DATE OF APPROVAL LETTER: APRIL 7, 2000

FREEDOM OF INFORMATION SUMMARY

Combined use of BMD® and SAFE-GUARD® and in Swine Feeds

I. GENERAL INFORMATION

NADA: 141-144

Sponsor: Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

Generic Names: Bacitracin methylene disalicylate
Fenbendazole

Trade Names: BMD®
SAFE-GUARD®

Marketing Status: OTC

II. INDICATIONS FOR USE

Fenbendazole is indicated for the removal of:

- Lungworms: adult (*Metastrongylus apri, M. pudendotectus*)
- Gastrointestinal worms: adult and larvae (L3, L4 stages – liver, lung, and intestinal forms) large roundworms (*Ascaris suum*), adult nodular worms (*Oesophagostomum dentatum, O. quadrispinulatum*), small stomach worms (*Hyostrongylus rubidus*), adult and larvae (L2, L3, L4 stages – intestinal mucosal forms) whipworms (*Trichuris suis*)
- Kidneyworms: adult and larvae (*Stephanurus dentatus*)

Bacitracin methylene disalicylate is indicated for:

- Increased rate of weight gain and improved feed efficiency in growing and finishing swine
- Control of clostridial enteritis in suckling pigs caused by *Clostridium perfringens* when fed to pregnant sows during the period from 14 days before farrowing through 21 days after farrowing
- Control of swine dysentery associated with *Treponema hyodysenteriae* in growing and finishing swine on premises with a history of swine dysentery but where signs of disease have not yet occurred or following an approved treatment of the disease

III. DOSAGE

A. Dosage form: This original NADA provides for the combined use of these two Type A medicated articles, bacitracin methylene disalicylate (BMD) as per 21 CFR 558.76 and fenbendazole as per 21 CFR 558.258(c)(1). Bacitracin methylene disalicylate is supplied as a

Type A medicated article in concentrations of 10, 25, 30, 40, 50, 60, and 75 grams bacitracin activity per pound. Fenbendazole is supplied as a Type A medicated article in concentrations of 40, 80, and 200 grams fenbendazole activity per kilogram.

B. Route of Administration: Oral, in feed

C. Recommended Dosage:

Bacitracin methylene disalicylate	Bacitracin methylene disalicylate is added to swine feed at concentrations from 10 to 30 grams/ton for increased rate of weight gain and improved feed efficiency in growing and finishing swine. BMD is added to feed of pregnant sows 14 days before farrowing through 21 days after farrowing at a concentration of 250 grams/ton for control of clostridial enteritis caused by *Clostridium perfringens* in suckling pigs. BMD is added to swine feed at a concentration of 250 grams/ton for control of swine dysentery associated with *Treponema hyodysenteriae* in growing and finishing swine.
Fenbendazole	fenbendazole is added to swine feed at concentrations from 10 to 300 grams/ton to provide a total dose of 9 mg/kg of body weight; the total dose is divided over a period of 3 to 12 days.

The resultant feed containing both drugs is then fed as the only feed for the durations as specified in 21 CFR 558.76 and 21 CFR 558.258(c)(1), but not for more than 3 to 12 days which is the recommended duration for fenbendazole.

IV. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act (ADAA) of 1996, if the active ingredients or animal drugs intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the Agency finds that the NADA fails to demonstrate that 1) there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population, or 3) where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness (21 USC 360b(d)(4)(D)).

The effectiveness of fenbendazole in a total dose of 9 mg/kg body weight as a swine anthelmintic is codified in 21 CFR 558.258(c)(1). The effectiveness of BMD 10 to 30 grams/ton in swine feed for increased rate of weight gain and improved feed efficiency is codified in 21 CFR 558.76(d)(1)(vi). The effectiveness of BMD 250 grams/ton in swine feed for the control of clostridial enteritis caused by *Clostridium perfringens* is codified in 21 CFR 558.76(d)(1)(xi)(2). The effectiveness of BMD 250 grams/ton in swine feed for the control of swine dysentery associated with *Treponema hyodysenteriae* is codified in 21 CFR 558.76(d)(1)(xi)(1). Effectiveness for each drug, (Fenbendazole and BMD) when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Hoechst Roussel's approved NADA 131-675 and in Alpharma Inc.'s approved NADA 46-592, respectively.

Because fenbendazole and BMD each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that fenbendazole plus BMD provide appropriate concurrent use for the intended target population. The use of fenbendazole plus BMD provides appropriate concurrent use because these drugs are intended to treat different conditions (fenbendazole, antiparasitic; bacitracin methylene disalicylate, swine dysentery, clostridial enteritis, increased rate of weight gain and improved feed efficiency) likely to occur simultaneously with sufficient frequency in growing and finishing swine and sows. There is no more than one nontopical antibacterial (bacitracin methylene disalicylate) contained in this combination animal drug intended for use in Type C medicated feed. Fenbendazole is not considered to be an antibacterial animal drug for use in swine for the purposes of 512(d)(4) of the FFDCA, because fenbendazole is approved only for removal of lungworms, gastrointestinal worms, and kidneyworms in swine.

V. ANIMAL SAFETY

In accordance with the FFDCA, as amended by the ADAA of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination or a scientific issue is raised by target animal observations contained in studies submitted to the NADA for the combination and FDA finds that the application fails to establish that such combination active ingredient or animal drug is safe for the target animal.

Target animal safety for each drug, fenbendazole and BMD, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Hoechst Roussel's approved NADA 131-675 and Alpharma Inc.'s approved NADA 46-592, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of fenbendazole or BMD when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of this NADA for this combination. Thus, pursuant to FFDCA, as amended by the ADAA of 1996, no specific target animal safety study(ies) is (are) required for approval of NADA 141-144.

VI. HUMAN FOOD SAFETY

A. Tolerances

Toxicity and residue studies that establish the safety of fenbendazole have been submitted to NADA 128-620 and NADA 131-675. Similar data establishing the safety of bacitracin methylene disalicylate have been submitted to NADA 46-592. Tolerances for residues of fenbendazole in swine are established at 6 ppm in liver and 2 ppm in muscle, both measured as unchanged fenbendazole (21 CFR 556.275). Tolerances for bacitracin are established at 0.5 ppm (0.02 unit per gram), negligible residue, in uncooked edible tissues of swine (21 CFR 556.70).

B. Residue and Assay Noninterference Data

A comparative residue study was conducted to confirm that the presence of bacitracin methylene disalicylate does not adversely impact the levels of fenbendazole residues in swine liver when both drugs are fed to swine at the maximum level approved for their individual claims. The study was entitled, "A Study of Tissue Residues in Swine Receiving Diets Containing Bacitracin Methylene Disalicylate (BMD) and Fenbendazole (FBZ)." The in-life phase of the study was conducted by Southwest Bio-Labs, Las Cruces, NM, Study Director, Dr. J.W. Campbell, and the analytical phase was conducted at Hoechst Marion Roussel in Germany.

The residue study was conducted using a randomized complete block design structure and consisted of three treatment groups. The first was a control group, the second group was treated with the combination of fenbendazole (89 ppm) plus bacitracin methylene disalicylate (250 g/ton), and the third group was treated with fenbendazole alone (89 ppm).

The pigs in the control group (1 gilt and 1 barrow) were offered unmedicated feed continuously for the 17-day treatment period. The combination-treated pigs (4 gilts and 4 barrows) received feed containing 250 g bacitracin methylene disalicylate activity per ton for the initial 14 days of the study period. On each of the final 3 days (i.e., days 15, 16, and 17), each pig in the combination treatment group was offered feed containing both bacitracin methylene disalicylate and fenbendazole (fenbendazole at 89 ppm). The pigs treated with fenbendazole alone (4 gilts and 4 barrows) received unmedicated feed for the initial 14 days of the study period. On each of the final three days (i.e., days 15, 16, and 17), each pig in that treatment group was offered feed containing fenbendazole at 89 ppm. With this treatment scheme, the pigs in both the second and third treatment groups received fenbendazole at the rate of 3 mg fenbendazole/kg BW on each of the final three days of the treatment period.

All pigs were slaughtered within 8 to 12 hours after removing feed at the end of the treatment period. Samples of liver tissue were collected, shipped to Hoechst Marion Roussel in Frankfurt, Germany, where they were assayed for the presence of residues of fenbendazole. The analytical method used was based on HPLC, and it included an oxidation step with peracetic acid. The analyte measured was fenbendazole sulfone, and the values reported correspond to the combined residues of fenbendazole plus its major extractable metabolites.

The concentrations of combined fenbendazole residues in the livers of fenbendazole-treated pigs averaged 7.5 ppm and were not statistically different from those of pigs receiving the combination, which had an average value of 5.9 ppm ($P = 0.266$, SEM = 0.98). That result demonstrated that

bacitracin methylene disalicylate does not adversely affect the tissue residues of fenbendazole in swine when used in combination with fenbendazole with a zero day withdrawal.

Note: The analytical method used to assay the livers in this study measured combined residues of fenbendazole and its major extractable metabolites, and the results were reported as ppm fenbendazole sulfone. Residue values obtained by that assay are significantly higher than by methods that measure only parent fenbendazole. Levels of unchanged fenbendazole as measured by other analytical methods are expected to be below the tolerances of 6 ppm in liver and 2 ppm in muscle under the approved conditions of use of the fenbendazole-bacitracin methylene disalicylate combination in swine.

Noninterference by bacitracin methylene disalicylate on the assay used to measure residues of fenbendazole was demonstrated by the assay of control liver samples spiked with 1.0 ppm fenbendazole (as a combination of fenbendazole, oxfendazole, and fenbendazole sulfone, 33% each by weight), with and without 0.5 ppm (0.02 unit per gram) bacitracin methylene disalicylate. Assay by the HPLC method for combined residues of fenbendazole gave values that were 94% of the spiking level for fenbendazole alone, and 97% of the spiking level with fenbendazole plus bacitracin methylene disalicylate. Those recoveries confirmed that the presence of bacitracin methylene disalicylate did not interfere with the assay used to measure combined residues of fenbendazole.

Substantial scientific evidence provided by Alpharma has demonstrated that the likelihood is extremely remote that other drugs in combination with bacitracin methylene disalicylate would alter the levels of bacitracin residues in animal tissues. As such, studies to evaluate tissue residues and to demonstrate assay noninterference for bacitracin methylene disalicylate are no longer required for combination drugs when each drug is included at approved levels. Data collected over many years have demonstrated that tissue residues of bacitracin methylene disalicylate are not detected, whether the drug is used alone or in combination in food-producing animals. Furthermore, studies using radiolabeled bacitracin confirm that nearly all radiolabeled residues are excreted in the feces, and only small amounts of radioactivity are voided in the urine.

The available residue chemistry data support the assignment of a zero withdrawal period for swine fed the combination where bacitracin methylene disalicylate is administered at 250 g/ton and fenbendazole at 10 to 300 g/ton to provide a total dose of 9 mg/kg bw over a 3- to 12-day period.

C. Analytical Methods for Residues

A microbiological assay method is used to assay tissues for residues of bacitracin. The method is entitled, “Modified Microbiological Assay for Determination of Bacitracin in Tissues” and is on file at the Center for Veterinary Medicine, Food and Drug Administration (HFV-199), 7500 Standish Place, Rockville, MD 20855.

The use of fenbendazole in swine was originally approved with zero withdrawal and waiver of the regulatory method. As a result, the official method for the determination of fenbendazole residues in cattle tissues is recommended also for the assay of fenbendazole in swine tissues. That method measures residues of parent fenbendazole, and a copy of the procedure is on file at the center for veterinary Medicine, Food and Drug Administration (HFV-199), 7500 Standish Place, Rockville, MD 20855.

VII. AGENCY CONCLUSION

In accordance with Section 512 of the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless one or more of the active ingredients or animal drugs used in the combination at the longest withdrawal for the respective active ingredients or animal drugs in the combination exceeds the established tolerance, or one or more active ingredients or animal drugs in the combination interferes with the method of analysis for another active ingredient or drug in the combination.

The information submitted in support of this NADA comply with the requirements of section 512 of the FFDCA and demonstrate that fenbendazole (10 to 300 g/ton) and bacitracin methylene disalicylate (10 to 30 or 250 g/ton) are safe and effective for the claims indicated in section II of this FOI Summary.

The available residue chemistry information supports the assignment of a zero withdrawal period for swine fed the combination where bacitracin methylene disalicylate is administered at 250 g/ton and fenbendazole at 10 to 300 g/ton to provide a total dose of 9 mg/kg over a 3 to 12 day period.

There is reasonable certainty that the conditions of use, including directions on labeling, can and will be followed by swine producers. Accordingly, the agency has concluded that this product shall retain over-the-counter marketing status.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action qualifies for a categorical exclusion from the requirement of preparing an environmental assessment in accordance with 21 CFR 25.33(a)(2).

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for food-producing animals does not qualify for marketing exclusivity because the application does not contain substantial evidence of the effectiveness of the drugs 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.

VIII. ATTACHED LABELING

Type B Blue Birds:	BMD + FBZ SD	Type C Blue Birds:	BMD + FBZ SD
	BMD + FBZ CE		BMD + FBZ CE
	BMD + FBZ G/FE		BMD + FBZ G/FE