Date of Approval Letter: September 29, 2000

FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-147

Combination of DECCOX® AND CHLORMAX® in Cattle Feed
(decoquinate and chlortetracycline)

"Calves, beef and non-lactating dairy cows. For the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*; for the treatment of bacterial enteritis caused by *Escherichia coli*; for bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline"

Sponsored by:

Alpharma, Inc.

I. GENERAL INFORMATION

NADA Number:	141-147
Sponsor:	Alpharma, Inc. One Executive Drive P.O. Box 1399 Fort Lee, New Jersey 07024
Established Names	decoquinate chlortetracycline
Trade Names:	DECCOX® CHLORMAX®
Marketing Status:	Over-The-Counter

II. INDICATIONS FOR USE

Calves, beef and non-lactating dairy cattle. For the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*; for the treatment of bacterial enteritis caused by *Escherichia coli*; for the treatment of bacterial pneumonia caused by *Pasteurella multocida* organisms susceptible to chlortetracycline.

III. DOSAGE

A. *Dosage Form:* This original NADA provides for the combined use of these two Type A medicated articles, decoquinate as per 21 CFR 558.195(d) and chlortetracycline as per 21 CFR 558.128(d)(1)(xii). Decoquinate is supplied as a Type A Medicated Article containing 27.2 grams of decoquinate per pound (6%). Chlortetracycline is supplied as Type A Medicated Article in concentrations of 50, 65, 70, or 100 grams (Micro-CTC 100) of chlortetracycline per pound.

B. *Route of Administration:* Oral, in feed

C. *Recommended Dose:*

DECCOX®:	13.6 to 27.2 g/ton (22.7 mg/100 lb bodyweight/day)
CHLORMAX®:	500 to 1000 g/ton (10 mg/lb bodyweight/day)

The resultant feed containing both drugs is then fed as the only feed for the durations as specified in 21 CFR 558.195(d) and 21 CFR 558.128(d)(1)(xii), but not for more than 5 days which is the recommended duration for chlortetracycline.

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)).

Decoquinate at 13.6 to 27.2 g/ton, as provided by Alpharma Inc., has previously been separately approved for use in cattle feed for the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*, and is codified in 21 CFR 558.195(d).

Chlortetracycline at 500 to 1000 g/ton, as provided by Alpharma Inc., has previously been separately approved for use in cattle feed for the treatment of bacterial enteritis caused by *Escherichia coli*, and for the treatment of bacterial pneumonia caused by *Pasteurella multocida* organisms susceptible to chlortetracycline, and is codified in 21 CFR 558.128(d)(1)(xii).

The effectiveness for the two drugs, decoquinate and chlortetracycline, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in the approved NADAs 039-417 and 046-699, respectively.

Because decoquinate and chlortetracycline each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that decoquinate plus chlortetracycline provide appropriate concurrent use for the intended target population. The use of decoquinate plus chlortetracycline provides appropriate concurrent use because these drugs are intended to treat different conditions (decoquinate, coccidiosis; chlortetracycline, bacterial enteritis and pneumonia) likely to occur simultaneously with sufficient frequency in calves, beef, and non-lactating dairy cattle. There is no more than one nontopical antibacterial (chlortetracycline) contained in this combination animal drug intended for use in Type C medicated feed. Decoquinate is not considered to be an antibacterial animal drug for use in cattle for the purposes of 512(d)(4) of the FFDCA, because decoquinate is approved for the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii* in calves, beef and non-lactating dairy cattle.

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

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, decoquinate and chlortetracycline, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma's approved NADAs 039-417 and 046-699, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of decoquinate or chlortetracycline when used in combination in 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 the approval of NADA 141-147.

VI. HUMAN 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 condition of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on human 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. Safety for the approved products, decoquinate and chlortetracycline, has been established by data submitted to NADAs 039-417 and 046-699, respectively.

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 039-417 for decoquinate and NADA 046-699 for chlortetracycline.

B. *Tolerance and Acceptable Daily Intake:* Tolerances for decoquinate in cattle have been codified previously under 21CFR 556.170: 2 ppm in tissues other than skeletal muscle and 1 ppm in skeletal muscle. Tolerances for chlortetracycline in cattle have been codified previously under 21 CFR 556.150: 2 ppm in muscle, 6 ppm in liver, and 12 ppm in fat and kidney.

   An Acceptable Daily Intake (ADI): of 0.075 mg/kg bodyweight/day has been established for total residues of decoquinate. An ADI of 0.025 mg/kg bodyweight/day has been established for total residues of tetracyclines including chlortetracycline, oxytetracycline, and tetracycline (proportioned as 40% to tissues and 60% to milk).

C. *Residue Non-Interference Study:* Residue data supporting the individual uses of decoquinate and chlortetracycline, having zero and twenty-four hour withdrawal times, respectively, were submitted in their original applications (see Part A above). The in-life portion of the following study (Study No. RC002-98CH53xx) was

conducted at Southwest Bio-Labs, Las Crues, New Mexico with assays conducted at Analytical Development Corporation, Colorado Springs, Colorado and Colorado Animal Research Enterprises (CARE), Fort Collins, Colorado, to establish that each drug in the presence of the other does not exceed its established tolerance at twenty-four hours withdrawal and that the presence of the drugs in the same cattle tissue do not interfere with the assay for either drug.

Crossbred control cattle (1 steer, 1 heifer) were fed unmedicated feed for 14 days. Crossbred test cattle (3 steers, 3 heifers) received feed containing 27.2 grams decoquinate/ton for 16 days to which 10 mg chlortetracycline/lb body weight were included during the final five days. All cattle were slaughtered within 12 hours after removing the feed. Liver tissue was collected and analyzed for residue. Decoquinate residues were measured using an HPLC method ("Analysis of Decoquinate Residues in Animal Tissues Using Zymate Robotic System", Analytical Chemistry Guidebook, USDA, FSIS, Winter, 1991). Chlortetracycline residues were measured using the official microbiological method.

Mean Residues of Decoquinate and Chlortetracycline in Liver Collected from Cattle Treated with Medicated Feed Containing 27.2 grams Decoquinate for 16 Days to Which 10 mg Chlortetracycline/lb Body Weight Were Included During the Final 5 Days		
Withdrawal Time in Hours	Decoquinate (ppm)	Chlortetracycline (ppm)
24	<LOQ	0.486 +/- 0.117

LOQ: decoquinate = 0.15 ppm, chlortetracycline = 0.025 ppm

Samples of control liver were fortified with decoquinate and chlortetracycline. The data showed that the presence of decoquinate did not interfere with the assay of chlortetracycline and the presence of chlortetracycline did not interfere with the assay of decoquinate.

Residues of decoquinate and chlortetracycline were below their respective tolerances at twelve hours withdrawal, thereby confirming the established twenty-four hour withdrawal period for chlortetracycline, as well as indicating an absence of interference.

D. *Analytical Methods for Residues (Regulatory Methods):* The regulatory method for the determination of decoquinate in tissues uses a fluorometric assay procedure and is found in *Official Methods of Analysis of AOAC International,* 16th edition. The regulatory method for detection of chlortetracycline residues is a microbiological test using *Bacillus cereus* var. *mycoides* (ATCC 11778) as the test organism (Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods Reports, and Protocols, Food and Drug Administration, Washington, D.C., 1968). These methods are on file at the Center for Veterinary Medicine, Food and Drug Administration (HFV-199), 7500 Standish Place, Rockville. Maryland 20855.

VII. AGENCY CONCLUSIONS

The information submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that decoquinate (13.6 to 27.2 g/ton) and chlortetracycline (500 to 1000 g/ton to provide 10 mg/lb bodyweight/day) are safe and effective for the claimed indications in section II of this FOI summary.

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.

For decoquinate, a tolerance of 2 ppm in tissues other than skeletal muscle and 1 ppm in skeletal muscle in cattle has been codified previously under 21 CFR 556.170. For chlortetracycline, a tolerance of 2 ppm in muscle, 6 ppm in liver, and 12 ppm in fat and kidney in cattle has been codified previously under 21 CFR 556.150. The data demonstrate that residues for decoquinate and chlortetracycline were below their respective tolerance at twelve hours withdrawal, thereby confirming the established twenty-four hour withdrawal period for chlortetracycline, as well as indicating an absence of interference.

There is reasonable certainty that the conditions of use, including directions on labeling, can and will be followed by cattle 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. APPROVED LABELING (attached)

Specimen (Blue Bird) label - Type B and Type C medicated feed.