantage was not significant (p=.19), possibly due to sampling errors.

FIELD TRIAL SUMMARY

Study Number	Investigator/ Location	No. OFZ Treated	No. Controls	Median % EPG Reduction	
				OFZ Treated	Controls
1134-607	Edwards/NC	50	50	100%	0%
1134-607.1	Hendry/FL	50	50	100%	0%
1134-607.1 (1)	Kearley/CA	49	50	92%	44%
1134-607.1 (2)	Mehr/TN	44	50	100%	0%
1134-607	Meyer/NE	48	49	100%	0%

Additional Study - Pharmacokinetics Biocomparability Study (corroborative), K. Bairden, Glasgow University, Scotland - Study IAS 1103-C470

The pharmacokinetics of oxfendazole were not significantly different when administered orally or by intraruminal injection. A 4.5 mg/kg dose of oxfendazole produced peak plasma concentrations of 0.20 µg by the intraruminal injection route and 0.18 µg by the oral route. Both routes produced nearly identical areas under the curve. For both routes, efficacy against inhibited L-4 *O. ostertagi*was 97%, 100% for adult *O. ostertagi*, and 100% for all stages of *C. oncophora*.

III. TARGET ANIMAL SAFETY

The following studies to evaluate the safety of oxfendazole were performed both in the United States and internationally:

A. Pivotal Studies

Acute and Sub-Acute Target Species Toxicity Study

1) **Target Species Safety Study (pivotal), R.D. Glock, Casa Grande, AZ - Study ITS 42-CW-85** Three each of 6- to 8-month-old mixed beef-breed heifers and bulls were assigned randomly to 5 treatment groups. The test article was 22.5% oxfendazole suspension. Control animals received intraruminal doses of unmedicated suspension. Cattle received doses of 0, 4.5, 13.5, or 22.5 mg of oxfendazole per kilogram of body weight intraruminally via injection through the left paralumbar fossa on study days 1, 4, and 8. Cattle receiving 112.5 mg/kg were given a single intraruminal dose. Necropsies were performed 10 days after the last dose of animals receiving 0 through 22.5 mg/kg; necropsies were performed 14 days after the single dose of 112.5mg/kg. Predose and terminal body weights and hematologic and clinical chemistry values were determined. Multiple clinical observations were made daily.

   The single intraruminal dose of 112.5 mg/kg caused only transient gastric disturbance characterized by non-productive eructation in one of three males and in one of three females. Minor swellings occurred at the sites of the multiple injections in some animals in all groups, including controls.

Hematologic data, clinical chemistry values, and body weights were not altered by the treatment regimen. No gross or microscopic pathologic change attributable to oxfendazole treatment was observed in any dose group.

Reproductive Studies:

2) **Target Species Reproductive Study - Heifers (pivotal), T.A. Miller, Milford, IN - Study ITS 44-CW-85** Ninety-nine beef type heifers were randomized into three equal groups, were estrus synchronized using fenprostalene, and artificially inseminated with semen from an Angus bull. Heifers that did not conceive following artificial insemination were bred naturally. Oxfendazole, as 22.5% suspension, was administered intraruminally in individual doses of 4.5 or 13.5 mg/kg. Corresponding control cattle received doses of water intraruminally. Oxfendazole suspension or water was administered prior to artificial insemination and at weekly intervals from day 14 through day 42 of gestation and at approximately 60 day intervals for the remainder of the gestation. Dosing continued at approximately monthly intervals for two months during lactation. The study terminated when the calves were approximately 90 days old. Intraruminally-administered oxfendazole in multiple doses did NOT cause:

    a) anatomical abnormalities in calves

    b) decreases in calf birth weights

    c) decreases in average daily weight gain of calves

    d) alterations in conception rates

    e) alterations in length of gestation for artificially or naturally bred heifers

    f) alterations in time to pregnancy

    g) increases in the number of services required for pregnancy

    h) adverse effects on weight gains of heifers during gestation or lactation.

3) **Target Species Reproductive Study - Bulls (pivotal), Robert H. BonDurant, University of California, Davis, CA ITS 18-BO-86** Eighteen sexually mature mixed beef-breed bulls were assigned randomly to 3 treatment groups of 6 bulls each. Scrotal circumference was used as the randomization factor for study group assignments. Groups 1, 2, and 3 were designated as control, 1X oxfendazole, or 3X oxfendazole groups, respectively. Doses were 0 (vehicle), 4.5, and 13.5 mg oxfendazole/kg for groups 1, 2, and 3, respectively. Test materials were vehicle suspension (control) which contained no oxfendazole, and 22.5% oxfendazole suspension. Oxfendazole was administered at one or three times the intended clinical use level. Three doses of the test materials were administered by intraruminal injection within 8 days, (e.g., study days 1, 4, and 8). Breeding soundness parameters, including scrotal circumference measurement, assessment of sperm morphology, sperm motility, semen volume, and sperm counts, were evaluated during the 4-week acclimatization period and at weekly intervals for the 14-week observation period following treatment.

Oxfendazole administered intraruminally three times within 8 days at doses of one or three times the intended clinical use level did not cause effects on breeding soundness parameters, weight gains, or clinical health of sexually mature beef bulls.

B. Corroborative Studies:

Acute Target Species Toxicity Studies

1. **Target Species Safety Study (corroborative), Syntex Research, Palo Alto, CA. - Studies 50X-8858-CA and 73-CW-76** Three each young, beef-type steers and heifers were dosed once with 125 mg/kg oxfendazole, as the 2.265% suspension, using a small bore (1/4 inch) stomach tube. Clinical observations in the drug treated cattle included reduced appetite, feed consumption and rumen activity, fever, diarrhea, weight loss, and general weakness. Four of the six animals died prior to the end of the 14-day observation period. Gross gastrointestinal changes,observed at necropsy, included congestion, mucosal erosions/ulcers, hemorrhage, free blood with fibrin, and sloughed mucosa along with increased fluid contents. Healed gastric ulcers were present in one survivor.

   Five each young crossbred beef-type heifers were administered single doses of either 0, 2.5, or 12.5 mg/kg oxfendazole, as the 2.265% suspension, by stomach tube. No clinical signs of oxfendazole toxicosis were observed and all cattle survived the one-week observation period. Body weights, feed intakes, hematology values, clinical chemistry parameters, or urinalysis values were not altered by the treatment regimen. There were no gross or microscopic pathologic changes nor alterations in organ weights or organ weight to body weight ratios attributable to oxfendazole treatment.

2. **Target Species Safety Study (corroborative), Syntex Research, Palo Alto, CA - Study IAS 1103-339** This study was conducted to determine the reliability of the intraruminal device to deposit test material into the contents of the rumen. When the device was intact, it was found to enter the rumen consistently (100%) in 239 animals. Three additional animals were injected unsuccessfully when a part of the device became unglued. This device was a prototype and the production model has greater reliability. It was concluded that, in the absence of mechanical failure, the device was 100% accurate for the intraruminal administration of pharmaceutical preparations.

3. **Target Species Safety Study (corroborative), J.F.S. Reid and S.P. Dean, Syntex Research, Louvain-La-Neuve, Belgium - Study IAS 1103-C611** A total of 4,239 animals, weighing from 100 to 550 kg, were administered oxfendazole intraruminally using the intraruminal injector. The animals were located in various areas of Belgium, the United Kingdom, and Ireland. By 24 hours after injection, 91 animals (2.2%) had slight post-treatment reactions ranging from slight bleeding to swellings at the injection sight. After 7 days, all reactions had disappeared. It was concluded that the intraruminal administration of oxfendazole was safe and reliable whether used by a veterinarian or a layman.

4. **Target Species Safety Study (corroborative), J.F.S. Reid, Syntex Research, Louvain-La-Neuve, Belgium - Study IAS 1103-C453** A total of 562 steers,

heifers, and bulls weighing from 150 to 400 kg were administered oxfendazole intraruminally using the intraruminal injector. The animals were located in various areas of Ireland. By 24 hours after injection, only 22 animals (4%) showed minor swelling up to 6 cm at the injection site. It was concluded that the intraruminal administration of oxfendazole was safe and reliable whether used by a veterinarian or layman.

5. **Target Species Safety Study (corroborative), P.J. Kieran et al, Wellcome Research Foundation, Sydney,Australia Study IAS 1103-C398** Over 5,000 cattle, located in New Zealand and Australia, were administered oxfendazole intraruminally using the intraruminal injector. All injections were made by laymen. Of the 114 reactions recorded in these animals(<3%), 14 were abscesses, 60 were lumps in the abdominal wall, 3 were plaques, and 37 had a thickening of the skin in the injection area. Most of these reactions were seen in cattle that were wet when treated with the rumen injector. It was concluded that treatment with the rumen injector is contraindicated when the animals are wet. No treatment-related losses were recorded in any of the slaughtered animals.

6. **Target Species Safety Study (corroborative), J.B. Bentley, Wellcome, Australia - Study IAS 1067-C152** The safety of 90.6 g/l oxfendazole cattle concentrate formulation at 5, 10, 15 mg/kg was demonstrated under field conditions on properties located in New South Wales, Victoria, and South Australia and involved the treatment of 914 head of cattle. Cattle were treated at 5 mg/kg, 10 mg/kg and 15 mg/kg and concurrent treatment carried out with flukicide, lousicides, vaccines and injectable copper. No adverse reactions alone or in conjunction with the ancillary treatments simultaneously applied were observed.

IV. HUMAN FOOD SAFETY

A. Toxicity and Teratology Studies

Sub-chronic Toxicity Studies in Rats:

- **Investigator: Syntex Research, Palo Alto, CA, - Study 30-R-76** Equivalent doses of oxfendazole or mebendazole were administered by gavage daily for 2 weeks to groups of rats in doses ranging from 5 to 160 mg/kg/day. At doses of 80 and 160 mg/kg/day of oxfendazole, neutrophil levels were depressed at the end of the dosing period. When examined again after a two-week drug-withdrawal period, neutrophil levels in oxfendazole dose groups had returned to control values. Within the dose range tested, mebendazole did not affect neutrophil levels.

- **Investigator: Syntex Research, Palo Alto, CA - Study 38-R-75** Oxfendazole was administered to rats by gavage at levels of 11, 33, or 100 mg/kg/day for 14 days. Decreased weight gain was seen in females treated with 33 mg/kg/day of oxfendazole and in both males and females treated with 100 mg/kg/day of oxfendazole. At the end of the two-week dosing period, no differences between drug-treated and control animals were observed in clinical chemistries. Decreased neutrophil levels were observed in the females given 33 mg/kg/day and in both males and females given 100 mg/kg/day. Reduced hemoglobin and hematocrit values were also noted in females given 100 mg/kg/day. Hepatocytic vacuolation was seen at all doses of oxfendazole. Doses of 33 and 100 mg/kg/day were

associated with gastroenteropathy and reduced activity in lymphoid, testicular and bone marrow tissues.

- **Investigator: Syntex Research, Palo Alto, CA - Study 108-R-74** Oxfendazole was compared to a related series of candidate compounds in a 1-month study in rats. Each compound was admixed with the diet at a level of 600 ppm and administered to a group of male and female rats. Oxfendazole was associated with decreased neutrophil levels and/or decreased hemoglobin/hematocrit levels. SGOT levels were slightly increased with all test compounds and hepatic enlargement was evident with oxfendazole.

- **Investigator: Bio/dynamics Inc., East Millstone, New Jersey - Study 256-R-73** In a three-month oral dosing study using rats, oxfendazole was admixed with the diet. The study was originally started using dietary levels of 200, 600, or 2000 ppm. However, since 13/30 rats fed the 2000 ppm diet died by the end of the first week of dosing, this group was terminated and additional groups were started which were fed diets containing 50 or 100 ppm of oxfendazole. By the end of the 3-month feeding period, 24/30 rats fed the 600 ppm diet had died. There were no deaths in any of the other groups.

  At the end of the three-month feeding period, dose-related changes were seen in the liver, consisting of hepatocytic hypertrophy, vacuolation and/or rarefaction in the rats fed the 600 ppm diet. Minimal to slight hepatocytic hypertrophy was seen in 4/20 rats fed the 200 ppm diet. No gross or microscopic changes related to treatment were seen in livers of rats fed 100 or 50 ppm of oxfendazole.

  Related clinical chemistry changes included elevation of plasma glutamic transaminase and alkaline phosphatase levels in the 600 ppm group. Slightly elevated alkaline phosphatase levels were seen in both sexes of the 200 ppm group and in the 100 ppm females.

  Other pathologic changes seen in the rats from the 600 ppm group consisted of testicular atrophy, splenic necrosis or atrophy, abscesses and bone marrow hyperplasia or diffuse atrophy.

Sub-acute Toxicity Studies in Beagle dogs:

- **Investigator: Bio/dynamics Inc., East Millstone, New Jersey - Study 257-D-73** Oxfendazole was administered to dogs in hard shell gelatin capsules at doses of 1.5, 3.0, or 6.0 mg/kg/day for three months. No meaningful differences were seen between these dogs and control dogs given empty gelatin capsules in hematology, clinical chemistry or in gross or microscopic pathology when then dogs were sacrificed at the end of the dosing period.

- **Investigator: Syntex Research, Palo Alto, CA - Study 39-D-75** An oxfendazole formulation was administered by gavage to dogs for two weeks at 11, 33 or 100 mg/kg/day. Reduced myeloid maturation in bone marrow was seen in some dogs in all drug-treated groups. In addition, most drug-treated male dogs exhibited reduced splenic lymphoid tissue and thymic atrophy. No meaningful changes were seen in any of the other parameters examined.

- **Investigator: Syntex Research, Palo Alto, CA - Study 97-D-76** In a 2 week study in dogs, oxfendazole was administered at 3, 6, or 11 mg/kg/day. In this study all dose levels were well-tolerated and no drug-related effects were noted.

Teratology and Reproduction Studies:

- **Investigator: Bio/dynamics, East Millstone, New Jersey - Study 247-M-73** Mice were fed diets containing 200, 600, or 2000 ppm of oxfendazole during the period of organogenesis. The diet containing 2000 ppm of oxfendazole was fetotoxic for mice. Only 2/22 mice maintained pregnancies through day 18 of pregnancy and in these two pregnancies there were three live fetuses and one dead fetus.Neither fetotoxicity or teratologic changes were seen when mice were fed diets containing either 200 or 600 ppm of oxfendazole during organogenesis. The dietary level of 200 ppm (36 mg/kg/day) was considered to be the no-effect level.

- **Investigator: Bio/dynamics, East Millstone, New Jersey - Study 248-R-73** Oxfendazole was administered by gavage to rats during the period of organogenesis at doses of 10, 20 or 60 mg/kg/day. These doses correspond to dietary intakes of 200, 400, or 1200 ppm of oxfendazole, respectively. Evidence of fetotoxicity characterized by decreased litter size and fetal weight with a high incidence of total litter resorption was seen in the group dosed with 60 mg/kg/day. Further evidence of fetotoxicity was provided by the changes seen in fetuses from animals dosed with either 20 or 60 mg/kg/day of oxfendazole. The changes seen in fetuses from these groups were typical of those produced by delayed development and included reduced ossification of the cranial bones, sternebrai and vertebrae. The dose of 10 mg/kg/day, corresponding to a dietary level of 200 ppm of oxfendazole, did not cause fetotoxic or teratologic changes in the rat.

- **Investigator: Syntex Research, Palo Alto, CA - Study 48-B-77** In rabbits, oxfendazole was administered by gavage at doses of 0, 0.025, 0.125, or 0.625 mg/kg/day during theperiod of organogenesis. No biologically meaningful changes were seen in maternal parameters which included litter size, fetal weight, resorptions, implantations, corpora lutea, gestation survival index, resorption index and implantation index.

  No teratologic change was seen. Minor changes including abnormal carpal and tarsal flexion, and low incidence of gallbladder hypoplasia or aplasia were seen in fetuses from treated animals. Although greater numbers of high dose fetuses had minor skeletal variants, the incidences of these changes were not significantly different ($p>0.05$) from the controls. Similar numbers of control fetuses with those minor skeletal variants have been seen in prior rabbit studies. The no-effect level was considered to be 0.625 mg/kg/day.

- **Investigator: Syntex Research, Palo Alto, CA - Study 83-R-84** Male rats were administered oxfendazole in their diet at concentrations of 0, 10, 30, or 100 ppm, beginning 10 weeks prior to cohabitation with females. Females were treated with the same concentrations of oxfendazole until weaning of the first generation of offspring. Representative F1 animals of both sexes were treated similarly and then mated to produce an F2 generation.

  No drug effect was noted on the clinical condition, mean body weight or average daily food intake of treated rats. Also, no drug effect was noted for incidence of

pregnancy, length of gestation, live litter size or gestation index. Upon pathologic examination, one high-dose male had hepatocytic cytoplasmic vacuolation, and high-dose females had increased mean liver weights and liver to body vacuolation. Increased incidence of eosinophilic cytoplasmic material was present in hepatocytes of high-dose females. These changes were attributed to oxfendazole treatment.

All dose groups including controls had high pup mortality from postpartum days 7 to 14. Male F1 pups born to high-dose dams weighed less at first observation and had a decreased rate of growth compared to male pups from control dams. At weaning, both male and female pups had statistically significant lower mean body weights relative to pups from control dams. No oxfendazole-related anomalies occurred. Pups from high-dose litters that were submitted to necropsy had liver changes similar to those found in high-dose parents. The dietary level of 10 ppm (0.8 mg/kg/day) was considered to be the no-effect level.

Chronic Toxicity Studies in Dogs and Rats

- **Investigator: Syntex Research, Palo Alto, CA - Study 18-D-84** Beagle dogs were administered oxfendazole orally at levels of 0 (vehicle), 1.5, 4.5, or 13.5 mg/kg/day for one year. Eye examinations, hematology, and serum chemistry evaluations were conducted predose and at periodic intervals during treatment. After at least one year of treatment, gross and histopathologic examinations were performed.

- No treatment related changes were noted in in-life observations, clinical pathology parameters or pathology. Daily oral doses of oxfendazole up to 13.5 mg/kg were well tolerated by beagle dogs, and this was considered to be the no-effect level.

- **Investigator: Syntex Research, Palo Alto, CA - Study 101-R-74** Rats were administered oxfendazole in the diet at levels of 0, 10, 30, or 100 ppm for one year. Blood samples for hematology and serum chemistry evaluations were collected at four intervals during the study. Also, eye examinations were performed predose and at four intervals during the study. Dietary levels of 30 and 100 ppm of oxfendazole caused mild hepatotoxicity. At 10 ppm, the only effects observed were physiologic changes in BUN and serum alkaline phosphatase that were not considered to be biologically meaningful. The dietary level of 10 ppm (0.7 mg/kg/day) was considered to be the no-effect level.

Carcinogenicity Studies in Mice and Rats

- **Investigator: Syntex Research, Palo Alto, CA - Study 66-M-84** Mice were administered oxfendazole in the diet for 18 months at levels of 0, 100, 300, or 1000 ppm. Blood samples were collected from designated animals at six and twelve months following treatment and at study termination from surviving animals. Complete necropsies and histopathological examinations were performed at termination of the study.

  No treatment-related effects were noted for clinical condition or survival. Mean body weights for treated males were often lower than those for controls during the first year of the study. High-dose females had significantly higher body weights than controls during the first year. Food intakes were higher for all treated groups during the first year.

No biologically-significant hematologic effects were noted. There were no treatment-related increases in the incidence of any type of neoplasm. Histologically, an increased incidence of hepatocellular vacuolation was present in high-dose females and the incidence of hepatocytic hypertrophy was increased in high-dose males. There was no evidence of a carcinogenic effect of oxfendazole in mice. The dietary level of 1000 ppm (150 mg/kg/day) was considered to be the no-effect level.

- **Investigator: Syntex Research, Palo Alto, CA - Study 53-R-83** Oxfendazole was administered to weanling rats of each sex at dietary levels of 10, 30, or 100 ppm. During the two year period, the female dose groups consumed 0.88, 2.53, and 8.8 mg/kg/day while the males consumed 0.7, 2.1, and 7.0 mg/kg/day of oxfendazole, respectively. The animals were treated for a minimum of 104 weeks. There were no treatment related clinical signs, and the survival of the animals was not affected by oxfendazole treatment. No biologically significant effects were noted on body weight, food intake, or hematology. There were no treatment-related increases in the incidence of any type of neoplasm. Hepatocellular vacuolation was present in the livers of 30 and 100 ppm dose groups. No evidence of carcinogenic effect of oxfendazole was noted in this study. The no-effect level was determined to be 0.7 mg/kg/day.

The no effect levels for the significant studies are:

1. Two year carcinogenicity study in rats	0.7 mg/kg/day
2. Eighteen month carcinogenicity study in mice	150 mg/kg/day
3. One year chronic dog study	13.5 mg/kg/day
4. One year chronic rat study	0.7 mg/kg/day
5. Rabbit teratology study	0.625 mg/kg/day
6. Three generation reproduction study in rats	0.8 mg/kg/day

B. Safe Concentration of Residues: The most oxfendazole sensitive species was found to be the rat, at 0.7 mg/kg/day. On the basis of chronic toxicity studies, a 100-fold safety factor is applied for calculating a safe concentration.

$$\text{Safe Concentration} = \frac{((\text{Average human wt (kg)} \times \text{NEL (mg/kg)}))}{((\text{Food factor for meat}^* \times \text{safety factor}))}$$

*Normal Food Factors:

Muscle	-0.50 kg/day
Liver (1/2 muscle)	-0.25 kg/day
Kidney (1/3 muscle)	-0.165 kg/day
Fat (1/4 muscle)	-0.125 kg/day

Muscle = 60 x 0.7 / 0.5 x 100 = 0.84 ppm

The safe concentration for total oxfendazole residues in muscle is 0.84 ppm. After applying the appropriate consumption factors the safe concentration in liver is 1.7 ppm, kidney - 2.5 ppm, and fat - 3.3 ppm.

C. Total Residue and Metabolism Studies

Total residues of oxfendazole in the tissues of cattle treated with C-14 oxfendazole were determined in two studies. Study No. 77-CA-29 was a range-finding study and involved four steers and four heifers which each received a single 4.5 mg/kg dose of C-14 oxfendazole administered by stomach tube. One calf was sacrificed on days 3, 7, 14, and 21 days post dosing, and the remaining four animals were sacrificed as a group at 30 days post dosing. Radioassay of the tissues gave the results shown below.

Total Radioactivity (ppm) in Tissues of Calves Treated with a Single 4.5 mg/kg Oral Dose of C-14-Oxfendazole (Study No. 77-CA-29)

Days Post Dosing	Muscle	Liver	Kidney	Fat
3	0.25	15.90	2.079	0.22
7	0.007	3.954	0.504	0.025
14	0.003	1.577	0.184	0.009
21	0.002	0.366	0.076	0.006
30	0.002 (±0.001)	0.356 (±0.097)	0.043 (±0.004)	0.006 (±0.002)

Study No. 78-CA-18 was a larger investigation and was conducted with a slightly higher dose level, 5.0 mg/kg. The study involved 12 steers and 12 heifers which each received a single 5.0 mg/kg dose of C-14-oxfendazole by stomach tube. The animals were sacrificed in groups of six (three steers and three heifers) at 7, 14, 21 and 28 days post dosing. Radioassay of the tissues yielded the total radioactivity values shown below.

Total Radioactivity (ppm) in Tissues of Cattle Treated with a Single 5.0 mg/kg Oral Dose of C-14-Oxfendazole (Study No. 78-CA-18)

Days Post Dosing	Muscle	Liver	Kidney	Fat
7	0.041 (±0.011)	5.348 (±1.243)	0.954 (±0.183)	0.040 (±0.013)
14	0.010 (±0.004)	2.372 (±0.562)	0.249 (±0.059)	0.009 (±0.005)
21	0.005 (±0.002)	1.245 (±0.196)	0.097 (±0.025)	0.011 (±0.002)
28	0.004 (±0.001)	0.723 (±0.160)	0.056 (±0.014)	0.010 (±0.004)

The extraction of liver samples in the studies summarized above revealed that liver contained a significant amount of nonextractable residue and that the relative proportion of that residue increased with the length of time post dosing. At three days post dosing, 24% of the total radioactivity was nonextractable with ethyl acetate. That percentage increased to 77% at seven days and to about 94% by days 14 and 21. The extractable fraction of the radioactivity in liver was subjected to a procedure involving thin layer chromatography, high performance liquid

chromatography, and mass spectrometry. This resulted in the isolation and identification of parent oxfendazole and its thioether (febendazole) and sulfone metabolites. The percentages of the metabolites in the extractable fractions at three days and at seven days post dosing are shown below. The chromatography also showed that a small amount of more polar metabolite fraction was present, but its components were not identified.

Approximate Percentages of Oxfendazole and its Metabolites Present in the Extractable Fraction of Liver at Three Days and Seven Days Post Dosing with C-14-Oxfendazole

Days Post Dosing	Oxfendazole	Thioether (Fenbendazole)	Sulfone
3	68%	12%	15%
7	55%	6%	8%

The metabolite pattern of oxfendazole was also studied in the plasma and liver of rats at sacrifice intervals from one-half hour to 24 hours post dosing with a 6 mg/kg dose of C-14-oxfendazole. Extraction with ethyl acetate or chloroform, followed by thin layer chromatography of the extract, demonstrated that the extractable radioactivity in rat plasma and liver consisted predominantly of oxfendazole and its thioether and sulfone metabolites. The quantitative distribution of the three compounds in rat liver was quite similar to that observed in calf liver. The metabolite workup showed that nonextractable (bound) residues in rat liver amounted to about 40% of the total radioactivity at 1 hour post dosing. That percentage increased to more than 90% by 24 hours post dosing.

A comparison was made of the metabolite patterns presents in cattle liver with those present in rat liver, and its was concluded that the major identifiable metabolites were the same in both species. A very similar quantitative distribution was observed, and an appreciable nonextractable (bound) residue was shown to be present in the liver of both species. The comparison thus indicated that the test species was exposed to all of the metabolites shown to be present in the liver of cattle.

D. Bioavailability of the Cattle Liver Bound Residue and Calculation of the Total Residue of Human Food Safety Concern

A bioavailability study in the rat based on the Gallo Torres model*(Methodology for the Determination of Bioavailability of labeled Residues," H.E. Gallo-Torres, *Journal of Toxicology and Enviromental Health, 2,* 827-845 (1977)) was conducted with the nonextractable residue of C-14-oxfendazole present in cattle liver. This study (87-RT-124/IM) established the relative bioavailability of the cattle liver bound residue compared with the bioavailability of the parent drug and allowed a portion of the bound residue in cattle liver to be discounted from human food safety concern. The investigation yielded bioavailability values of 8.8% for the bound residue in cattle liver and of 69.8% for C-14 oxfendazole. This yielded a relative bioavailability of 13%.

$$Relative\ Bioavailablity = \frac{\%\ bioavailability\ of\ bound\ residue}{\%\ bioavailability\ of\ parent\ drug} = \frac{8.8\ \%}{69.8\ \%} = 0.13\ or\ 13\%$$

The results of the bioavailability study and the residue data in studies 77-CA-29 and 78-CA-18 (Section C) were used to calculate values for a decline curve of the total C-14-oxfendazole residue in liver after the discount of a portion of the bound residue. That curve represents the total residues that are of human food safety concern, and it allows the calculation of a tolerance as explained in Section E. Values for the decline curve were obtained by a procedure which used 23% and 77% as the percentages of extractable and nonextractable total residue in cattle liver at seven days and longer post dosing. The values for the decline curve were calculated as shown below by adding the extractable residue (23% of the total residue at each time point) and the portion of bound residue that is of concern (13% of 77% of the total residue) at each time point.

Days Post Dosing		Nonextractable (Bound) Residue (ppm)		Extractable Residue (ppm)	Residue of Concern (ppm)
7	0.13* x	4.12	= 0.54** +	1.23	= 1.76
14	0.13 x	1.83	= 0.24 +	0.54	= 0.78
21	0.13 x	0.96	= 0.12 +	0.29	= 0.41
28	0.13 x	0.55	= 0.07 +	0.17	= 0.24

* The 0.13 factor in this column is the relative bioavailability from study 87-RT-124/IM.
** The values in this column represent the amount of nonextractable residue that is of human food safety concern.

E. Target Tissue, Marker Residue, Tolerance and Rm Assignments The data reported in total residue studies 77-CA-29 and 78-CA-18 (Section C) established that liver contains the highest levels of total residues of oxfendazole and that it is the tissue in cattle from which residues are slowest to deplete to the safe concentration. The fact that total residues in liver were generally eight to tenfold higher than in other tissues strongly suggested liver as the choice for the target tissue.

The metabolism data described earlier confirmed liver as the target tissue and revealed that there were two candidate marker substances for oxfendazole in liver. One choice was the combined residues of oxfendazole and its two metabolites (its thioether and sulfone), and the other choice was fenbendazole (the thioether metabolite).

Two things complicated the selection of a marker residue for oxfendazole. The first was the fact the fenbendazole already is a regulated drug in cattle and serves as its own marker (21 CFR 556.275). The second is the fact that fenbendazole and oxfendazole are very closely related structurally with oxfendazole simply being the sulfoxide of fenbendazole. Both compounds are rapidly metabolized in cattle to a common pool of metabolites that consists of fenbendazole, its sulfoxide (oxfendazole) and its sulfone. Evidence for this exists in the published literature (For a leading reference see "Pharmacokinetics of Fenbendazole and Oxfendazole in Cattle," A.J. Ngomuo, S.E. Marriner, and J.A. Bogan, *Veterinary Research Communications* , 8, 187-193 (1984)) and in a residue comparison study conducted in the course of data collection for this NADA.

The studies demonstrating the common pool of metabolites showed that the quantitative relationship of the three metabolites was so close that cattle treated

with oxfendazole cannot be distinguished from cattle treated with fenbendazole on the basis of the residues present in their edible tissues. This suggested two things. The first was that fenbendazole should be the marker because the residue pattern of oxfendazole is the same in cattle as that for fenbendazole and the latter drug is currently regulated with fenbendazole as its marker. The second was that it would be necessary to confirm that the 0.8 ppm tolerance established under 21 CFR 556.275 is also a valid tolerance for fenbendazole as the marker for oxfendazole, if it were to be used as the marker residue.

Fenbendazole was the final choice between the two candidate marker substances, and the steps used to arrive at that choice are described below.

Prior to the approval of fenbendazole as an anthelmintic drug in cattle, the combined metabolites of oxfendazole were the marker substance being developed for oxfendazole. Because the total residue studies that support this NADA were conducted at that time, combined metabolites were measured as the marker in that work. Values for the combined metabolite marker were reported in total residue study 78-CA-18, which is described in Section C. The measurements were made by an HPLC assay of liver, and the assay included an oxidation step to convert oxfendazole and the fenbendazole metabolite to the sulfone which was the entity actually measured. The levels of the combined metabolites reported for liver tissue are shown below.

Days Post Dosing	Levels (ppm) of combined Oxfendazole Metabolites in Liver Tissue
7	1.116
14	0.026
21	0.005
28	0.003

The graphical representation of these data along with the total residue values of human food safety concern allowed the calculation of a tolerance for oxfendazole based on the combined metabolite marker. Using the value of 1.7 ppm as the safe concentration in cattle liver, this procedure yielded a tolerance of 1.0 ppm. That value is the level of the combined metabolite marker expected to be in liver tissue when the oxfendazole total residue of concern in that tissue has depleted to the safe concentration of 1.7 ppm. The two candidate marker substances and their respective tolerances were compared to see how equivalent they were in terms of setting a withdrawal time for oxfendazole. This was believed to be the only practical test for comparing the two, and it was done with the data in withdrawal study IAS 1134-952 described in Section G. That study contained residue values in liver for oxfendazole as well as for fenbendazole and the sulfone. This allowed withdrawal times based on fenbendazole and on the sum of the three metabolites to be calculated days from the same data set. The results were a withdrawal time of seven days for the fenbendazole marker with its 0.8 ppm tolerance. Seven days was also the withdrawal time calculated for the combined metabolite marker substances and its 1.0 ppm tolerance. This served to show that the two marker substances and tolerances were equivalent in terms of the regulatory withdrawal time. Once this was done, fenbendazole was assigned as the marker residue with 0.8 ppm as the Rm (tolerance). That choice allows a single common marker to serve for the group of benzimidazole anthelmintics that yield the same common pool of metabolites in the tissues of cattle.

F. Regulatory methods
The determinative and confirmatory methods that serve to regulate residues of oxfendazole by its marker residue, fenbendazole, are the official methods for fenbendazole. Those methods are filed in the Food Additives Analytical Manual on display in FDA's Freedom of Information Public Room (Room 12A-30, 5600 Fishers Lane, Rockville, MD 20857.

G. Withdrawal Time
A withdrawal time for the 22.5% and 9.06% oxfendazole suspensions was calculated from the residue data in study IAS 1134-952. That investigation involved a total of 20 steers and heifers, and each animal received a single 4.5 mg/kg intraruminal dose of the 22.5% oxfendazole suspension. A Synanthic Tru-Fire Injector was used to inject the dose. The animals were killed in groups of four (two steers and two heifers) at 4, 5, 6, 7 and 8 days post dosing. Liver samples were collected from each of the animals, and the assays were performed with a method developed by Syntex. The assay (BMS method 87005) which was based on high performance liquid chromatography individually quantitated oxfendazole, fenbendazole and the sulfone at levels to 0.005 ppm. The levels of the combined metabolites were obtained by adding the values for oxfendazole and its two metabolites. The assay results are shown below.

Average Concentrations (ppm) of Fenbendazole, Oxfendazole, and Fenbendazole Sulfone in Liver Tissue of Cattle Dosed with a Single 4.5 mg/kg Intraruminal Injection of a 22.5% Oxfendazole Suspension (IAS Study 1134-952)

Days Post Dosing	Fenbendazole	Oxfendazole	Oxfendazole Sulfone	Total Metabolites
4	0.927(±0.232)	1.479(±0.349)	0.039(±0.001)	2.445(±0.370)
5	0.591(±0.221)	0.635(±0.162)	0.023(±0.012)	1.249(±0.362)
6	0.126(±0.032)	0.216(±0.027)	0.008(±0.003)	0.349(±0.045)
7	0.073(±0.030)	0.078(±0.048)	0.007(±0.003)	0.158(±0.080)
8	0.022(±0.014)	0.047(±0.038)	0.006(±0.001)	0.075(±0.053)

In order to obtain a withdrawal time from the residue data listed above, 99% tolerance limits (95% confidence) were calculated in two statistical analyses. The first of these considered the combined metabolites as the marker substance with its tolerance of 1.0 ppm as calculated in Section E. The second analysis used fenbendazole as the marker with its 0.8 ppm tolerance. Both analyses yielded seven days as the time required for the upper tolerance limit to fall below the tolerance. Seven days was assigned as the withdrawal period for the intraruminally administered 22.5% suspension as well as for the 22.5% suspension administered as a drench and for the 9.06% suspension administered as a drench. The latter two treatments were considered an alternate dosing scheme and an alternate formulation of the intraruminal treatment investigated in residue study IAS 1134-952. The differences they represented were considered unlikely to alter the concentration of oxfendazole residues in liver to the extent that the withdrawal time would be changed. This assumption was supported by results from a bioequivalence study. As

a result, separate withdrawal studies were not required for the oral dosing with the 22.5% suspension or for the 9.06% suspension.

V. USER SAFETY

Studies have been conducted to evaluate the effects of human exposure to oxfendazole. These studies indicate that no adverse effects would occur to persons handling oxfendazole according to label recommendations.

- **Investigator: Syntex Research, Palo Alto, CA - Study 70-B-76, 19-B-77 and 46-G-77** When evaluated in a standard primary irritation study in rabbits with intact and abraded skin, oxfendazole was not a skin irritant, nor did the formulation produce irritation when tested in the rabbit eye. Neither oxfendazole nor the vehicle formulation produced contact sensitization when tested in the guinea pig.

- **Investigator: J. Reynolds, Wellcome Research, England - Study IAS 1067-C036** A dose of 0.1 ml of oxfendazole formulation was instilled into the conjectival sac of the rabbit's left eye without further treatment. It was considered that under normal conditions of use in the field this formulation should present no ocular hazard.

- **Investigator: D.W. Harper, Wellcome Research, England, Study IAS 1067-C041** The results of this study in guinea pigs showed that oxfendazole produced no sensitizing effect and no primary irritation of the skin.

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 with 21 CFR 514 of the implementing regulations. The data demonstrate that oxfendazole "Synanthic®" 9.06% and 22.5% suspension when used under the labeled conditions of use are safe and effective.
A tolerance is established for total oxfendazole residues in edible cattle tissues based on a marker residue concentration of 0.8 ppm fenbendazole in the target tissue liver. A fenbendazole concentration of 0.8 ppm in liver corresponds to a total safe concentration of oxfendazole residue of 0.84 ppm in muscle, 1.7 ppm in liver, 2.5 ppm in kidney, and 3.3 ppm in fat. Oxfendazole and fenbendazole are benzimidazole anthelmintics with an identical metabolite pattern. Fenbendazole is a major metabolite of both drugs.
The agency has granted an exemption under 21 CFR 201.105 from the requirement of "adequate directions for use" in section 520(f)(1) of the act for the oxfendazole "Synanthic®" 22.5% suspension for oral or intraruminal administration. Therefore, labeling will restrict this drug to use by or on the order of a licensed veterinarian. This decision was based on the following factors: (a) the intraruminal route needs prior training before it can be used, (b) the intraruminal route of administration is the first for this anthelmintic product to be approved in the U.S.A., and (c) because of (a) and (b) adequate direction for over-the-counter use of the drug for its labeled route of administration could not be prepared at this time. However, because of the drug's route of administration, conditions to be treated, and the ability of a layperson to determine these conditions, the agency has concluded that oxfendazole "Synanthic®" 9.06% suspension labeling for oral use contains adequate directions for use by layperson and, thus, the drug may be marketed over-the-counter.

Section 512(c)(2)(F)(ii) of the act provides a three year period of exclusivity to NADAs for previously approved active ingredient because of report of new clinical trial, field investigation, and human food safety studies were required for approval.

VII. LABELING (Attached)

1. Synanthic® (Oxfendazole) Bovine Dewormer Suspension 9.06%, package label
2. Synanthic® (Oxfendazole) Bovine Dewormer Suspension 22.5%, package label

Copies of these labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.