# FREEDOM OF INFORMATION SUMMARY

**1. GENERAL INFORMATION** **ANADA 200-008**

**ANADA/GENERIC SPONSOR:**

Boehringer Ingelheim Animal Health, Inc.
2621 North Belt Highway
St. Joseph, Missouri 64506

| | | |
|---|---|---|
| a. | Established Name: | oxytetracycline injection |
| b. | Trade/Proprietary Name: | OXY-TET™ 200 and BIO-MYCIN® 200 |
| c. | Dosage Form: | sterile injectable solution |
| d. | How Supplied: | 100 mL and 500 mL bottles |
| e. | How Dispensed: | OTC |
| f. | Amount of Active Ingredient: | 200 mg/mL |
| g. | Route of Administration: | Intramuscular in swine, intramuscular or intravenous in cattle |
| h. | Species: | Beef cattle, non-lactating dairy cattle, and swine |
| i. | Pioneer Product/ "Listed" Product: | Liquamycin® LA-200; oxytetracycline injection; NADA # 113-232 |

**2. INDICATIONS**

OXY-TET 200/BIO-MYCIN 200* is intended for use in the treatment of the following diseases in beef cattle, nonlactating dairy cattle and swine when due to oxytetracycline susceptible organisms.

CATTLE

OXY-TET 200 is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Hemophilus* 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 lignieresi*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococci and streptococci organisms sensitive to oxytetracycline

* OXY-TET 200 will hereafter denote both OXY-TET 200 & BIO-MYCIN 200 throughout this summary.

SWINE

In swine, OXY-TET 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, OXY-TET 200 is indicated as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli.*

**3. DOSAGE**

CATTLE

OXY-TET 200 is to be administered by intramuscular or intravenous injection to beef cattle and nonlactating dairy cattle.

A single dose of 9 mg of OXY-TET 200 per pound of body weight administered intramuscularly is recommended in the treatment of the following conditions: 1) bacterial pneumonia caused by *Pasteurella* spp. (shipping fever) in calves and yearlings, where retreatment is impractical due to husbandry conditions, such as cattle on range, or where their repeated restraint is inadvisable; 2) infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*.

OXY-TET 200 can also be administered by intravenous or intramuscular injection at a level of 3 to 5 mg of oxytetracycline per pound of body weight per day. In the treatment of severe foot-rot and advanced cases of other indicated diseases, a dosage level of 5 mg per pound of body weight per day is recommended. Treatment should be continued 24 to 48 hours following remission of disease signs; however, not to exceed a total of four consecutive days. Consult your veterinarian if improvement is not noted within 24 to 48 hours of the beginning of treatment.

SWINE

In swine a single dose of 9 mg of OXY-TET 200 per pound of body weight administered intramuscularly is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where retreatment is impractical due to husbandry conditions or where repeated restraint is inadvisable.

OXY-TET 200 can be administered by intramuscular injection at a level of 3 to 5 mg of oxytetracycline per pound of body weight per day. Treatment should be continued 24 to 48 hours following remission of diseases signs; however, not to exceed a total of four consecutive days. Consult your veterinarian if improvement is not noted within 24 to 48 hours of the beginning of treatment.

For sows, administer once intramuscularly 3 mg of oxytetracycline per pound of body weight approximately 8 hours before farrowing or immediately after completion of farrowing.

For swine weighing 25 lb of body weight and under, OXY-TET 200 should be administered undiluted for treatment at 9 mg/lb but should be administered diluted for treatment at 3 or 5 mg/lb.

**4. TARGET ANIMAL SAFETY and DRUG EFFECTIVENESS:**

a. PIVOTAL STUDY:

1) Type of Study: BIOEQUIVALENCE STUDY (CALVES)

Two-period crossover design using 24 calves divided into two groups. Each calf received single intramuscular doses of either test or reference products at rates of 20 mg oxytetracycline per kg (9 mg/lb) of body weight in each of two crossover test periods.

Test Product: Oxytetracycline 200 mg/mL Injectable Solution (BIAHI) labeled as OXY-TET 200.

Reference Product: LIQUAMYCIN LA-200, 200 mg/mL oxytetracycline injectable solution (Pfizer, Inc.).

2) Investigator: Phillip W. Geeding, D.V.M.
Boehringer Ingelheim Animal Health, Inc.
St. Joseph, Missouri 64506

Statistician: Thomas J. Keefe, Ph.D.
EnviroStat Associates
Fort Collins, Colorado 80526

3) General Design of Investigation:

a) Purpose of Study:

To demonstrate bioequivalence between an oxytetracycline 200 mg/mL injectable solution generic formulation (OXY-TET 200) and LIQUAMYCIN LA-200 using production type beef cattle which are a target species and class for which the product is intended.

b) Test Animals:

Twenty-four (24) healthy commercial crossbred steer and heifer calves, 12 of each sex, from 5 to 6 months of age, weighing an average of 496 pounds each, were randomly assigned to one of two groups. Selection was based upon health status, serum chemistry and hematology values, and body weight uniformity.

c) Dosage Form:

Sterile injectable solution.

d) Route of Administration:

The products were administered by intramuscular injection, within the semimembranosus muscles on the left side of the animal in Phase I and the right side in Phase II. Intended injection sites were marked by clipping the hair in the area. No more than 10 mL was injected at any one site.

e) Dosage Used:

Both the test product and the reference product were administered at the 20 mg/kg (9 mg/lb) body weight level.

f) Test Duration:

In Phase I, the calves in Group 1 received a single dose of the test product and calves in Group 2 received a single dose of the reference product. After a 42-day washout interval, the dosing was repeated with Group I calves receiving the reference product and Group 2 calves receiving the test product. The time period from the initial Phase I injection to final observations of Phase II was 48 days.

g) Pertinent Parameters Measured:

The primary test parameter was the determination of serum oxytetracycline concentration at the following intervals: predose (baseline), 0.5, 1, 2, 4, 6, 8, 10, 16, 24, 36, 48, 60, 72, 84, 96, and 108 hours following intramuscular injection in each study period.

4) Results:

| MAJOR PHARMACOKINETIC MEASURES | OXY-TET 200[a] | LA-200[a] |
|---|---|---|
| Maximum observed serum concentration (CMAX) (µg/mL) | 4.39 | 4.14 |
| Time corresponding to the CMAX (TMAX) (hrs) | 6.29 | 8.25 |
| Terminal elimination half life (T1/2) (hrs) | 22.23 | 23.98 |
| Area under the moment curve ($AUMC_{0-108}$) (µg*hr$^2$/mL) | 5557 | 5496 |
| Area under the concentration-time curve ($AUC_{0-108}$) (µg*hr/mL) | 183.39 | 177.68 |

[a] arithmetic means

5) Statistical Analysis:

a) Identification of Statistical Methods:

The bioavailability of the test product (OXY-TET 200) relative to the reference product (LIQUAMYCIN LA-200) was compared on the basis of the untransformed study data. Differences between the test and reference products were statistically evaluated by means of confidence intervals. Each pharmacokinetic measure was analyzed via an analysis of variance procedure (ANOVA) using a linear model identifying the effects attributable to intersubject variability, sequence, treatment, and period. This ANOVA model is considered appropriate for comparing treatment effects based upon a two-period, two-treatment, two-sequence crossover study design.

The criterion for product bioequivalence was whether the 90% confidence intervals about the difference in product means (test minus reference values) were within ± 20% of the reference mean. Using this criterion, the test product was demonstrated to be equivalent to the reference product with respect to the rate ($AUMC_{0-108}$, CMAX) and extent ($AUC_{0-108}$) of oxytetracycline absorption. These results meet the requirements for demonstrating product bioequivalence.

6) Conclusion:

The two products are bioequivalent.

7) Adverse Reactions:

No adverse drug reactions were observed.

b. PIVOTAL STUDY:

1) Type of Study: BIOEQUIVALENCE STUDY (SWINE)

Two-period crossover design using 24 pigs allotted to two groups. Each pig received a single intramuscular dose of either test or reference product at a rate of 20 mg oxytetracycline per kg (9 mg/lb) of body weight in each of the two crossover test periods.

Test Product: Oxytetracycline 200 mg/mL Injectable Solution (BIAHI), labeled as OXY-TET 200.

Reference Product: LIQUAMYCIN LA-200, 200 mg/mL oxytetracycline injectable solution (Pfizer, Inc.).

2) Investigator: Phillip W. Geeding, D.V.M.
Boehringer Ingelheim Animal Health, Inc.
St. Joseph, Missouri 64506

Statistician: Thomas J. Keefe, Ph.D.
EnviroStat Associates
Fort Collins, Colorado 80526

3) General Design of Investigation:

a) Purpose of Study:

To demonstrate bioequivalence between an oxytetracycline 200 mg/mL injectable solution generic formulation (OXY-TET 200) and LIQUAMYCIN LA-200 using production type swine which are a target species and class for which the products are intended.

b) Test Animals:

Twenty-four (24) healthy commercial crossbred barrows and gilts, 12 of each sex, from 2 to 3 months of age, weighing an average of 37 pounds, were randomly assigned to one of two groups. Selection was based upon health status, serum chemistry and hematology values, and body weight uniformity.

c) Dosage Form:

Sterile injectable solution.

d) Route of Administration:

The products were administered by intramuscular injection, within the semimembranosus muscles on the left side of the animal in Phase I and the right side in Phase II. Intended injection sites were marked by clipping the hair in the area. No more than 5 mL was injected at any one site.

e) Dosage Used:

Both test product and reference product were administered at the 20 mg/kg (9 mg/lb) body weight level.

f) Test Duration:

In Phase I, the pigs in Group 1 received a single dose of the test product and pigs in Group 2 received a single dose of the reference product. After a 24-day washout interval, the dosing was repeated with Group 1 pigs receiving the reference product and Group 2 pigs the test product. The time period from the initial Phase I injection to final observations of Phase II was 48 days.

g) Pertinent Parameters Measured:

The primary test parameter was the determination of serum oxytetracycline concentration at the following intervals: predose (baseline), 0.5, 1, 2, 4, 6, 10, 16, 24, 36, 48, 60, 72, 84, 96, and 108 hours following intramuscular injection in each study period.

h) Results:

| MAJOR PHARMACOKINETIC MEASURES | OXY-TET 200[a] | LA-200[a] |
|---|---|---|
| Maximum observed serum concentration (CMAX) (µg/mL) | 4.12 | 4.11 |
| Time corresponding to the CMAX (TMAX) (hrs) | 1.80 | 1.75 |
| Terminal elimination half life (T1/2) (hrs) | 16.08 | 15.42 |
| Area under the moment curve[b] ($AUMC_{0-108}$) (µg*hr$^2$/mL) | 1204 | 1206 |
| Area under the concentration-time curve[b] ($AUC_{0-108}$) (µg*hr/mL) | 72.24 | 71.59 |

[a] arithmetic means

[b] test and reference values represent geometric means

5) Statistical Analysis:

The bioavailability of the test product (OXY-TET 200) relative to the reference product (LIQUAMYCIN LA-200) was compared on the basis of the untransformed data for CMAX and TMAX and the log-transformed data for $AUC_{0-108}$ and $AUMC_{0-108}$. Differences between the test and reference products were statistically evaluated by means of confidence intervals. Each pharmacokinetic measure was analyzed via an analysis of variance procedure (ANOVA) using a linear model identifying the effects attributable to intersubject variability, sequence, treatment, and period. This ANOVA model is considered appropriate for comparing treatment effects based upon a two-period, two-treatment, two-sequence crossover study design.

The criterion for product bioequivalence was whether the 90% confidence intervals about the difference in product means (test minus reference values) were within ± 20% of the reference mean. Using this criterion, the test product was demonstrated to be equivalent to the reference product with respect to the rate ($AUMC_{0-108}$, CMAX) and extent ($AUC_{0-108}$) of oxytetracycline absorption. These results meet the requirements for demonstrating product bioequivalence.

6) Conclusion:

The products are therapeutically bioequivalent. However, a statistically significant period by sequence interaction was seen in the ANOVA for comparing product apparent terminal elimination rates. This observation resulted in the collection of additional data to address human food safety concerns (see Section 6).

7) Adverse Reactions:

No adverse drug reactions were seen.

**5. HUMAN FOOD SAFETY:**

Tolerance

The tolerances established for the pioneer product apply to the generic product. A tolerance of 0.1 ppm is established for the uncooked edible tissues of cattle, beef calves, nonlactating dairy cattle, dairy calves, and swine under 21 CFR 556.500.

Withdrawal Time

a. Withdrawal Period in Cattle

A tissue irritation study and a blood level bioequivalence study (summarized under the effectiveness section) were conducted which showed the bioequivalence of OXY-TET 200 and Pfizer's Liquamycin LA-200 in calves.

1) Tissue Irritation Study

The level of tissue irritation of OXY-TET 200 injectable was evaluated in a well-controlled study with 25 calves receiving a 10 mL dose intramuscularly.

| | |
|---|---|
| Investigator(s): | Dan Ronning, M.S.<br>Colorado Animal Research Enterprises (C.A.R.E.)<br>Fort Collins, Colorado 80524 |
| Statistician: | Thomas J. Keefe, Ph.D.<br>EnviroStat Associates<br>Fort Collins, Colorado 80526 |

General Design of Investigation:

a) Purpose of Study:

To evaluate injection site tissue irritation following intramuscular administration of OXY-TET 200 at a dose level of 20 mg/kg body weight, with no more than 10 mL per site in beef cattle.

b) Test Animals:

Twenty-five (25) healthy, commercial, production type, crossbred calves (10 heifers and 15 steers), weighing an average of 500 pounds of body weight and estimated at 5-6 months of age.

c) Route of Drug Administration:

The test article was administered by intramuscular injection.

d) Time and Duration of Dosing:

Each calf received 20 mg/kg body weight of oxytetracycline with no more than 10 mL per injection site. The sites that received a full 10 mL dose were selected for examination.

e) Results:

The right semimembranosus muscle injection site was clinically evaluated by palpation prior to injection; then 4 hours following injection; and on days postdose 1, 2, 6, 9, 16, 23, and 30 on animals that remained on each of those days. Clinical parameters evaluated included heat at injection site, degree of swelling, induration (increased tissue density), pain response from tactile contact, and measurement of swollen tissue diameter with a caliper.

SUMMARY OF ANTEMORTEM OBSERVATIONS ON 25 CALVES INJECTED INTRAMUSCULARLY WITH A 10 mL DOSE OF OXY-TET 200

| Parameter | | Pre-Dose | 4 hr. Post-Dose | 1 Day | 2 Day | 6 Day | 9 Day | 16 Day | 23 Day | 30 Day |
|---|---|---|---|---|---|---|---|---|---|---|
| Palpation Temperature | Mean[a] | 0.0 | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | (S.D.) | 0.00 | 0.28 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Palpation Swelling | Mean[b] | 0.0 | 2.1 | 0.2 | 0.2 | 0.4 | 0.2 | 0.2 | 0.1 | 0.0 |
| | (S.D.) | 0.00 | 1.00 | 0.50 | 0.45 | 0.88 | 0.77 | 0.56 | 0.32 | 0.00 |
| Palpation Induration | Mean[c] | 0.0 | 1.8 | 1.7 | 1.0 | 0.9 | 0.9 | 0.7 | 0.8 | 0.4 |
| | (S.D.) | 0.00 | 0.37 | 0.69 | 1.00 | 0.72 | 0.64 | 0.80 | 0.79 | 0.55 |
| Palpation Pain | Mean[c] | 0.0 | 0.0 | 0.0 | | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | (S.D.) | 0.00 | 0.00 | 0.00 | | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Swelling Diameter | Mean[d] | 0.0 | 46.1 | 4.8 | 0.0 | 8.8 | 4.2 | 4.1 | 2.9 | 0.0 |
| | (S.D.) | 0.00 | 22.10 | 13.49 | 0.00 | 21.67 | 16.27 | 11.14 | 7.17 | 0.00 |

a Scores: 0=Normal 1=Slightly Warm 2=Warm 3=Hot

b Scores: 0=Normal 1=Very Slight 2=Slight 3=Moderate 4=Severe

c Scores: 0=None 1=Slight 2=Moderate 3=Severe

d Scores: Overall diameter measured in mm

f) Conclusions:

Injection site swelling, of slight to moderate severity which subsided over time, was the only significant antemortem post injection observation. Postmortem injection site irritation observations were made on core samples taken from the right semimembranosus muscle of each treated animal. By Day 28, only trace to mild amounts of fibrosis, inflammation, and Zenker's degeneration were noted. This study confirms that a 28 day withdrawal period is appropriate for this generic product.

2) Blood Level Bioequivalence Study in Cattle (see Section 4 above).

When bioequivalence is demonstrated by a blood level study, the generic product is assigned the same withdrawal time as the pioneer's product. Therefore, a withdrawal time of 28 days has been assigned for the use of the generic product in beef cattle and non-lactating dairy cattle.

b. Withdrawal Period in Swine

A tissue residue study was conducted in market weight swine using OXY-TET™ 200 at a dose of 20 mg/kg body weight.

Investigator: Diane Fagerberg, Ph.D.
Colorado Animal Research Enterprises, Inc.
Fort Collins, Colorado 80524

Statistician: Thomas J. Keefe, Ph.D.
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Fort Collins, Colorado 80526

Thirty-four pigs were randomly allocated to six groups of 5 pigs each. Four pigs served as treated controls. Each pig was treated once intramuscularly with OXY-TET™ 200 (200 mg oxytetracycline/mL) at a dose of 20 mg/kg. Animals were slaughtered at 2, 5, 8, 11, 21, and 28 days postinjection. Tissues were collected from the kidney intra-abdominal fat, liver, muscle, and injection site for residue analysis. Tissue samples were analyzed using a validated adaptation of the regulatory method.

Mean tissue residues (PPM) of oxytetracycline in swine treated once intramuscularly with 20 mg/kg body weight OXY-TET™200.

| Slaughter Time (days) | Kidney | Liver | Muscle | Fat | Injection Site |
|---|---|---|---|---|---|
| 2 | 7.39 ± 3.26 | 1.78 ± 0.48 | 1.46 ± 0.54 | 0.12 ± 0.06 | 566.68 ± 528.04 |
| 5 | 1.79 ± 0.80 | 0.41 ± 0.17 | 0.42 ± 0.14 | NDT | 67.93 ± 56.94 |
| 8 | 0.58 ± 0.20 | 0.16 ± 0.07 | 0.16 ± 0.09 | NDT | 26.23 ± 53.56 |
| 11 | 0.28 ± 0.04 | NDT | NDT | NDT | 1.24 |
| 21 | 0.21 ± 0.07 | NDT | NDT | NDT | NDT |
| 28 | <0.1 | NDT | NDT | NDT | NDT |

NDT = no detectable residues; no zone of inhibition
$LOQ_{fat}$ = 0.075 ppm $LOQ_{other}$ = 0.100 ppm

A left-censoring regression algorithm was used to calculate a withdrawal period for the use of OXY-TET™ 200 in swine. Using one-sided upper 95% confidence bound for the 99th percentile yields a 42-day withdrawal.

Regulatory Method:

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

## 6. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that oxytetracycline injection when used under the proposed conditions of use, is safe and effective for its labeled indications.