Approval Date:_____

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-135

Salinomycin (BIO-COX®) plus Roxarsone (3-NITRO®)

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in roaster and replacement (breeder and layer) chickens.

Sponsored by:

Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

FREEDOM OF INFORMATION SUMMARY

Combined use of BIO-COX® and 3-NITRO® in Roaster and Replacement Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-135

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

Generic Names: Salinomycin
Roxarsone

Trade Names: BIO-COX®
3-NITRO®

Marketing Status: OTC

II. INDICATIONS FOR USE:

For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in roaster and replacement (breeder and layer) chickens.

III. DOSAGE:

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles, salinomycin as per 21 CFR 558.550(d)(3) and roxarsone as per 21 CFR 558.530(d)(1). Salinomycin is supplied as a Type A medicated article in concentrations of 30 or 60 grams salinomycin activity per pound. Roxarsone is supplied as a Type A medicated article in concentrations of 45.4, 90, 227 or 360 grams of roxarsone activity per pound.

B. Route of Administration: Oral, *via* the feed.

C. Recommended Dosage:

Salinomycin sodium	Salinomycin is added to roaster and replacement (breeder and layer) chicken feeds at concentrations from 40 to 60 grams/ton for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*.

Roxarsone	Roxarsone is added to growing chicken feed at concentrations from 22.7 to 45.4 grams/ton for increased rate of weight gain, improved feed efficiency, and improved pigmentation.

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 animal drugs/active ingredients 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/drug intended only for the same use as another active ingredient/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/animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients/animal drugs makes a contribution to the labeled effectiveness.

Salinomycin, as provided by Roche Vitamins Inc., has previously been separately approved for use in roaster and replacement (breeder and layer) chicken feeds for the prevention of coccidiosis caused *by Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* (21 CFR 558.550(d)(3)(i)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in growing chicken feed for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR 558.530(d)(l)(i)). Effectiveness for each drug, salinomycin and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 128-686 (to which Alpharma, Inc. has a right of reference) and 7-891, respectively.

Because salinomycin and roxarsone each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that salinomycin plus roxarsone provides appropriate concurrent use for the intended target population. The use of salinomycin plus roxarsone provide appropriate concurrent use because these drugs are intended to treat different conditions (salinomycin, coccidiosis; roxarsone, performance problems) likely to occur simultaneously with sufficient frequency in roaster and replacement chickens. There is no nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed. Salinomycin is not considered to be an antibacterial animal drug for such use in roaster and replacement chickens for the purposes of section 512(d)(4) of the FFDCA, because salinomycin is approved only for prevention of a protozoal disease (coccidiosis) in roaster and replacement (breeder and layer) chickens.

Roxarsone is not considered to be an antibacterial animal drug for such use in roaster and replacement (breeder and layer) chickens for the purposes of section 512(d)(4) of the FFDCA, because roxarsone is not approved for use in roaster and replacement (breeder and layer) chickens for the diagnosis, cure, mitigation, treatment or prevention of bacterial disease and is not approved for any other use the Center for Veterinary Medicine deems attributable to its antibacterial properties.

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.

Salinomycin, as provided by Roche Vitamins Inc., has previously been separately approved for use in roaster and replacement (breeder and layer) chicken feed for the prevention of coccidiosis caused *by Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* (21 CFR 558.550(d)(3)(i)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in growing chicken feed for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR 558.530(d)(l)(i)). Target animal safety for each drug, salinomycin and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 128-686 (to which Alpharma, Inc. has a right of reference) and 7-891, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of salinomycin or roxarsone when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the 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 141-135.

VI. HUMAN 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 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.

A. Tolerances

Data establishing the safety of salinomycin and roxarsone have been established by NADA 128-686 and 7-891, respectively. No tolerance is required for salinomycin. However, under NADA 128-686, a research tolerance, or upper limit, of 200 ppb of unchanged salinomycin in skin/fat has been established. Tolerances for residues of arsenic from roxarsone in chickens are established at 0.5 ppm in uncooked muscle tissue, 2 ppm in uncooked edible by-products and 0.5 ppm in eggs (21 CFR 556.60).

B. Residue Data

Tissue residue studies in chickens fed salinomycin (90 g/ton), roxarsone (45 g/ton), and either of two antibiotics (Lincomycin or Flavomycin) were conducted. Male and female broiler chickens were fed one of two 3-way combinations from day-old to day 52. At day 52, all birds were switched to a non-medicated ration and birds were sacrificed at daily intervals for five days. Regardless of the antibiotic used in the combination, the arsenic residue level in the edible tissues were below the tolerance by 5-days withdrawal. The average residues of unchanged salinomycin in skin/fat at zero withdrawal did not exceed the research tolerance of 200 ppb. Additional information regarding tissue residues for the combination of salinomycin and roxarsone may be obtained from the Freedom of Information Summary for NADA 132-447.

The available residue chemistry information supports the assignment of a five day withdrawal period for replacement chickens fed the combination of salinomycin sodium (40 to 60 g/ton) and roxarsone (22.7 to 45.4 g/ton).

C. Regulatory Methods for Residues

A regulatory analytical method for salinomycin is not required.

A spectrophotometric method is used to assay tissues for roxarsone residues. The method entitled “Arsenic (Total) Residues in Animal Tissues, Spectrophotometric Method” is published in the AOAC, 15th Edition 973.78, page 626.

VII. AGENCY CONCLUSIONS:

The data submitted in support of this NADA comply with the requirements of section 512 of the FFDCA and demonstrate that salinomycin (40 to 60 g/ton) plus roxarsone (22.7 to 45.4 g/ton) are safe and effective for the claims indicated in section II of this FOI Summary.

Pursuant to 21 CFR 514.106(b)(2)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs. The drugs are to be fed in Type C medicated feeds, in accordance with section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

The available residue chemistry information supports the assignment of a five day withdrawal period for roaster and replacement (breeder and layer) chickens fed the combination of salinomycin sodium (40 to 60 g/ton) and roxarsone (22.7 to 45.4 g/ton).

Attached labeling: Type C Medicated Feed (Blue Bird) – Roaster and replacement chickens

Net weight lb (kg) on bag or bulk

Salinomycin/Roxarsone
Roaster and Replacement (Breeder and Layer) Chicken Ration
Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in roaster and replacement (breeder and layer) chickens.

ACTIVE DRUG INGREDIENTS

Salinomycin……40 to 60 g/ton
Roxarsone……22.7 to 45.4 g/ton

GUARANTEED ANALYSIS

Crude Protein, not less than……_____%
Lysine, not less than……_____%
Methionine, not less than……_____%
Crude Fat, not less than……_____%
Crude Fiber, not more than……_____%
Calcium, not less than……_____%
Calcium, not more than……_____%
Phosphorus, not less than……_____%
Salt[1], not less than……_____%
Salt[1], not more than……_____%
Sodium[2], not less than……_____%
Sodium[2], not more than……_____%

[1]If added.
[2]Shall be guaranteed only when total sodium exceeds that furnished by the maximum salt guarantee.

INGREDIENTS

Each ingredient must be named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

DIRECTIONS FOR USE

Feed continuously as the sole ration. Discontinue use prior to sexual maturity.

(Over)

WARNING: Withdraw 5 days before slaughter.

CAUTION: For roaster and replacement (breeder and layer) chickens only. Do not feed to laying chickens. May be fatal if fed to adult turkeys or to horses. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis. Not approved for use with pellet binders.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

SIGNATURE PAGE FOR THE
FREEDOM OF INFORMATION SUMMARY

NADA OR ANADA # 141-135

SPONSOR Alpharma Inc.

NAME OF DRUG Salinomycin + Roxarsone

	CONCURRENCE: (Signature-date)		CONCURRENCE WITH REVISIONS, IF REVISED
1.	Primary Reviewer HFV-128	Date	INITIAL
2.	Team leader HFV-128	Date	INITIAL
3.	Division Director HFV-120	Date	INITIAL
4.	QAST, HFV-102	Date	INITIAL
5.	Director, ONADE, HFV-100	Date	INITIAL
6.	Director, CVM, HFV-1	Date	INITIAL

Team/Reviewer: Attach this form to draft FOI Summary in Folder A of Approval Package.
HFV-199: Attach this form to dated FOI Summary when filed in NADA.