Date of the NADA Approval:_____

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-002

OXY 500 & 1000 CALF BOLUS
(Oxytetracycline)

"...for oral administration for the control and treatment of the following diseases of beef and dairy calves caused by *Salmonella typhimurium* and *Eschericha coli (colibacillosis*); bacterial pneumonia (shipping fever complex, pasteurellosis) caused by *Pasteurella multocida."*

Sposored by:
Boehringer Ingelheim Vetmedica, Inc
2621 North Belt Highway
St. Joseph, MO 64506-2002

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION

A. NADA No.: 141-002

B. Sponsor: Boehringer Ingelheim Vetmedica, Inc.
2621 North Belt Highway
St. Joseph, MO 64506-2002

C. Generic Name: Oxytetracycline hydrochloride

D. Trade Name: Oxy 500 Calf Bolus & Oxy 1000 Calf Bolus

E. Marketing Status: OTC

2. INDICATIONS FOR USE

Oxy (oxytetracycline hydrochloride) Calf Boluses are indicated for the control and treatment of the following diseases of beef and dairy calves caused by organisms sensitive to oxytetracycline: bacterial enteritis caused by *Salmonella typhimurium* and *Escherichia coli* (colibacillosis); bacterial pneumonia (shipping fever complex, pasteurellosis) caused by *Pasteurella multocida*.

3. DOSAGE

For the control of bacterial enteritis and bacterial pneumonia in beef and dairy calves: administer orally 250 mg oxytetracycline hydrochloride per 100 lb of body weight every 12 hours (5 mg/lb of body weight daily in divided doses) for up to four consecutive days.

For the treatment of bacterial enteritis and bacterial pneumonia in beef and dairy calves: administer orally 500 mg oxytetracycline hydrochloride per 100 lb of body weight every 12 hours (10 mg/lb of body weight daily in divided doses) for up to four consecutive days.

Dosage should continue until the animal returns to normal and 24 to 48 hours after symptoms have subsided. Treatment should not exceed four consecutive days.

4. EFFECTIVENESS

The bioequivalency study and residue data were reviewed under the 1985 Bioequivalency Guideline and generated prior to the 1988 implementation of the Generic Animal Drug and Patent Restoration Act and was designated the DESI "me-too" status for approval purposes.

Effectiveness of the proposed Boehringer Ingelheim Vetmedica, Inc. (BIVI) products, Oxy (oxytetracycline hydrochloride) Calf Boluses, was established via a two-way blood level crossover study which demonstrated *in vivo* bioequivalency with the pioneer drug product.

Relative Bioavailability Study: A blood level study was conducted at Fermenta Animal Health Research Center in Fort Collins under an INAD exemption to establish the relative bioavailability of BIVI's Oxy (oxytetracycline hydrochloride) Calf Boluses compared to the pioneer's tablets when given to nonruminating calves.

The study was a two-way crossover design using thirty-six healthy calves weighing approximately 70 to 100 pounds (less than one week of age). The study was conducted in three replicates with six animals randomly assigned to each group in each replicate. Animals in Groups I, III (Rep 2) and III (Rep 3) were administered a single oral dose of BIVI's Oxy (oxytetracycline hydrochloride) Calf Bolus, 500 mg, at the rate of 10 mg of oxytetracycline hydrochloride per pound of body weight (one bolus per 50 pounds body weight). Animals in Groups II, IV (Rep 2) and IV (Rep 3) were administered a single oral dose of pioneer's tablets, 250 mg, at the rate of 10 mg of oxytetracycline hydrochloride per pound of body weight (one tablet per 25 pounds body weight). Calves were given one quart of warm water before and after dosing.

After a seven day washout period, the procedure was repeated with Groups I, III (Rep2) and III (Rep 3) receiving pioneer's product and Groups II, IV (Rep 2) and IV (Rep 3) receiving BIVI's product.

Venous blood samplers were collected from each animal immediately prior to treatment and at 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 60 and 72 hours post-treatment.

The BIVI Oxy (oxytetracycline hydrochloride) Calf Bolus, 500 mg, and the pioneer tablet, 250 mg, had areas-under-the-curve (AUCs) of 106.52 and 120.98 ppm-hr, respectively. This represents an 11.95% difference in AUC.

The peak serum levels (Cmax) of BIVI Oxy (oxytetracycline hydrochloride) Calf Bolus and the pioneer tablet were 5.32 and 5.62 µg/mL, respectively. This represents an observed difference of 5.34%.

BIVI Oxy (oxytetracycline hydrochloride) Calf Bolus and the pioneer tablet had time-to-peak levels (Tmax) of 6.74 and 7.74 hours, respectively. This represents an observed difference of 12.92%.

The observed differences are within the an expected range considering the dosage regimen and the varying metabolism and activity rate of individual animals. The discriminating power to detect significant differences in the AUC and Cmax were near 25% and are not unexpectedly high considering that young calves are very fragile at this age and represent a large animal-to-animal variation compared to more mature test animals. The discriminating power for the Tmax data is an unexpected result due largely to biological variability in newborn calves.

Consequently, BIVI's Oxy (oxytetracycline hydrochloride) Calf Boluses are considered equivalent to pioneer's approved tablets.

5. ANIMAL SAFETY

The re-evaluation of animal safety for approval of the proposed product is not required as the BIVI's Oxy (oxytetracycline hydrochloride) Calf Boluses labeling will bear the same indications for use, route of administration, recommended dosages and limitations as the approved drug product.

6. HUMAN FOOD SAFETY

Withdrawal time: Twenty healthy ruminating calves, ranging in weight from 175 to 285 pounds, were randomly assigned to each of five slaughter groups. Each group contained two males and two females. Calves were dosed twice daily at 12-hour intervals for four days at a rate of 5 mg. oxytetracycline hydrochloride per pound body weight. Two calves served as untreated controls. Treated calves were slaughtered at 12, 24, 72, 120 and 168 hours. Samples of perirenal fat, skeletal muscle, both kidneys and the liver were collected for residue analysis. Oxytetracycline concentrations in the tissues were determined using a modification of the regulatory microbiological assay.

Oxytetracycline Concentration (ppm) in Tissues

Time (hrs)	Liver	Kidney	Muscle	Fat
12	1.13±0.18	1.51±0.38	*	*
24	0.69±0.11	1.02±0.17	*	*
72	0.23±0.00	0.32±0.07	*	*
120	*	*	*	*
168	*	*	*	*

* = below level of quantification (LOQ)
LOQ: 0.176 ppm (liver); 0.255 ppm (kidney);
0.238 ppm (muscle); 0.129 ppm (fat)

The withdrawal period was calculated on the basis of residues of oxytetracycline using a 99% tolerance limit with 95% confidence. Using the statistical tolerance limit algorithm, and in accordance with the revised tolerances (61FR 67453) codified under 21 CFR 556.600, (12 ppm in kidney), there is no pre-slaughter withdrawal period when used at the recommended dosage levels.

Regulatory Method for Residues: The analytical method for the detection of residues in tissues is the cylinder plate microbiological method using *Bacillus cereus* var. *mycoides* (ATCC 11778), as outlined in "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports and Protocols," October 1968, National Center for Antibiotic and Insulin Analysis, FDA, Washington, DC 20204.

7. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Act and demonstrate that OXY Calf Bolus (500 & 1000 mg) when used under its proposed conditions of use is safe and effective for its labeled indications.

The sponsor submitted bioequivalency data for nonruminating calves which demonstrated biological equivalence to the approved pioneer product. For human food safety considerations, the firm submitted a tissue residue study in ruminating calves. The withdrawal period was calculated on the basis of residues of oxytetracycline using a 99% tolerance limit with 95% confidence. Using the statistical tolerance limit algorithm, and in accordance with the revised tolerances (61FR 67453) codified under 21 CFR 556.600, (12 ppm in kidney), there is no pre-slaughter withdrawal period when used at the recommended dosage levels. This is a DESI "me-too" approval and in this case the withdrawal period is based on residue data submitted.

Oxytetracycline Boluses are marketed as an over-the-counter product. Over-the-counter oxytetracycline products are currently on the market for use in food animals. Adequate directions for use have been written for the layman, and the conditions for use prescribed on labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product be granted over-the - counter marketing status.

This approval does not qualify for an exclusivity period under any of the provisions of section 512 (c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act of 1988. This application does not contain substantial evidence if the effectiveness of the drug 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 and conducted or sponsored by the applicant.

8. APPROVED PRODUCT LABELING (Attached)

OXY 500 CALF BOLUSES
25's, 50's, 100's and Package Insert

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