Approval Date: April 23, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 113-232

B. Sponsor

Pfizer Animal Health
Exton, Pennsylvania 19341

C. Proprietary Name

LIQUAMYCIN® LA-200®

D. Established Name

oxytetracycline amphoteric

E. Dosage Form

Liquamycin® LA-200® is a sterile, ready-to-use broad spectrum antibiotic parenteral formulation. Each milliliter contains 200 milligrams of oxytetracycline base as oxytetracycline amphoteric in an aqueous vehicle containing 2-pyrrolidone and povidone.

F. Dispensing Status

OTC

G. Dosage Regimen

CATTLE

A single dose of 9 mg of LIQUAMYCIN® LA-200® per pound of body weight administered intramuscularly or subcutaneously 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.*

LIQUAMYCIN® LA-200® can also be administered by intravenous, intramuscular, or subcutaneous 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 LIQUAMYCIN® LA-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.

LIQUAMYCIN® LA-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 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.

For sows, administer once intramuscularly at a dose of 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, LIQUAMYCIN® LA-200® should be administered undiluted for treatment at 9 mg/lb but should be administered diluted for treatment at 3 or 5 mg/lb

H. Route of Administration

This supplemental application provides for the addition of the subcutaneous route of administration to calves, including pre-ruminating (veal calves), and cattle. The following paragraph contains revised language.

Liquamycin® LA-200® should be administered by intramuscular, subcutaneous, or intravenous injection to calves, including pre-ruminating (veal calves), beef cattle and nonlactating dairy cattle, and by intramuscular injection to swine.

I. Indication

This supplemental application provides for the addition of "pre-ruminating (veal) calves" to the indications section. The following paragraph contains revised language.

In beef cattle, non-lactating dairy cattle, and calves, including pre-ruminating (veal calves), Liquamycin® LA-200® is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp.; bovine keratoconjunctivitis caused by *Moraxella bovis*; foot-rot and diphtheria caused by *Fusobacterium necrophorum*; bacterial enteritis (scours) caused by *Escherichia coli*; wooden tongue caused by *Actinobacillus ligniersii*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococci and streptococci organisms sensitive to oxytetracycline.

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

J. Effect of Supplement

This supplement provides for changes to the product labeling to include a subcutaneous (SC) route of administration in cattle. Also, the indications section of the labeling will be revised to include "pre-ruminating (veal) calves."

II. EFFECTIVENESS

Efficacy was demonstrated in a study which compared the serum pharmacokinetics of a single 20 mg/kg intramuscular (IM) or subcutaneous (SC) injection of Liquamycin® LA-200®.

1. **Study number**: 2532E-60-95-021
2. **Investigator**:
   Terry N. TerHune, DVM, PhD
   Health Management Services
   Tulare, California 93275
3. **General Design**
   a. **Purpose**: To determine and compare the serum pharmacokinetics and tissue toleration of a single 20 mg/kg intramuscular (IM) and subcutaneous(SC) injection of Liquamycin® LA-200®, over a seven day period in beef cattle.
   b. **Animals**: Thirty-two male and male castrate Holstein cattle (6 per group) ranging in age from 6 to 8 months. The initial mean weight was 420 pounds.
   c. **Dosage form**: 200 mg/mL injectable solution
   d. **Route of administration**: intramuscular or subcutaneous injection
   e. **Doses**: One treatment only at 20 mg/kg of body weight. SC injections were administered into the left neck area cranial to the scapula. IM injections were administered into the left neck muscle mass. The maximum volume per injection site was 10 mL. A full 10 mL was given into two sites. The third site received the residual volume needed to provide the required dose.
   f. **Test Duration**: 28 days
   g. **Pertinent Parameters Measured**: Pharmacokinetic parameters of: Area Under Curve (AUC), Time to Maximum Concentration (TMAX), and Maximum Concentration (CMAX). Swelling, heat, and pain at injection sites were also evaluated.
4. **Results**
   a. Least square means and confidence interval boundary information for the variables AUC and CMAX are presented in Table 4.1.

Table 4.1 Least Square Means and Confidence Intervals comparing IM and SC routes of injection for Liquamycin® LA-200®

Metric	Mean IM Dose	Mean SC Dose	Ratio SC/IM	Lower Cla	Upper Cla
CMAX* (µg/mL)	4.74	3.68	0.78	65%	91%
AUC last (µg*hr/mL)	119.5	118.3	0.99	87%	111%
TMAX* (hr)	2.5	5.0	-	-	-
TLAST (hr)	116	96	-	-	-
C0.5* (µg/mL)	3.029	1.23	0.40	-	-
C24 (µg/mL)	1.763	1.99	1.13	-	-
C48 (µg/mL)	0.54	0.67	1.25	-	-
C96 (µg/mL)	0.10	0.14	1.34	-	-

*statistically significantly different (p<0/05).
a 90% confidence intervals about the difference in treatment means using IM doses of LA-200® as the reference treatment. Equivalence is based upon a test and reference means differing by not more than 20% (untransformed data).

b. Swelling at injection sites was evaluated using a scale of 1 to 4 with 1 being normal and 4 being swelling of > 10 cm3. Swelling scores for LA-200® SC injection sites were predominately scored as 3 and 4 through Day 8 post-treatment and 2, 3, and 4 through Day 11 post-treatment. Injection sites returned to normal (no swelling) in all six animals at approximately Day 26. Gross pathology revealed that there was incomplete resolution of the inflammation associated with all IM, and some SC, injection sites at 28 days post-treatment.

Pain at the injection site was evaluated using a scale of 1 to 4, with 1 being no pain and 4 being severe pain. There was no report of any pain associated with the administration of LA-200®, by either route, nor was any pain, or heat, reported in association with the subsequent inflammation. There was no report of tissue sloughing or any other event that would appear to threaten animal health.

5. Conclusions:

Although the extent of bioavailability was not affected by the route of LA-200® administration, the rate of absorption was significantly less following SC injection. Accordingly, CMAX was significantly lower and TMAX occurred significantly later. However, the clinical efficacy of oxytetracycline is most closely aligned with time above Minimum Inhibitory Concentration (MIC) rather than the magnitude by which drug concentrations exceed an MIC. Therefore, the acceptability of the proposed alternate route of administration was determined on the basis of the extent of oxytetracycline bioavailability and the relative ability of IM and SC injections to maintain elevated serum oxytetracycline concentrations.

The rate of terminal depletion of the blood oxytetracycline concentrations resulting from an SC dose was slower than those associated with an IM dose. By Hour 24

post-dose, mean oxytetracycline serum concentrations of the SC treatment group exceeded those of the IM group (1.953 g/mL versus 1.797 g/mL respectively). By Hour 96 post-dose, the average SC blood oxytetracycline concentration was 7% greater than those observed after IM dosing (0.126 g/mL versus 0.118 g/mL for the SC and IM treatments respectively). Consequently, it can be assumed that once effective concentrations have been reached, a SC dose will be able to maintain effective blood concentrations for at least as long as that associated with an IM injection.

III. ANIMAL SAFETY

A. Injection Site Irritation

1. **Study number**: 2532D-60-96-164

2. **Investigator**:
   Diane J. Fagerberg, PhD
   Colorado Animal Research Enterprises, Inc.
   Ft. Collins, Colorado 80524

3. **General Design**:
   This study was conducted in accordance with GLP regulations and CVM guidelines. Calves were sorted by sex such that there were two groups of heifers and two groups of steers. Treatments that represented withdrawal intervals of 4, 10, 16, 22, 28 and 35 days, respectively, were randomly assigned to animals within a sex by weight block such that each treatment was represented within each block. Treatment groups (withdrawal intervals) each contained four animals, two heifers and two steers.

   a. **Purpose**: The objectives of the study were to determine the depletion profile of oxytetracycline residue in uncooked edible beef tissue following a single subcutaneous administration of LA-200® at 20 mg/kg and to investigate in-life injection site reaction, post-mortem gross pathology and the histopathological effect of a 10 mL subcutaneous injection on underlying tissue at the site of injection.

   b. **Animals**: 26 mixed breed production-type beef calves, with an initial mean weight of 557 pounds (253 kg)

   c. **Control**: one steer and one heifer

   d. **Dosage Form**: 200 mg/mL injectable solution

   e. **Route of Administration**: injected subcutaneously

   f. **Dose**: 20 mg/kg body weight

   g. **Test Duration**: 35 days

   h. **Pertinent Measurements and Observations**: General health of each animal was assessed twice daily during the study period. Injection site reaction variables included: pain upon palpation, temperature (heat) at injection site, swelling dimension (length, width and depth) and swelling characteristics. The study also included gross and histopathology

observations.

At designated post-treatment intervals (4, 10, 16, 22, 28 and 35 days), calves of respective groups were euthanatized. Injection sites from the animals were excised, weighed and color photographed. The injection site was examined by a board-certified pathologist. Gross pathology (or lack thereof) was recorded and additional color photographs were taken of the exposed, incised site. A section of tissue for histopathologic evaluation was collected from the excised injection site.

4. Results

a. Clinical Observations:
Animals remained healthy for the duration of the study and no adverse reactions attributable to treatment (other than injection site swelling) were observed. Swelling was apparent in a few animals by Day 1 and in all animals by Day 3. Swelling dimensions increased until they peaked, with an average surface area of 77 millimeters by 111 millimeters and a depth of approximately 19 millimeters, on Day 7. Swelling size gradually decreased through Day 28 and no swelling was apparent on Day 35.

b. Post-mortem Observations:
Gross lesions were sizable by Day 4 (269 cm3 average) and were larger by Day 10 (330 cm3 average). After Day 10, lesion dimensions gradually decreased until Day 35, when they were barely discernible (< 4 cm3 average). Lesions generally consisted of a yellow-green core surrounded by a firm white layer commonly surrounded or interspersed with a hemorrhagic or hyperemic layer. Over time, the core changed coloration to tan, yellow-tan, red and gray, brown or white.

Histopathological examination revealed a progressive healing process. Mild Zenker's degeneration was observed in Day 4 samples only. Edema/proteinaceous debris, fibrosis, granulation, inflammation and necrosis ranging from severe to mild/trace were observed at various intervals post-treatment. By Day 35, mild fibrosis, inflammation and necrosis were reported at some sites.

5. Conclusions:

Subcutaneous administration of Liquamycin® LA-200® resulted in transient swelling that occurred as early as 1 day post-treatment, peaked at approximately 7 days, and then slowly resolved without veterinary intervention. Injection site lesions are to be expected whether the product is administered as an IM or SC injection. The SC route results in a smaller lesion than does IM use. The lesions underlying the injection sites do not resolve completely by the end of the 28-day slaughter withdrawal period.

IV. HUMAN SAFETY

A. Tolerances for residues

The FDA has established tolerances for the sum of residues of tetracyclines, including chlortetracycline, oxytetracycline and tetracycline, in tissues of beef cattle, non-lactating dairy cows, calves, swine, sheep, chickens, turkeys and ducks (61 FR

67453, December 23, 1996). The tolerances established for oxytetracycline under 21 CFR 556.500 are as follows: 2 ppm in muscle, 6 ppm in liver, and 12 ppm in kidney and fat.

B. Residue depletion study in cattle treated subcutaneously with Liquamycin® LA-200®

Study 2532D-60-96-164 provided data for both human food safety, and animal safety. For more details about the study, please refer to section V. of this document.

This study was conducted in accordance with GLP regulations and CVM guidelines at Colorado Animal Research Enterprises, Ft. Collins, Colorado under the direction of Dr. Diane J. Fagerberg. The objective was to determine the depletion profile of oxytetracycline residue in uncooked edible beef tissue following a single subcutaneous administration of LA-200® at 20 mg/kg.

At designated post-treatment intervals (4, 10, 16, 22, 28 and 35 days), calves of respective groups were euthanized. Samples of muscle, fat, liver, kidney and all three injection sites were collected from each animal for oxytetracycline residue analysis. All samples were assayed fresh using a validated microbiological agar diffusion method. Some injection site samples from Days 10, 16 and 28 were re-assayed after being frozen and thawed because oxytetracycline concentrations in the initial assay were found to exceed the range of the standard curve. Also, all kidney tissues were re-assayed after freeze/thaw because storage stability data suggested greater oxytetracycline levels (at high concentrations) after frozen storage. Tissue residue values are presented in table 6.1.

Table 6.1 Mean residues (ppm SD) of oxytetracycline in fresh bovine tissues following a single subcutaneous injection of Liquamycin® LA-200® at a dose of 20 mg/kg body weight

	Tissue residue				Injection Site residue		
Days Post-Treatment	Muscle	Liver	Kidney	Fat	Site 1	Stie 2	Site 3
4	0.372 (±0.093)	1.451 (±0.276)	1.687	0.117 (±0.098)	439 (±149)	463 (±157)	370 (±172)
10	0.147 (±0.071)	0.593 (±0.277)	0.593 (±0.212)	ND	205 (±89.7)	161 (±102)	74.4 (±62.9)
16	0.172	0.227 (±0.056)	0.318 (±0.070)	ND	130 (±119)	85.8 (±111)	36.5 (±58.5)
22	ND	0.118 (±0.028)	0.141 (±0.023)	ND	9.34 (±9.23)	20.8 (±24.5)	1.309 (±0.96)
28	ND	0.159	0.162	ND	1.056* (±0.286)	5.40 (±6.00)	6.44 (±8.43)
35	ND	ND	ND	ND	ND	0.431	ND
Limit of Quantitation	0.075	0.1	0.075	0.075		0.075	

* A single aberrant value has been deleted from the calculation of the mean

ND = not detectable

C. Residue depletion study in pre-ruminating calves treated with Liquamycin® LA-200®.

1. **Study number:** 2532E-60-95-112

2. **Investigator:**

   Terry N. TerHune, DVM, PhD
   Health Management Services
   Tulare, California 93275

3. **General Design**

   a. **Purpose:** This is a tissue residue depletion study for oxytetracycline injection, 200 mg/mL, conducted in veal calves. The study was conducted to comply with Good Laboratory Practices, 21CFR 58. Tissue analyses were conducted by Colorado Animal Research Enterprises, Inc. (CARE). Diane J. Fagerberg, PhD, is the CARE President and General Manager. Donald J. Bade, BS, served as the CARE Microbiology Laboratory Director.

   b. **Animals:** Thirty-two healthy male castrate Holstein calves, age 12 weeks.

   c. **Dosage form:** 200 mg/mL Injectable solution

   d. **Route of administration:** intramuscular injection

   e. **Doses:** One treatment only, administered in the neck muscle

   f. **Test Duration:** 18 days

   g. **Pertinent Parameters Measured:** Approximately 500 g of liver (cross-section of each lobe), 500 g each of injection site and noninjection site (semimembranosus) muscle, 200 g (or the maximum obtainable) abdominal fat, and both kidneys**.**

4. **Results**

   a. Residue analyses were conducted at CARE, Fort Collins, CO 80524, using an adapted validated microbiological assay. The data are presented in Table 6.2.

Table 6.2 Mean oxytetracycline residue concentrations (ppm) in uncooked edible tissue of fancy (formula fed) veal calves treated once at 20 mg/kg body weight with Liquamycin LA 200

	Tissue residue				
Days Post-treatment	**Muscle**	**Liver**	**Kidney**	**Fat**	**Injection**
3	0.58±0.03	1.60±0.22	2.06±0.56	0.21±0.09	168.30±144.67
6	0.21±0.03	0.28±0.04	0.43±0.11	0.41	35.93±51.88
9	0.16±0.05	0.19±0.08	0.34±0.08	0.18	5.37 ± 4.96
12	ND*	0.19	0.24±0.05	ND	21.17 26.35
15	ND	0.27	0.22±0.04	0.19±0.05	0.38
18	ND	0.21	0.29±0.06	ND	ND
Limit of Quantitation	0.075	0.100	0.100	0.075	0.075

* ND = not detectable

5. Conclusions

These residue data demonstrate that the 28-day pre-slaughter withdrawal period currently assigned for the intramuscular use of Liquamycin® LA-200® may be applied to the subcutaneous use of the product in beef and non-lactating dairy cattle and in veal calves not intended for slaughter prior to 28 days of age.

V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of Section 512 of the Act and demonstrate that Liquamycin® LA-200® for subcutaneous injection in beef cattle, non-lactating dairy cattle, and calves, including pre-ruminating (veal) calves, is safe and effective for the indications stated on the product labeling.

Under the Center's supplemental approval policy [21 CFR 514.106(b)(2)(iv) and (v)], this is a Category II supplement which required a re-evaluation of the safety and effectiveness data.

For cattle the tolerance of residues for oxytetracycline, as specified in 21 CFR 556.500, are as follows: 2 ppm in muscle, 6 ppm in liver, and 12 ppm in kidney and fat. A tissue residue study was conducted to determine the depletion profile of oxytetracycline residue in uncooked edible beef tissue following a single subcutaneous administration of Liquamycin® LA-200® at a dose of 20 mg/kg of body weight (9 mg/lb), using production type beef cattle; a target species and class for which the product is intended. A second tissue residue study was conducted, using a single intramuscular injection, at the same dose, in pre-ruminating cattle. Residues in the tissues of pre-ruminating calves following intramuscular administration of Liquamycin® LA-200® were comparable to the tissue residue levels seen in the original approval supporting the intramuscular administration of Liquamycin® LA-200® in adult cattle. A pharmacokinetic study provides data to bridge

the intramuscular and subcutaneous routes of administration in adult cattle. It was concluded that a separate subcutaneous residue depletion study would not be needed in pre-ruminating calves to support the assignment of a 28-day withdrawal period for this route of administration.

These residue data demonstrate that the 28-day pre-slaughter withdrawal period currently assigned for the intramuscular use of Liquamycin® LA-200® may be applied to the subcutaneous use of the product in beef and non-lactating dairy cattle and in veal calves not intended for slaughter prior to 28 days of age. A trim-out statement is necessary due to the tissue discoloration present at injection sites examined up to 28 days post-treatment.

The original approval of Liquamycin® LA-200® was for Over-the-Counter use. Adequate directions for use of the subcutaneous injection route in cattle 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.

The agency has determined under 21 CFR 25.24 (d)(1)(i) that this action is of the type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

In 1991, the Center for Veterinary Medicine completed a review of New Animal Drug Applications (NADA) that covered products either approved, or permitted by regulation, for use in calves or cattle without restriction. The Center conducted the review to determine whether the data in the NADA supported the use of the labeled withdrawal period in special-fed veal calves, or other pre-ruminating calves. The review was necessary because, at the time of the approval of these NADAs, the knowledge of pharmacokinetics for drugs used in cattle did not indicate that pre-ruminating calves should be considered a unique class of animals requiring specific residue depletion studies to ensure adequate withdrawal periods. In a letter dated April 28, 1992, all sponsors of such applications that did not contain data in the NADAs to support the withdrawal period currently appearing in the product's labeling with respect to veal calves were asked to submit supporting residue depletion data from pre-ruminating calves. The sponsor has provided such data in this supplemental application (see Human Safety section), thereby adequately addressing the pharmacokinetic concerns raised in the April 28, 1992 letter. The basis for determination of target animal safety and effectiveness in pre-ruminating cattle is contained in the original approval for Liquamycin® LA-200®. Accordingly, Liquamycin® LA-200® remains approved for use in pre-ruminating (veal) calves.

The indication for pre-ruminating (veal) calves does not qualify for an exclusivity period because the supplement does not contain reports of new clinical or field investigations (other than bioequivalence or residue studies) or human food safety studies (other than bioequivalence or residue studies) essential to the approval of the supplement and conducted or sponsored by the applicant.

Under Section 512(c)(2)(F)(iii) of the FFDCA, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of 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 of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the subcutaneous route of administration in beef cattle, non-lactating dairy cattle, and calves including pre-ruminating (veal) calves, for which the supplemental application was approved.

Liquamycin® LA-200® patent number US 4,018,889 expired April 19, 1994.

VI. ATTACHMENTS

Draft labeling consisting of the box carton, vial label, temporary "hang tag", and package insert for the 100 mL, 250 mL, and 500 mL vials is attached.

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.