Date of Approval Letter: November 30, 2001

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-085

ZOAMIX® + BMD®
(zoalene + bacitracin methylene disalicylate)

"...for the development of active immunity to coccidiosis
and as an aid in the prevention and control of necrotic enteritis caused or complicated by
Clostridium spp.
or other organisms susceptible to bacitracin
in replacement chickens."

"...for the prevention and control of coccidiosis
and as an aid in the prevention and control of necrotic enteritis caused or complicated by
Clostridium spp.
or other organisms susceptible to bacitracin
in broiler chickens."

Sponsored by:
Alpharma, Inc

I. GENERAL INFORMATION

NADA Number:	141-085
Sponsor:	Alpharma, Inc. One Executive Drive Fort Lee, New Jersey 07024
Established Names and Pharmacologic Category:	zoalene (anticoccidial) bacitracin methylene disalicylate (BMD) (antibacterial)
Trade Names:	ZOAMIX® BMD®
Marketing Status:	over-the-counter (OTC)
Effect of the Supplement:	The supplemental NADA provides for using approved single ingredient bacitracin methylene disalicylate and zoalene Type A medicated articles to make two-way combination drug Type C medicated feeds used for the management of necrotic enteritis and coccidiosis in replacement and broiler chickens.

II. INDICATIONS FOR USE

"...for the development of active immunity to coccidiosis and as an aid in the prevention and control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin in replacement chickens."

"...for the prevention and control of coccidiosis and as an aid in the prevention and control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin in broiler chickens."

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. *Dosage Form:* Type A medicated articles to be mixed with chicken feed to produce a Type C medicated complete feed for use as the sole ration.

B. *Route of Administration:* Oral, *via* a complete feed. Feed for 5 to 7 days or as long as signs of necrotic enteritis persist.

C. *Recommended Dosage:* replacement chickens: zoalene: 36.3 to 113.5 g/ton, plus BMD: 50g/ton (prevention) or 100 to 200 g/ton (control)
broiler chickens: zoalene: 113.5 g/ton, plus
BMD: 50 g/ton (prevention) or 100 to 200 g/ton (control)

IV. EFFECTIVENESS

In accordance with 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 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 demonstrate 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 §512(d)(4)(D)).

Zoalene, as provided by Alpharma Inc., has previously been separately approved for use in replacement chicken feed for development of active immunity to coccidiosis (21 CFR § 558.680(c)(1)(i)). Bacitracin methylene disalicylate (BMD), as provided by Alpharma Inc., has previously been separately approved as an aid in the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin methylene disalicylate in replacement chickens (21 CFR § 558.76(d)(1)(ix)). Effectiveness for each drug, zoalene and BMD, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma Inc.'s approved NADAs 11-116 and 46-592, respectively. Because zoalene 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 zoalene plus BMD provide appropriate concurrent use for the intended target population. The use of zoalene plus BMD provides appropriate concurrent use because these drugs are intended to treat different conditions (zoalene, coccidiosis; BMD, necrotic enteritis) likely to occur simultaneously with sufficient frequency in replacement chickens. 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. Zoalene is not considered to be an antibacterial animal drug for use in replacement chickens for the purposes of Section 512(d)(4) of the FFDCA, as amended by the Animal Drug Availability Act of 1996, because zoalene is approved only for development of active immunity to a protozoan disease (coccidiosis) in replacement chickens. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific effectiveness studies are required for the approval of NADA 141-085.

V. ANIMAL SAFETY

In accordance with 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 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 a combination active ingredient or animal drug is safe for the target animal.

Zoalene, as provided by Alpharma Inc., has previously been approved for use in replacement chicken feed for development to coccidiosis (21 CFR § 558.680(c)(1)(i)). Bacitracin methylene disalicylate (BMD), as provided by Alpharma Inc., has previously been separately approved as an aid in the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin methylene disalicylate in broiler chickens (21 CFR § 558.76(d)(1)(ix)). Target animal safety for each drug, zoalene and BMD, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma Inc.'s approved NADAs 11-116 and 46-592, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of zoalene 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 Animal Drug Availability Act of 1996, no specific target animal safety study(ies) is (are) required for approval of NADA 141-085.

VI. HUMAN SAFETY

A. *Toxicity Studies:* Data in the single ingredient applications demonstrate that the use of these drugs does not constitute a hazard to human health when used in accordance with approved labeling. The information related to Human Safety may be found in NADA 046-592 for bacitracin methylene disalicylate and NADA 011-116 for zoalene.

B. *Tolerances:* Tolerances for bacitracin from bacitracin methylene disalicylate are established at 0.5 ppm (0.02 unit per gram), negligible residue, in uncooked edible tissues of chickens and eggs (21 CFR 556.70; 42 FR 18614, Apr. 8, 1977). The tolerances for zoalene and its metabolite in uncooked edible tissues of chickens are 6 ppm in liver and kidney, 3 ppm in muscle, and 2 ppm in fat (21 CFR. 556.770).

C. Tissue Residue Depletion: Data supporting the approved individual uses of bacitracin methylene disalicylate and zoalene and their respective withdrawal times of 0 and 0 days have been submitted in the respective single ingredient applications.

At approximately 16 days of age, chickens were fed feed containing zoalene (at 0.125%) alone or in combination with bacitracin zinc (at 200 g/ton) until they were sacrificed at approximately 10 weeks for tissue samples.

Muscle from treated chickens sacrificed with a zero withdrawal period contained an average of 1.6 ppm residues of zoalene plus ANOT (3-amino-5-nitro-o-toluamide), while liver had an average of 2.4 ppm residues of zoalene plus ANOT. The residues of zoalene and ANOT in both muscle and liver tissues of chickens fed the combination are essentially the same as those from the zoalene treatment. The observed residues were well below the tolerances of 6 ppm in liver and 3 ppm in muscle for zoalene and ANOT at zero withdrawal.

On the basis of substantial scientific information showing that the likelihood of other drugs in combination with BMD altering the bacitracin residues in tissues of animals is extremely improbable, there are no longer requirements for conducting studies demonstrating tissue residue and analytical method non-interference for BMD where each drug is included at already approved levels. Such is the case for this combination. Data generated over many years show that residues of BMD are not detected whether the drugs are used alone or in combination. Studies using radiolabeled drug confirm that bacitracin is recovered mostly with the feces, with only small amounts of radioactivity associated with the urine.

The available residue chemistry information supports the assignment of a zero withdrawal period for replacement and broiler chickens fed the combination of bacitracin methylene disalicylate (50 g/ton or 100 to 200 g/ton) and zoalene (36.3 to 113.5 g/ton).

D. *Analytical Methods for Residues (Regulatory Methods):*

1. Bacitracin methylene disalicylate:

   A microbiological assay method is used to assay tissues for bacitracin residues. The method entitled "Modified Microbiological Method for Determination of Bacitracin in Tissues" is on file at the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

2. Zoalene:

   A spectrophotometric method is used to assay tissues for zoalene residues. The method entitled, "Zoalene Residues in Animal Tissues, Spectrophotometric Method," is published in the AOAC, 15th Edition 973.78, page 635.

   A spectrophotometric method is used to assay tissues for ANOT residues. The method entitled, "ANOT Residues in Animal Tissues, Spectrophotometric Method," is published in the AOAC, 15th Edition 961.23, page 625

VII. AGENCY CONCLUSIONS

The information submitted in this supplemental NADA and in the referenced files satisfies the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act, as amended by the Animal Drug Availability Act (ADAA) of 1996, and implementing regulations. The data demonstrate that the combination Type C medicated feed is safe and effective in replacement chickens and in broiler chickens for the uses approved in this supplemental application.

The human food safety of the single ingredients has been established under their applications as codified at 21 CFR 556.70 and 21 CFR 556.770. The combination use in chicken feed does not impose an increased risk of unsafe residues.

Adequate directions for use have been written in labeling and there is reasonable certainty they will be followed in practice by poultry producers. Accordingly, the agency has concluded that this combination use shall have over-the-counter marketing status.

In accordance with 21 CFR 514.106(b)(2), this combination NADA approval is regarded as a Category II change which did not require a reevaluation of safety and efficacy data in the parent, single-ingredient applications.

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 to prepare an environmental assessment in accordance with 21 CFR 25.33(a)(2).

VIII. APPROVED LABELING (attached)

Specimen (Blue Bird) label - Type C medicated feed for replacement chickens.

Specimen (Blue Bird) label - Type C medicated feed for broiler chickens.