Approval Date: May 31, 1994

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 121-473

B. Sponsor

Hoechst-Roussel Agri-Vet Co.
Route 202-206; P.O. Box 2500
Somerville, New Jersey 08876-1258

C. Proprietary Name

Panacur® 22.2% Granules

D. Established Name

Fenbendazole

E. Dosage Form

22.2% Granules

F. Dispensing Status

Rx

G. Dosage Regimen

Felidae and Ursidae: 10 mg/kg/bw daily for 3 days

H. Route of Administration

Orally, mixed with food or as a top dressing

I. Indication

Panacur® (fenbendazole) is used for control of the following internal parasites in the families Felidae and Ursidae.

Felidae:

Lion (*Panthera leo*). For control of ascarids (*Toxocara cati*, *Toxascaris leonina*), hookworms (*Ancylostoma* spp.). Tigers (*Panthera tigris*). For control of ascarids (*Toxocara cati*, *Toxascaris leonina*), hookworms (*Ancylostoma* spp.) Cheetah (*Acinonyx jubatus*). For control of ascarids (*Toxocara cati*, *Toxascaris leonina*). Pumas (*Felis concolor*), Panthers (*Panthera* spp.), Leopards (*Panthera pardus*), Jaguars (*Panthera onca*). For control of ascarids (*Toxocara cati*, *Toxascaris leonina*),

hookworms (*Ancylostoma* spp.), tapeworms (*Taenia hydatigena*, *T. krabbei*, *T. taeniaeformis*).

Ursidae:

Black Bears (*Ursus americanus*). For control of ascarids (*Baylisascaris transfuga*, *Toxascaris leonina*), hookworms (*Ancylostoma caninum*), tapeworms (*Taenia hydatigena*, *T. krabbei*). Polar Bears (*Ursus maritimus*) and Grizzly Bears (*Ursus horribilis*), for control of ascarid (*Baylisascaris transfuga*, *Toxascaris leonina*).

J. Effect of Supplement

This supplement provides a claim as an anthelmintic in the following species within the families Felidae and Ursidae: lion (*Panthera leo*), tiger (*Panthera tigris*) cheetah (*Acinonyx jubatus*) Puma (*Felis concolor*), Jaguars (*Panthera onca*), Leopard (*Panthera pardus*), Panther (*Panthera* spp), Grizzly Bear (*Ursus horribilis*), Polar Bear (*Ursus maritimus*), and Black Bear (*Ursus americanus*).

II. EFFECTIVENESS

The effectiveness of fenbendazole as an anthelmintic in Felidae and Ursidae is established by data from six controlled studies. There are three studies involving 29 members of the family Felidae and three studies involving 26 members of the family Ursidae. The Ursidae studies involved administration of the drug for two days. There was 100% reduction in ascarid ova observed for some of the studies in bears while an 80% reduction of ascarid ova was observed in one study; whereas, there was 100% reduction in *Ancylostoma* and *Taenia* spp. ova in the studies where they were observed. Because of the lack of substantial adverse effects and in order to assure that bears consume an adequate dose for ascarids, bears should be treated for three days which is the labeled duration of treatment in the major species for which the drug is labeled.

Critical trials in minor species are often not feasible due to obvious difficulty in obtaining adequate numbers and the value of the animals. Therefore, each animal served as its own control as authorized under 21 CFR 514.111(a)(5)(ii)(a)(2)(iii). The control procedure used was a comparison of pre and post treatment parasite ova counts. Pre and post treatment ova counts is the most appropriate control procedure available for species included under wild Felidae and Ursidae.

Although false positive and false negative fecal samples do occur, the pronounced difference in pre versus post treatment values in greater than 90% of animals tested significantly illustrates the effectiveness of Panacur® when administered according to label instructions. Statistical methodology was not applied to these studies because the animals served as their own controls and the results are obvious.

Well controlled data supporting the approval of fenbendazole in major species (21 CFR 520.905) horses, cattle, domestic dogs and swine) have demonstrated substantial evidence of efficacy.

A. Felidae

1. Dr. P. J. Knapmann
   Six Flags Great Adventure

Jackson, N.J. 08527

A pivotal clinical field trial providing evidence for efficacy and safety of Panacur® was conducted on four (4) lions and seventeen (17) Siberian tigers. Fecal samples were obtained on 4 lions and 6 of 17 Siberian tigers. The four lions were positive for *Toxascaris* pre-treatment. Fenbendazole was administered at a dosage of 10 mg/kg/bw daily for three (3) days.

In the lions, there were no ova seen on day 7 post treatment, but reappearance at day 30 post-treatment. One animal was also positive for *Toxocara* at day 30.

Four of the 6 Siberian tiger samples were positive for *Toxascaris* pre-treatment. All 17 animals were treated, and fecal samples from the six animals were negative for *Toxascaris* at days 7 and 30. Unspecified tapeworm segments were noted at day 7 in two of the samples. There were no were (sic) side effects noted.

2. Dr. William Foster
Louisville Zoological Gardens
1100 Trevilian Way, Louisville, KY 40213

This pivotal clinical field trial providing evidence for efficacy and safety of Panacur® included 5 (five) Siberian tigers. They included animals of both sexes and ranged in age from 1 1/2 years to 10 years old. The animals weighed 250 lbs. to 400 lbs. Pre-treatment fecal examination revealed the presence of ascarid spp. Treatment of the tigers with a dose of 10 mg/kg/bw (one animal received 13.3 mg/kg) daily for three days resulted in total reduction of ova shedding at days 7 and 14 post-treatment. There were no adverse reactions noted.

3. Mr. Gerald Brady
Bear Country, U.S.A.
Rapid City, S.D. 57709

This pivotal clinical field trial providing evidence of efficacy and safety of Panacur® included 13 (thirteen) pumas. Pre-treatment fecal examinations of six of the pumas revealed the presence of ova from *Toxocara*, *Toxascaris*, *Ancylostoma*, and *Taenia* spp. Treatment with Panacur® at 10 mg/kg/bw daily for three (3) days resulted in total elimination of ova shedding at day 7 post-treatment for *Toxocara*, *Toxascaris*, and *Taenia*. There was one animal positive for *Ancylostoma* spp. pre-treatment and one animal positive for *Ancylostoma* spp. post-treatment. All but two of the animals took the drug without hesitation. There were several reports of loose stools among the pumas ingesting the Panacur® granules.

B. Ursidae

1. Mr. Gerald Brady
M.S. Bear Country U.S.A.
Rapid City, S.D. 57709

This pivotal clinical field trial providing evidence of efficacy and safety of Panacur® consisted of 105 (one hundred five) bears of which 20 (twenty) had

pre-treatment fecal exams examined for parasite ova. Sixteen of the twenty were positive for ascarids, *Ancylostoma*, and/or *Taenia* spp. The bears were treated with Panacur® orally at a dose level of 10 mg/kg/bw daily for two days. Results demonstrated a 100% reduction in ova shedding for *Ancylostoma* and *Taenia* spp. and 80% reduction in ascarid ova. All but two animals took the drug without hesitation. There were several reports of loose stools among the bears ingesting the Panacur® granules.

2. Dr. P. J. Knapmann
   Six Flags Great Adventure
   Jackson, N.J. 08527

   This pivotal clinical field trial providing evidence of efficacy and safety of Panacur® consisted of seven (7) brown bears. Fecal counts were conducted on seven animals and three were positive for ascarids and one for *Ancylostoma* spp. ova. Treatment consisted of fenbendazole administered at a rate of 10 mg/kg/bw daily for two consecutive days. This treatment resulted in 100% negative stools at 7 and 30 days post- treatment. There were no reported adverse effects.

3. Dr. William Foster
   Louisville Zoological Gardens
   Louisville, KY 40213

   This pivotal clinical field trial providing evidence of efficacy and safety of Panacur® included two female and one male 7 and 8 year old polar bears weighing 400 lbs to 600 lbs, which were diagnosed via pre- treatment fecal exams as having ascarid spp. Treatment consisted of administering Panacur® granules at 10 mg/kg/bw daily for two days. Results, as measured by detection of ova shedding, indicate that the drug was 100% effective at 7 and 14 days post treatment.

Corroborative Studies

1. Dr. William Foster
   Louisville, Zoological Gardens
   1100 Trevilian Way
   Louisville, KY 40213

   This corroborates field trial included one male and one female cheetah, both 5 years old and weighing 80 lbs to 85 lbs, which showed evidence of *Toxascaris* ova on pretreatment fecal examination. They were treated with 6.5 mg/kg/bw for one day and did not show evidence of ova shedding when feces were examined on days 7 and 14. There were no reports of adverse effects.

2. Professor K. Enigk
   Parasitology Institute
   University of Hannover
   W. Germany

   This corroborative field trial involved sixty-six (66) animals including 25 lions, 20 tigers, 10 pumas, 4 leopards, 1 black panther, and 6 jaguars. A dose level of 10 mg/kg/bw for one treatment proved to be effective in the above species against

Toxascaris spp. This level did not provide acceptable efficacy against *Toxocara* or *Ancylostoma* spp. Ten mg/kg/bw daily for three (3) days provided 100% reduction in *Toxocara*, *Toxascaris*, and *Ancylostoma* spp. infections in the 11 tigers dosed for that time period.

3. Dr. D. C. Hall
Vilas Park Zoo
Madison, Wisconsin 53715

The corroborative study involved one polar bear (weighing 797 lbs) and two grizzly bears (weighing 175 lbs). Pre-treatment fecal examination of the polar bear and one grizzly bear was positive for ascarid shedding. Animals were dosed at a level of 10 mg/kg/bw daily for two days. Post treatment fecal examination of the polar bear was negative at days 7, 14, and 21. The grizzly bear continued to shed diminishing numbers of ova on days 7 and 14, and becoming negative at day 21.

Efficacy Summary Statement

Efficacy studies submitted to support the use of Panacur® granules in wild Felidae and Ursidae were conducted using fecal egg counts to monitor effectiveness. The traditional controlled efficacy study (where animals are sacrificed and worms are counted) could not be used in these studies due to the rarity and high value of the animals. Parasites were often only identified to the genus level (and sometimes only to order level, i.e. ascarids) from egg identification following fecal examination. This was done because of the relative host specificity and likelihood of helminth species affecting wild Felidae and Ursidae. Based on the following references, the species that would be expected to be found in wild Felidae and Ursidae and against which Panacur® would expect to have efficacy based on the studies conducted, are used in the label indications.

Felidae

For ascarid species in Felidae *Toxocara cati* and *Toxascaris leonina* are both common and either or both species could be present in animals at any location or from any sources (Soulsby).

The identification of *Taenia* spp. is used based on the fact that one of several species may be present, and the actual distribution of different species in wild Felidae has not been fully delineated. Identification of species by egg examination is impossible.

For hookworm species, *Ancylostoma tubaeforme*, *A. braziliense*, *A. paraduodenale* or *A. ceylanicum* may be present depending on geographic location of the zoo or the source of the animal (Soulsby). The eggs of these species cannot be distinguished from one another; therefore, the designation of *Ancylostoma* spp. is given on the label. This is also the designation used by Fowler (see reference).

Ursidae

In Ursidae, the most common ascarid species is *Baylisascaris transfuga*, being nearly ubiquitous (Soulsby, Pence et al). *Toxascaris leonina*, might be expected from black bears in southern coastal regions (Pence et al, Crum et al).

Pence et al identified two species of *Taenia*, *T. hydatigena* and *T. krabbei*. However, the researchers indicated that species identification was not always possible and groups these (and any other possible species) together as *Taenia* spp.

The hookworm species that has been identified in the black bear is *A. caninum* (Pence et al, Crum et al) which is found in southern regions.

References

Helminths, Arthropods and Protozoa of Domesticated Animals, E.J.L. Soulsby, 7th Edition, Lea & Febiger, Philadelphia, 1982, pp. 149, 150, 152, 199, 200.

Zoo and Wildlife Animal Medicine, M.E. Fowler, 1st edition and 2nd edition, W.B. Saunders Company, Philadelphia, 1978, pp. 615 and 1986, pp. 837-838.

Ecological Analyses of Helminth Populations in the Black Bear, *Ursus americanus*, from North America. D.B. Pence, J.M. Drum and J.A. Conti. Journal of Parasitology, 69(5) 1983, pp. 933-950.

Studies on Endoparasites of the Black Bear (*Ursus americanus*) in the Southeastern United States. J.M. Crum, V.F. Nettles, W.R. Davidson. Journal of Wildlife Diseases, 14(April), 1978, pp. 178-186.

III. TARGET ANIMAL SAFETY

1. Dr. William Foster
   Louisville Zoological Garden
   Louisville, KY 40213

   This study was a pivotal toxicity study providing information supporting the safety of Panacur® granules in members of the families Felidae and Ursidae. Five big cats, including two jaguars, one puma, one lion, and one Siberian tiger representing both sexes and ranging in age from 2 to 15 years of age were dosed with the drug. Additionally, three polar bears ranging in age from 7 to 9 years of age and representing both sexes were dosed with 100 mg/kg/bw of the drug for four (4) days. The Felidae were dosed with 100 mg/kg/bw for six (6) days.

   In one jaguar and the lion, there were periods of inappentence (sic) following the initial consumption of fenbendazole at ten times the recommended level. It is noted that the ambient temperature at the zoo during this study was higher than normal; therefore, the role of the extreme heat on appetite can be considered.

   Large cats offered 5X the dose for twice the duration and polar bears dosed at 10X the dose for 1.33 times the duration provides evidence that at exaggerated doses for greater than the indicated duration, the drug is not associated with

adverse reactions. The only remarkable finding is that the overdosed animal may not consume the drug.

Due to the nature of the study, safety parameters were limited to those which could be obtained from clinical observation of the animals. Necropsies were not necessary nor feasible because of the absence of adverse effects and the value of the animals.

Traditional clinical (laboratory) target animal toxicity studies would ordinarily not be feasible for rare, exotic, or endangered wildlife species. It is concluded that the safety of Panacur® granules in members of the families Felidae and Ursidae is demonstrated under actual conditions of use in clinical field trials (see "Effectiveness" section).

The margin of safety is demonstrated in a limited number of animals which are dosed with ten (10) times the recommended amount of the Panacur® granules for up to twice the recommended duration. The nature of the animals being studied necessitated avoidance of unacceptable or irreversible adverse reactions.

IV. HUMAN FOOD SAFETY

This supplement is for use of this product in zoo and wildlife animals. Because these types of animals do not constitute a component of the human diet, residue and metabolism studies were not required to support approval of the supplement to NADA 121-473. To cover the possibility that the fenbendazole granules may be used to treat animals in the wild that are hunted, the product is restricted from use for 14 days prior to and during the hunting season. The 14-day period provides an interval for residues of fenbendazole to deplete from animals that might be hunted and then used for food purposes.

V. AGENCY CONCLUSIONS

The data in support of this supplemental NADA complies with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Panacur® granules (22.2%) when used under the labeled conditions in indicated zoo and wildlife species is safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for the minor use claim as a dewormer in zoo and wildlife animals. The approval of this change has no adverse effect on the safety and effectiveness of this new animal drug.

Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for non-food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new species and claims for which the supplemental application was approved.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of endoparasitic infections in these species and to properly differentiate the most likely types of infections.

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.