Date of Approval: September 3, 2002

FREEDOM OF INFORMATION SUMMARY

ANADA 200-008

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

Bio-Mycin® 200
(oxytetracycline injection)

"For use in lactating dairy cattle "

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

1. GENERAL INFORMATION

a. ANADA Number:	200-008
b. Sponsor:	Boehringer Ingelheim Vetmedica, Inc. 2621 North Belt Highway St. Joseph, Missouri 64506 Drug Labeler Code: 000010
c. Established Name:	Oxytetracycline injection
d. Proprietary Name:	Bio-Mycin® 200
e. Dosage Form:	Sterile injectable solution
f. How Supplied:	100-, 250-, and 500-mL bottles
g. How Dispensed:	OTC
h. Amount of Active Ingredients	200 mg oxytetracycline base per mL
i. Route of Administration:	IM, SC, or IV
j. Species/Class:	Beef cattle, dairy cattle, and swine
k. Recommended Dosage:	Cattle: Bio-Mycin® 200 is to be administered by IM, SC, or IV injection to beef cattle and dairy cattle. Bio-Mycin® 200 can be administered intramuscularly or subcutaneously as single dosage of 9 mg/lb (20 mg/kg) bodyweight. Bio-Mycin® 200 can also be administered 3-5 mg/lb administered IV, SC, or IM once a day for up to 4 days
l. Pharmacological Category:	Antimicrobial
m. Indications:	Cattle: Bio-Mycin® 200 is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp.; infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*; foot rot and diphtheria caused by *Fusobacterium necrophorum*; bacterial enteritis

(scours) caused by *Escherichia coli*; wooden tongue caused by *Actinobacillus lignieresii*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococci and streptococci organisms sensitive to oxytetracycline.

Swine: Bio-Mycin® 200™ is indicated in the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; and leptospirosis caused by *Leptospira pomona*. In sows, Bio-Mycin® 200™ is indicated as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli*.

n. Pioneer Product: LIQUAMYCIN® LA-200, (NADA 113-232; Pfizer)

o. Effect of Supplement: This supplement provides for changes to the product labeling to include lactating dairy cattle.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS

This supplemental application does not affect this section of the FOI summary. Refer to the FOI summary for the original ANADA approved November 16, 1994, and for the supplemental approval, dated May 22, 1996.

3. HUMAN SAFETY

- **Tolerances for Residues:** The tolerances established for the pioneer product apply to all tetracycline products. An acceptable daily intake (ADI) for total tetracycline residues is 25 micrograms per kilogram of body weight per day. A tolerance of 2 ppm in muscle, 6 ppm in liver, and 12 ppm in fat and kidney in the uncooked edible tissues of cattle under 21 CFR 556.500, as published October 27, 1998 (63 FR 57245). 21 CFR 556.500 was amended to reflect the tolerance of 0.3 ppm established for milk effective September 5, 2001.

- **Withdrawal Times:**

  A. Title: BioMycin® 200 Milk Residue Study in Dairy Cows

  1) Type of Study: Milk Residue

  2) . Study Director: Dan Ronning

Colorado Animal Research Enterprises, Inc.
6200 East County Road 56
Fort Collins, CO 80526

3) General Design:

Purpose: To extend the label claim for use in lactating dairy cows by measuring the oxytetracycline residue levels in milk after one treatment of Bio-Mycin® 200.

Dosage Form: Bio-Mycin® 200 in 100 mL bottle.

Route of Administration: Intramuscular

Dosage Used: 20 mg/kg (9mg/lb) once.

Study Duration: Day -1 through Day 6

Parameters Measured:

Body Weights: Once on Day -1.

Physical Examination: Once on Day -1.

Daily Observations: Clinical observations conducted daily by veterinarian for duration of study.

Milk Sample Collection: Samples were collected from each cow on day -1 (pre-dose) and at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144 hours post-treatment.

Analyses of Milk Samples: Assays of oxytetracycline levels were conducted by the cylinder-plate microbiology method.

4) Results:

Body Weights: Ranged from 633.0-815.5 kg (1396-1798 lb.).

Physical Examination: All animals were healthy throughout duration of trial.

Daily Observations: No abnormal clinical signs were noted and no adverse events.

Oxytetracycline Residues in Milk (See Table 1)

Table 1. Overall mean Oxytetracycline residue values* (mcg/mL) + SD in milk over time (hr)

Time post dosing (hour)	Oxytetracycline mcg/mL	Number of Animals
Predose	ND	20
12	2.458 + 0.616	20
24	2.647 + 0.504	20
36	2.199 + 0.595	20
48	1.188 + 0.350	20
60	0.924 + 0.355	20
72	<0.522 + 0.258	20
84	<0.363 + 0.228	20
96	<0.202 + 0.173	20
108	<0.160 + 0.179	20
120	<0.150 + 0.142	20
132	<0.150 + 0.109	20
144	<0.150 + 0.064	20

*ND = not detectable, considered 0.0 for computation of means and standard deviations. The limit of quantification for the assay of <0.150 was considered as 0.150 for computations of means and standard deviations. (Individual values for each animal not shown in this table).

By the last sampling at 144 hours, the milk from 18 cows did not have detectable residues. At the time one cow had detectable but non-quantifiable oxytetracycline residue levels and one cow had residue levels of 262-269 ppb, which approached the 300 ppb tolerance limit. The milk oxytetracycline levels of that cow were comparable to the other test cows through the 36 hour time point. Thereafter, the milk oxytetracycline residues markedly exceeded those from any other cow. There were no unusual circumstances associated with the test article administration to her or atypical clinical to explain the divergent residue depletion profile.

5) Statistical Results:

The data on assayed oxytetracycline (OTC) concentrations were statistically evaluated according to FDA/CVM's "Guideline for Establishing a Withdrawal Period." Application of CVM's prescribed statistical analysis determined that at 96 hrs the 99% tolerance limit with 95% confidence equaled 0.451 ppm.

B. Pharmacokinetic Comparison of IM and SC Routes of Administration

The milk residue depletion study was conducted in cattle treated intramuscularly (see above). Comparative plasma pharmacokinetic data indicate that the depletion following subcutaneous administration is more rapid than that associated with intramuscular administration as shown in Table 2. This more rapid depletion results therefore in lower terminal oxytetracycline concentrations following subcutaneous administration.

Table 2. Least square means and confidence intervals comparing Bio-Mycin® 200 when administered by the intramuscular (IM) and subcutaneous (SC) routes

Parameter	Mean (IM Dosing)	Mean (SC Dosing)	Ratio (SC/IM)	Lower CI*	Upper CI*
C_{max} (μg/mL)	5.57	9.27	1.66	50%	83%
AUC_{108} (μg*hr/mL)	178.6	198.3	1.11	7%	15%
T_{max} (hr)	3.19	2.16	N/A	N/A	N/A
T_{108} (hr)	114.01	92.42	N/A	N/A	N/A
$C_{0.5}$ (μg/mL)	3.553	6.275	1.77	N/A	N/A
C_{24} (μg/mL)	3.079	3.148	1.02	N/A	N/A
C_{48} (μg/mL)	1.239	0.816	0.66	N/A	N/A
C_{96} (μg/mL)	0.177	0.107	0.60	N/A	N/A

* L = lower bound on the 90% confidence interval and U= upper bound on the 90% confidence interval for the difference between the IM and SC formulation product means

The 96 hour Oxytetracycline concentration ratio would indicate that milk residues of Oxytetracycline following subcutaneous administration could be as much as 60% lower than those with intramuscular administration.

C. Milk Discard Withdrawal Conclusion

A milk discard time of 96 hrs is assigned for the prescribed use of Bio-Mycin® 200 in lactating dairy cows. As mentioned above, application of CVM's prescribed statistical analysis determined that at 96 hrs the 99% tolerance limit with 95% confidence equaled 0.451 ppm. Although that values exceeds the tolerance of 0.3 ppm, it assumes that 100% of the animals in the herd have been treated with the drug at its maximum does and that milk from all of the treated animals will be consumed by humans. However, because oxytetracycline injection will be used therapeutically, it is assumed that no more that one-third of the herd will be treated at an given time and, as such, oxytetracycline residues are expected to be no more that approximately 0.15 ppm.

- **Regulatory Method for Residues:**

The regulatory analytical method for detection of residues in tissues and milk is a microbiological cylinder-plate method (Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports, and Protocols, FDA, 1968, as reprinted 1974). This method is found on file at the Center For Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

4. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetics Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that Bio-Mycin®, when used under its proposed conditions of use, is safe and effective for its labeled indications.

Adequate directions for use of the product to treat cattle and swine have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall continue to have over-the-counter marketing status.

This application would extend the use of oxytetracycline to lactating diary cows. The previously established tolerance for oxytetracycline in milk is 0.3 ppm. With reference to this tolerance, a milk discard of 96 hours was calculated from the results of a residue depletion study in lactating dairy cattle using a statistical analysis (99% tolerance limit with 95% confidence) and making an allowance for only one-third of the herd being treated at any one time.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)(v)), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug and, therefore, did not require a reevaluation of the human food or target animal safety data in the parent application.

The pioneer, Liquamycin® LA-200®, Pfizer, Inc., was approved for use in lactating dairy cattle on July 21, 1998.

Bio-Mycin® Injectable Solution is under U.S. patent number 5,075,295, which expires December 12, 2009.

5. ATTACHMENTS

A copy of the draft facsimile labeling is attached to this document.

A. BIO-MYCIN® 200 - Vial Labels

B. BIO-MYCIN® 200 - Package Inserts

Copies of applicable labeling may be obtained by writing to:

Freedom of Information Staff (HFI-35)
Food and Drug Administration, Room 12A16
5600 Fisher's Lane
Rockville, Maryland 20857