Date of Approval Letter: July 21, 2004

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-211

Combined Use of MECADOX 10 (carbadox) and TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200 (oxytetracycline) in Swine Feeds

For increased rate of weight gain, improved feed efficiency, treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* susceptible to oxytetracycline, and treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline.

Sponsored by:
Phibro Animal Health

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1. GENERAL INFORMATION:

a. File Number:	NADA 141-211
b. Sponsor:	Phibro Animal Health 710 Rt. 46 East, suite 401 Fairfield, NJ 07004 Drug Labeler Code: 066104
c. Established Names:	Carbadox; oxytetracycline dihydrate base (equivalent to oxytetracycline hydrochloride)
d. Proprietary Names:	MECADOX 10; TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200
e. Dosage Form:	Type A medicated articles
f. How Supplied:	Type C medicated feed
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	MECADOX 10: 10 g carbadox/lb; TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200: 50, 100, or 200 g oxytetracycline/lb.
i. Route of Administration:	Oral, in feed.
j. Species/Class:	Swine
k. Recommended Dosage:	Carbadox, 10 to 25 grams per ton of finished Type C medicated feed; plus oxytetracycline, 10 mg per pound of body weight, daily for 7 to 14 days.
l. Pharmacological Category:	Antimicrobial
m. Indications:	Treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* susceptible to oxytetracycline, and treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline; and increased rate of weight gain and improved feed efficiency.

2. 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 FDA finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient/drug intended only for the same use as another active ingredient/animal drug in combination makes a contribution to the labeled effectiveness.

- 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.

- 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.

Carbadox, an antimicrobial, has previously been separately approved (NADA 041-061, MECADOX 10 Type A medicated article, Phibro Animal Health) for use in swine feed for increased rate of weight gain and improved feed efficiency when fed continuously at 10-25 g/ton of feed, and is codified in 21 CFR 558.115. The effectiveness of carbadox, when administered alone in accordance with its approved uses and conditions of use, was demonstrated in the original approval.

Oxytetracycline, an antimicrobial, has previously been separately approved (NADA 095-143, TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200 Type A medicated articles, Phibro Animal Health) for use in swine feed for treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* susceptible to oxytetracycline, and treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline when fed at 10 mg/lb of body weight daily for 7-14 days, and is codified in 21 CFR 558.450. The effectiveness of oxytetracycline, when administered alone in accordance with its approved uses and conditions of use, was accepted through the Drug Efficacy Study Implementation (DESI) findings of the National Academy of Science National Research Council (NAS/NRC).

Because carbadox and oxytetracycline each have at least one use that is different from all other animal drugs used in the combination, the NADA must demonstrate that carbadox

and oxytetracycline provide appropriate concurrent use for the intended target population. The use of carbadox and oxytetracycline provides appropriate concurrent use because these drugs, when administered at the proposed dosages, are intended to treat different conditions (carbadox, rate of weight gain and feed efficiency; oxytetracycline, bacterial enteritis and pneumonia) likely to occur simultaneously with sufficient frequency in swine.

The following study was conducted to determine if the concurrent use of oral carbadox and oxytetracycline would compromise oxytetracycline bioavailability.

"Pharmacokinetics of Orally Administered Oxytetracycline in Swine When Administered Alone or Concurrently with Carbadox."
(Study Number 2522D-60-98-132)

Type of Study: Blood level non-interference study.

Objective: This study was conducted to determine if the presence of carbadox in feed at 25 g/ton would compromise the bioavailability of oxytetracycline and thereby interfere with its therapeutic activity.

Investigator: Dan C. Ronning, M.S., Colorado Animal Research Enterprises, Inc., Fort Collins, CO.

Study Design and Methods: Sixty-four crossbred growing swine were used in the study. Each of the two treatment groups consisted of 16 castrated males and 16 females. One group (T01) was fed a nonmedicated control diet for seven days. The other group (T02) was fed a diet containing 27.5 mg of carbadox/kg of feed for seven days. On the eighth day, both groups were given a single dose of oxytetracycline (10 mg of oxytetracycline/lb of body weight) by oral gavage.

Samples and Analysis: Blood samples were obtained via vena cava venipuncture prior to dosing with oxytetracycline and at the following times after dosing: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hours. Serum was harvested and oxytetracycline concentration in each sample was determined by a validated microbiological cylinder plate assay.

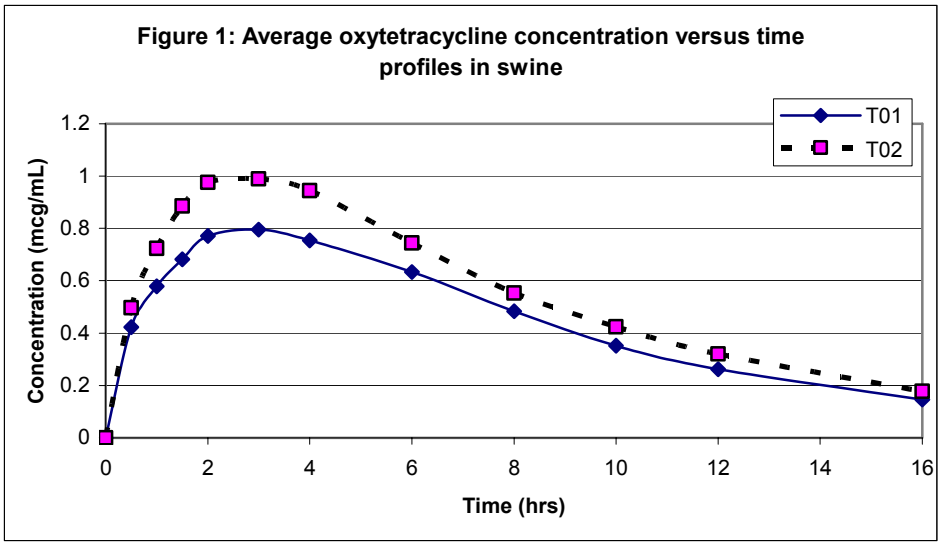
The serum drug concentrations were used to estimate the following pharmacokinetic parameters: the area under the curve (AUC) versus time profiles from time zero to the last quantifiable drug concentration ($AUC_{0\text{-last}}$) based upon the linear trapezoidal rule, the maximum observed drug concentration (C_{max}), the sampling time associated with C_{max} (T_{max}), and the terminal elimination half-life ($T_{½}$) (as estimated from the slope of the terminal portion of the Ln concentration versus time profile).

Results: The serum oxytetracycline concentrations observed in pigs fed carbadox (T02) prior to the administration of oxytetracycline were somewhat higher than were those observed in pigs that were given an unmedicated feed (T01) prior to oxytetracycline administration (Table 1, Figure 1).

Table 1: Relative bioavailability metrics comparing oxytetracycline bioavailability with and without carbadox

	Mean (%CV)		T02/T01	LCL*	UCL**
	T01	T02			
$AUC_{0\text{-last}}$ µg*hr/mL	7.75 (41)	9.65 (47)	1.25	1.02	1.41
C_{max} µg/mL	0.888 (41)	1.141 (46)	1.28	1.07	1.46
$T_{½}$ (hr)	5.12	5.08	--	--	--
T_{max} (hr)	3.13	3.19	--	--	--

* LCL = Lower Confidence Limit
** UCL = Upper Confidence Limit



There were no signs of toxicity or adverse reactions to either carbadox or oxytetracycline.

Conclusion: The administration of carbadox does not interfere with the oral bioavailability of oxytetracycline.

3. TARGET ANIMAL SAFETY:

In accordance with the 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 approved separately 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 that cannot adequately be evaluated based on the information contained in the application for the combination, and FDA finds that the application fails to show that the combination is safe, or

- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and FDA finds that the application fails to show that the combination is safe.

Carbadox, an antimicrobial, has previously been separately approved (NADA 041-061, MECADOX 10 Type A medicated article, Phibro Animal Health) for use in swine feed for increased rate of weight gain and improved feed efficiency when fed continuously at 10-25 g/ton of feed, and is codified in 21 CFR 558.115.

Oxytetracycline, an antimicrobial, has previously been separately approved (NADA 095-143, TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200 Type A medicated articles, Phibro Animal Health) for use in swine feed for treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* susceptible to oxytetracycline, and treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline when fed at 10 mg/lb of body weight daily for 7-14 days, and is codified in 21 CFR 558.450.

Target animal safety for each drug, carbadox and oxytetracycline, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in NADA 041-061 (carbadox) and NADA 095-143 (oxytetracycline).

4. HUMAN FOOD SAFETY:

In accordance with the 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 approved separately 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 food safety grounds unless FDA finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or

- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or drug in the combination.

a. Toxicity:

Safety for this combination product has been established by data in NADA 041-061, for carbadox, and NADA 095-143, for oxytetracycline as TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200.

b. Tolerances for Residue:

For carbadox, a tolerance of 30 parts per billion is established for the marker residue, quinoxaline-2-carboxylic acid (QCA), in swine liver (21 CFR 556.100).

Tolerances are established for the sum of residues of the tetracyclines in tissues of beef cattle, beef calves, non-lactating dairy cattle, dairy calves, swine, sheep, chickens, turkeys, finfish, and lobster, as follows: 2 parts per million (ppm) in muscle, 6 ppm in liver, and 12 ppm in fat and kidney (21 CFR 556.500).

c. Residue Data:

A study entitled "Concentration and Depletion of Quinoxaline-2-Carboxylic Acid (QCA) Residue in Liver of Growing Swine after Consumption of Carbadox and Oxytetracycline in Combination," was conducted at Southwest BioLabs, Mesilla Park, NM and Exygen Research, State College, PA under Phibro study number USD120-002, to demonstrate that 1) when carbadox is administered in conjunction with oxytetracycline residues of QCA do not exceed the established tolerance, and 2) oxytetracycline does not interfere in the assay of the carbadox. Only tissue residues of carbadox in swine liver were measured following administration of feed containing carbadox at 27.5 ppm, and oxytetracycline at 880 ppm. In lieu of a tissue residue depletion study for oxytetracycline, the sponsor conducted a pharmacokinetic study comparing blood levels of oxytetracycline when administered alone at a dose of 10 mg/lb and when administered in conjunction with carbadox, 25 g/ton. (Please refer to Section 2.)

The QCA concentration in the liver was determined in triplicate by the validated analytical method (LOQ = 5 ppb).

Table 2: Mean QCA concentration in liver for each treatment group

Treatment Group	Withdrawal (Days)	Number of observations	Mean (QCA ppb) ± SD
T1	Control	2	ND
T2	0	5	133.8 ± 82.5
T3	7	5	40.9 ± 9.4
T4	14	5	28.8 ± 11.9
T5	21	5	6.7 ± 3.1
T6	28	4	3.1 ± 0.2
T7	35	1	2.3 ± ---
T8	42	2	2.2 ± ---

Statistical analysis of the depletion data from this study demonstrated that the QCA concentration of the 99th percentile animal with 95% confidence would not exceed the 30 ppb tolerance limit after a 42-day withdrawal.

The possible interference of oxytetracycline with the analysis of QCA is liver was investigated by analyzing liver samples fortified with both QCA and oxytetracycline. A liver sample known to be free of QCA and a liver sample known to contain a moderate amount of QCA were fortified with oxytetracycline at 6 ppm tissue equivalents and extracted in triplicate. The resulting chromatograms illustrated that no oxytetracycline interference was present at the retention time of QCA.

d. Regulatory Methods for Residues:

Residues of QCA are determined using a gas chromatographic assay with electron capture detection. The method has a limit of quantification of 5 ppb in liver. The method is on file at the Center for Veterinary Medicine, FDA, 7500 Standish Place, Rockville, MD 20855.

The regulatory analytical method for detection of residues of oxytetracycline is a microbiological test using *Bacillus cereus* var. *mycoides* (ATCC 11778). The method is as published by the Food and Drug Administration, "Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Method, Reports, and Protocols," revised October 1968, reprinted December 1974.

5. USER SAFETY:

There are no human warnings on the Type C medicated feed labeling.

6. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512(d)(4) of the FFDCA and 21 CFR Part 514 of the implementing regulations. The combination of MECADOX 10 (carbadox) Type A medicated article and TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200 (oxytetracycline) Type A medicated articles, when administered as a Type C medicated feed for swine, is safe and effective for increased rate of weight gain, improved feed efficiency, treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* susceptible to oxytetracycline, and treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline.

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 effectiveness data in the parent NADAs.

The drugs are to be fed in Type C medicated feed in accordance with section 2 and 3 of the FOI Summary and the Blue Bird labeling that is attached to this document.

The Center for Veterinary Medicine has concluded that, for this combination product, adequate directions of use by the layperson have been provided. Label directions provide detailed instructions in plain language. The drug products are not controlled substances. Therefore, the combination product will have over-the-counter (OTC) status.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

No patents were submitted with this application.

7. ATTACHMENTS:

Facsimile labeling is attached as indicated below.

Specimen (Blue Bird) Type C medicated feed – carbadox plus oxytetracycline