Date of Approval: July 25, 2003

FREEDOM OF INFORMATION SUMMARY

NADA 141-143

TETRADURE 300 (Oxytetracycline) INJECTION
OXYTETRACYCLINE INJECTION 300 mg/mL

"In cattle ... for 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 lignieresi*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococcal and streptococcal organisms sensitive to oxytetracycline. TETRADURE™ 300 (only) is also indicated for the control of respiratory disease in cattle at high risk of developing Bovine Respiratory Disease (BRD) associated with *Mannheimia* (*Pasteurella*) *haemolytica* and the dosage range for the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp. and infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*."

"In swine ... for the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; and leptospirosis caused by *Leptospira pomona*. In sows, oxytetracycline is indicated as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli*."

NEW ANIMAL DRUG APPLICATION

Sponsored by:

Norbrook Laboratories Limited
Station Works
Newry, BT35 6JP
Northern Ireland

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1. GENERAL INFORMATION

a. File Number: NADA-141-143

b. Sponsor: Norbrook Laboratories Limited
Station Works
Newry
BT35 6JP
Northern Ireland
Drug Labeler Code: 055529

c. Established Name: Oxytetracycline injection

d. Proprietary Name: TETRADURE 300 (Oxytetracycline) Injection (R_x product)
OXYTETRACYCLINE INJECTION 300 mg/mL (OTC product)

e. Dosage Form: Injectable

f. How Supplied: TETRADURE 300 and OXYTETRACYCLINE INJECTION 300 mg/mL are supplied in 100, 250 and 500 mL bottles.

g. How Dispensed: R_x and OTC

h. Amount of Active Ingredients: Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline.

i. Route of Administration: The product is administered via intravenous, intramuscular or subcutaneous injection as described in the "Recommended Dosage" section below.

j. Species/Class: Beef cattle, Non-lactating dairy cattle, calves, including pre-ruminating (veal) calves and swine.

k. Recommended Dosage: CATTLE [beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves]:

A single intramuscular or subcutaneous dosage of 13.6 mg of oxytetracycline per pound of body weight, TETRADURE 300 is recommended for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia* (*Pasteurella*) *haemolytica*.

A single dosage of 9 to 13.6 milligrams TETRADURE 300 or 9 milligrams OXYTETRACYCLINE INJECTION 300 mg/mL 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 repeated restraint is inadvisable;
2) infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*.

For other indications TETRADURE 300 and OXYTETRACYCLINE INJECTION 300 mg/mL are to be administered intramuscularly, subcutaneously, or intravenously at a level of 3 to 5 milligrams 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 milligrams 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 (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of the treatment, diagnosis and therapy should be re-evaluated by a veterinarian.

SWINE:

A single dosage of 9 milligrams oxytetracycline 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.

TETRADURE 300 and OXYTETRACYCLINE INJECTION 300 mg/mL can also be administered by intramuscular injection at a level of 3 to 5 milligrams 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 (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of the treatment, diagnosis and therapy should be re-evaluated by a veterinarian.

For sows, administer once intramuscularly 3 milligrams of oxytetracycline per pound of body weight approximately eight (8) hours before farrowing or immediately after completion of farrowing as an aid in the control of infectious enteritis in baby pigs.

l. Pharmacological: Category — Antimicrobial

m. Indications: — *Beef and non-lactating dairy cattle, calves, including pre-ruminating (veal) calves*: for 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 lignieresi*; leptospirosis caused by *Leptospira pomona*; and wound infections and acute metritis caused by strains of staphylococcal and streptococcal organisms sensitive to oxytetracycline. Also, TETRADURE 300 is indicated (prescription use) for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia* (*Pasteurella) haemolytica*.

Swine: for the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; and leptospirosis caused by *Leptospira pomona*.

In sows, oxytetracycline is indicated as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli*.

2. EFFECTIVENESS:

This product is a "hybrid" NADA relying on approval of a listed (pioneer) animal drug to the extent it is allowed under 512 (n) of the Federal Food, Drug, and Cosmetic (FFD&C) Act and contains additional data needed to support changes in the generic product.

A. Dosage Characterization:

Dose Rationale:

The 3.0 to 5.0 mg/lb and 9 mg/lb doses and indications were established based on the pioneer product LIQUAMYCIN LA-200 approved under NADA 113-232.

The 13.6 mg/lb (30 mg/kg) dose for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica* was established based on label indications for similar European-approved products and studies conducted in Canada. The sponsor conducted field studies in the U.S. relying on the European approvals as dose establishment data.

The dosage range of 9 to 13.6 mg/lb for treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp. and infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis* was established based upon the pioneer product and additional safety studies conducted which demonstrated the safety of the upper end of the dose range (13.6 mg/lb) in cattle.

B. Substantial Evidence:

Dose Confirmation:

The requirements for establishing the effectiveness of the product at the dosages currently approved under NADA 113-232 were met by demonstrating comparable serum pharmacokinetics to LIQUAMYCIN LA-200 in both cattle and swine at a dose of 9 mg/lb.

CATTLE

1. Title: A Comparative Study of Plasma Level of Oxytetracycline in *Cattle* Following the Intramuscular Administration of Oxytetracycline 300 (Norbrook Laboratories Limited) and LIQUAMYCIN LA-200 (NADA 113-232, Pfizer)

2. Study Number: 039/94

3. Investigator: Mr. N. Orr
   Ballyedmond Castle Farms Limited
   101 Killowen Road
   Rostrevor
   Co. Down, BT34 3AG
   Northern Ireland

4. Study Design:

   a. Purpose: Effectiveness determination by comparison of plasma pharmacokinetics of the sponsor's oxytetracycline 300 mg/mL injection product to that of a pioneer product (oxytetracycline 200 mg/mL injection). Both products were administered intramuscularly at the recommended dosage in a cross-over design bioequivalence study.

   b. Test Animals: Twenty-four mixed breed, beef-type calves consisting of 12 males and 12 females weighing 910 to 1010 pounds were evaluated in the study.

   c. Control (reference): LIQUAMYCIN LA-200, NADA 113-232.

   d. Dosage form (test): 300 mg/mL injectable.

   e. Route of administration: intramuscular injection.

   f. Dose: Single treatment with 9 mg oxytetracycline per pound of body weight with a maximum of 10 mL administered in one site.

   g. Test duration: 49 days (42 day washout period).

   h. Pertinent parameters measured: Area Under the Curve (AUC) measured from time zero to the last quantifiable drug concentration ($AUC_{0\text{-last}}$), and Maximum Observed Drug Concentrations (C_{max}). Time to Maximum Concentration (T_{max}) values were used for qualitative comparisons.

5. Results:

Table 2.1. Pharmacokinetic variables of the test and the reference articles

Parameter	Mean Test	Mean Reference	Upper CL*	Lower CL*
$AUC_{0\text{-last}}$ (µg* hr/mL)	254.08	254.45	+3.4%	-3.7%
C_{max} (µg/mL)	8.20	8.34	+3.9%	-7.4%
T_{max} (hr)	5.5	4.5	-	-

* Confidence interval presented as % of reference article mean.

6. Conclusions: Norbrook's 300 mg/mL injectable oxytetracycline product and Pfizer's LIQUAMYCIN LA-200 are bioequivalent based on AUC and C_{max} values.

SWINE

1. Title: A Comparative Study of Plasma Levels of Oxytetracycline In *Pigs* Following the Intramuscular Administration of Oxytetracycline 300 (Norbrook Laboratories Limited) and LIQUAMYCIN LA-200 (NADA 113-232, Pfizer)

2. Study Number: 043/94

3. Investigator: Mr. N. Orr
   Ballyedmond Castle Farms Limited
   101 Killowen Road

Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. Study Design:

   a. Purpose: Effectiveness determination by comparison of plasma pharmacokinetics of the sponsor's oxytetracycline 300 mg/mL injection product to that of a pioneer product (oxytetracycline 200 mg/mL injection). Both products were administered intramuscularly at the recommended dosage in a parallel design bioequivalence study.

   b. Test Animals: Forty-eight Landrace/Large White crossbreed pigs consisting of 24 males and 24 females weighing 50 to 65 pounds were evaluated in the study.

   c. Control (reference): LIQUAMYCIN LA 200, NADA 113-232.

   d. Dosage form (test): 300 mg/mL injectable.

   e. Route of administration: intramuscular injection.

   f. Dose: Single treatment with 9 mg oxytetracycline per pound of body weight.

   g. Test duration: 7 days.

   h. Pertinent parameters measured: Area Under the Curve (AUC) measured from time zero to the last quantifiable drug concentration ($AUC_{0\text{-last}}$), and Maximum Observed Drug Concentrations (C_{max}). Time to Maximum Concentration (T_{max}) values were used for qualitative comparisons.

5. Results:

Table 2.2. Pharmacokinetic variables of the test and the reference articles

Parameter	Mean Test	Mean Reference	Upper CL*	Lower CL*
$AUC_{0\text{-last}}$ (µg* hr/mL)	114.8	107.5	+10.9%	+2.5%
C_{max} (µg/mL)	5.06	5.00	+7.4%	-5.0%
T_{max} (hr)	2.5	2.6	-	-

* Confidence interval presented as % of reference article mean.

6. Conclusions: Norbrook's 300 mg/mL injectable oxytetracycline product and Pfizer's LIQUAMYCIN LA-200 are bioequivalent based on AUC and C_{max} values.

Field Investigation:

A field investigation was undertaken to demonstrate the effectiveness of the 30 mg/kg (13.6 mg/lb) dose for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia* (*Pasteurella*) *haemolytica*. Two sites were included and the results from the trials combined statistically.

STUDY 1

1. Title: A Study to Evaluate the Prophylactic Effectiveness of Norbrook's OXYTET

30% Injectable Formulation in Reducing the Incidence and Severity of Bovine Respiratory Disease (BRD).

2. Study Number: KFL-4Q96-BRD-NB-K-02

3. Investigator: Alvin J. Edwards, D.V.M., Ph.D.
Knight Feedlot, Inc., Manhattan, KS

4. Study Design:

   a. Purpose: To evaluate the effectiveness of the product in reducing the incidence and severity of naturally occurring bovine respiratory disease (BRD) in calves.

   b. Test Animals: Approximately 1,200 mixed breed and crossbred beef-type steer and heifer calves weighing 330 to 714 pounds were obtained and randomly assigned to either the test or control group. All calves were treated within 96 hours of receipt at the feedlot.

   c. Control: Saline solution 0.9%.

   d. Diagnosis: Calves were observed daily for 30 days for signs, such as, poor general appearance, depressed attitude and reluctance to move. Rectal temperature was measured in animals displaying such signs and calves with temperatures greater than or equal to 104°F were treated with MICOTIL (single 10 mg/kg dose SQ) and returned to the pen. Calves were defined as "Healthy" that required no further treatment and had no evidence of BRD during the 30-day observation period. Calves were defined as "Failures" that required any supplemental treatment for BRD or died of respiratory disease.

   e. Dosage form: 300 mg/mL injectable.

   f. Route of administration: Intramuscular injection in the left side of the neck.

   g. Dose: Single treatment with 13.6 mg oxytetracycline per pound of body weight.

   h. Test duration: 30 days.

5. Results:

Table 2.3. Number of healthy and treatment failures administered the test or the control article

Treatment	n	Healthy	Failures
Test	601	426	175
Control	598	378	220
Total	**1199**	**804**	**395**

STUDY 2

1. Title: A Study to Evaluate the Prophylactic Efficacy of Norbrook's OXYTET 30% Injectable Formulation in Reducing the Incidence and Severity of Bovine Respiratory Disease (BRD).

2. Study Number: MVS-4Q96-N-BRD-NB-01

3. Investigator: Kelly F. Lechtenberg, D.V.M., Ph.D. &
Michael J. Hanna, D.V.M.
Midwest Veterinary Services, Inc.
Oakland, NE

4. Study Design:

   a. Purpose: To evaluate the effectiveness of the product in reducing the incidence and severity of naturally occurring bovine respiratory disease (BRD) in calves.

   b. Test Animals: 1,200 mixed breed and crossbred beef-type steer calves weighing 366 to 702 pounds were obtained and randomly assigned to either the test or control group. All calves were treated within 96 hours of receipt at the feedlot.

   c. Control: Saline solution 0.9%.

   d. Diagnosis: Calves were observed daily for 30 days for signs such as poor general appearance, depressed attitude and reluctance to move. Rectal temperature was measured in animals displaying such signs and calves with temperatures greater than or equal to 104°F were treated with Micotil (single 10 mg/kg dose SQ) and returned to the pen. Calves were defined as "Healthy" that required no further treatment and had no evidence of BRD during the 30-day observation period. Calves were defined as "Failures" that required any supplemental treatment for BRD or died of respiratory disease.

   e. Dosage form: 300 mg/mL injectable.

   f. Route of administration: Intramuscular injection in the left side of the neck.

   g. Dose: Single treatment with 13.6 mg oxytetracycline per pound of body weight.

   h. Test duration: 30 days.

5. Results:

Table 2.4. Number of healthy and treatment failures administered the test or the control article

Treatment	n	Healthy	Failures
Test	600	265	335
Control	600	245	355
Total	**1200**	**510**	**690**

6. Pooled Data Analysis from Field Studies:

Data from the two field studies described above were pooled and each case was designated to have resulted in a favorable or unfavorable response. Favorable responders are defined as animals that were treated with the test or control article

and did not require further treatment, i.e., "healthy" (i.e., no evidence of BRD during the 30-day observation period). Unfavorable responders are defined as animals that required additional medication even after being treated with the test or control article, i.e., "failures" (i.e., required any supplemental treatment for BRD or died of respiratory disease).

The resulting data were analyzed using an arcsine square root transformation on the proportion of healthy animals for each treatment for each pen adjusted for pen size. The model included terms for location (Kansas and Nebraska) and block within location (22 blocks; 15 at Nebraska and 7 at Kansas) as random effects. The model was also adjusted for the pen size variability. The analysis showed that the treatments were significantly different (p=0.0065, two-sided, F=9.13 with 1 and 21 degrees of freedom).

Table 2.5. Pooled data showing the number of healthy and treatment failures administered the test or the control article

Treatment/Location	n	Healthy	Failures
Oxytetracycline	1201	691	510
Control	1198	623	575
Total	**2399**	**1314**	**1085**

7. Conclusions: The results of these studies indicate that the product is effective in the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia* (*Pasteurella*) *haemolytica*.

Bioequivalence Study:

1. Title: A Comparative Study of Plasma Levels of Oxytetracycline in Cattle Following the Intramuscular and Subcutaneous Administration of OXYTET 30% (Norbrook Laboratories Limited).

2. Study Number: 058/97

3. Investigator: Mr. A. Carragher
   Ballyedmond Castle Farms Limited
   101 Killowen Road
   Rostrevor
   Co. Down, BT34 3AG
   Northern Ireland

4. Study Design:

   a. Purpose: Effectiveness determination by comparison of plasma pharmacokinetics of the sponsor's oxytetracycline 300 mg/mL injection product administered intramuscularly or subcutaneously at the recommended dosage in a cross-over design bioequivalence study.

b. Test Animals: Twenty-four mixed breed, beef-type calves consisting of 12 males and 12 females weighing 910 to 1020 pounds were evaluated in the study.

c. Control (reference): Norbrook oxytetracycline 300 mg/mL injectable.

d. Dosage form: 300 mg/mL injectable.

e. Route of administration: intramuscular or subcutaneous injection.

f. Dose: Single treatment per period with 13.6 mg oxytetracycline per pound of body weight with a maximum of 10 mL administered in one site. Subcutaneous injections were made in the neck area and intramuscular injections were made in the muscles of the rump.

g. Test duration: 53 days (42 day washout period).

h. Pertinent parameters measured: Area Under the Curve (AUC) measured from time zero to the last quantifiable drug concentration ($AUC_{0\text{-last}}$), and Maximum Observed Drug Concentrations (C_{max}). Time to Maximum Concentration (T_{max}) values were used for qualitative comparisons.

5. Results:

Table 2.6. Pharmacokinetic variables of Oxytetracycline administered subcutaneously or intramuscularly

Parameter	Mean** Test (SC)	Mean** Reference (IM)	Upper CL*	Lower CL*
$AUC_{0\text{-last}}$ (µg* hr/mL)	2.48	2.46	1.10*	1.00*
C_{max} (µg/mL)	0.94	0.9	1.20*	1.02*
T_{max} (hr)	9.7	9.6	-	-

*Confidence intervals estimated about the ratio of means using Ln transformed parameters.
**Geometric means

6. Conclusions: The products were considered bioequivalent based on AUC and C_{max} confidence intervals lying within –20%, +25% of the mean of the reference product using log transformed concentration data.

3. TARGET ANIMAL SAFETY:

A. Drug Tolerance

The toxicological effects of oxytetracycline are well documented based on studies conducted with other oxytetracycline products. It can be concluded that the principal effects following administration of large doses of oxytetracycline are nephrotoxicosis and hepatotoxicosis. References include:

1. Griffin D.D. *et al*. 1979. Experimental Oxytetracycline Toxicity in Feedlot Heifers. *The Bovine Practitioner*. **14**:37-41.
2. Lairmore M.D. *et al*. 1984. Oxytetracycline-associated nephrotoxicosis in feedlot calves. *JAVMA*, **185**(7):793-795.
3. Riond J-L. and Riviere J.E. 1989. Effects of Tetracyclines on the Kidney in Cattle and Dogs. *JAVMA*, **195**(7):995-997.
4. TerHune T.N. and Upson D.W. 1989. Oxytetracycline pharmacokinetics, tissue depletion, and toxicity after administration of a long-acting preparation at double the label dosage. *JAVMA*, **194**(7):911-917.
5. Vaala W.E. *et al*. 1987. Acute Renal Failure Associated with Administration of Excessive Amounts of Tetracycline in a Cow. *JAVMA*, **191**(12):1601-1603.

B. Toxicity Test (IM Safety in Cattle)

1. Title: A Target Animal Safety Study in cattle Following Intramuscular Administration of OXYTET 30.

2. Study Number: 079/96

3. Investigator: Mr. N. Orr, B.V.M.S., M.R.C.V.S.
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. General Design:

a. Purpose: To evaluate the safety of the test article in the target species (cattle). Treatment groups were administered the test article three times at rates 1, 2, and 4 times the recommended dose. Safety of the product was appraised via clinical examination, clinical pathology, and post mortem examination. The study was conducted in accordance with Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.

b. Animals: Twenty-four (12 steers and 12 heifers) cattle 6 to 9 months of age weighing 470 to 630 pounds.

c. Control: Normal saline at a rate of 1 mL per 11 pound.

d. Dosage form: 300 mg/mL injectable.

e. Route of administration: Intramuscular injection

f. Dose: 13.6, 27.2, and 54.4 mg/lb body weight at 0, 72, and 144 hours. A maximum volume of 10 mL was used per injection site.

g. Test duration: Twenty-one (21) days from first administration.

h. Pertinent measurements and observations: Physical and clinical examinations, clinical pathology (biochemistry, hematology and urinalysis), gross post mortem examination [one animal of each sex from each group and an extra calf in the high dose (4x) group which displayed signs of toxicity during the study], and histopathology.

5. Results:

a. Physical and Clinical Examinations:

With the exception of clinical signs related to the localized effects of product administration, the only animals demonstrating abnormality were in the high (4x) dose group. Anorexia was observed in the animals in this group for up to 8 days following the final injection. Localized injection site reaction was noted in all treatment groups and incidence tended to reflect the total dose administered. Incidence of hind limb lameness was noted in all treatment groups being most significant in the high dose (4x) group. A higher incidence of lameness was observed in the low dose (1x) group than the medium group, however, all lameness was resolved before 480 hours after the initial injections.

b. Clinical Pathology:

There were differences between the control and treated groups with transient increases in urea and creatinine (4x group), urine WBC count (4x) and transient decreases in total protein (2x, 4x), albumin (1x, 2x, 4x), sodium (2x, 4x) and potassium (4x) along with urine protein (4x) and urine pH (4x). These were attributed to renal dysfunction. The findings corroborate the known toxicity profile of oxytetracycline that is described as causing cortical epithelial necrosis at high dose rates. The high dose (4x) group was most severely affected. The clinical pathology findings supported the clinical observations made during the study.

c. Gross Post Mortem Examination and Histopathology:

Basophilic cortical and medullary tubules were detected in the high dose (4x) group corroborating the interpretation of renal dysfunction based on clinical pathology results. No findings of renal dysfunction were apparent in the control, 1x, or 2x groups based on post mortem examination. All other findings at gross examination were considered incidental. No hepatic pathology was noted.

6. Conclusion: TETRADURE 300 is safe when administered intramuscularly to cattle at a dose of 13.6 mg/lb body weight.

C. Toxicity Test (IV Safety in Cattle)

A pharmacokinetic study using the 13.6 mg/lb dose was provided in support of intravenous safety of the 300 mg/mL concentration product. The IV route of administration is applicable only to cattle.

1. Title: A Pharmacokinetic Study of Plasma Levels of Oxytetracycline in Cattle Following the Intramuscular and Intravenous Administration of OXYTET 30.

2. Study Number: 041/95

3. Investigator: Mr. A. Carragher, B.Sc.
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. Study Design: The safety information was collected as part of a pharmacokinetic study conducted in a two-period cross-over design with a 42-day washout period. Animals were randomly assigned to treatment group. Safety of the product was appraised via clinical observation of the calves after treatment with the test article and at subsequent blood collections. The study was conducted in accordance with Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.

   a. Purpose: The study was undertaken to determine the levels of oxytetracycline in plasma following the intramuscular and intravenous injection of the test article. Secondarily, it demonstrates safety of the product after intravenous injection.

   b. Test Animals: Twelve beef-type cattle (male and female) weighing between 900 to 970 pounds were tested.

   c. Control: The animals served as their own controls in the crossover study design.

   d. Dosage form: 300 mg/mL injectable.

   e. Route of administration: Intramuscular and intravenous injection.

   f. Dose: Single treatment with 30 mg oxytetracycline per kilogram (13.6 mg/lb) of body weight.

   g. Test duration: 54 days with blood samples collected for up to 12 days after each administration of test article with a 42-day washout period.

   h. Pertinent parameters measured: In regards to intravenous safety of the product, a general assessment of each calf was made at each blood sampling with particular attention paid to animals treated intravenously in each period of the

study. Additionally, injection sites were examined twice weekly after administration of the test article for signs of swelling, hardness/softness, heat, redness and pain indicative of adverse reaction to treatment.

5. Results: No evidence of collapse, neurological effects, changes in gait or states of consciousness were observed after administration of the test article. Various levels of hardness and swelling were observed after administration of the test article via both routes of administration with all reactions resolving by 28 days. No systemic reactions or any other significant adverse reactions were reported during the study.

6. Conclusions: Administration of the test article via the intravenous route was well tolerated by all calves at the dosage administered which was above the 3.0 to 5.0 mg/lb dose recommended for intravenous injection.

D. IM Irritation Study

1. Title: An Injection Site Evaluation Study of Oxytetracycline in Cattle Following Intramuscular Administration of OXYTET 30.

2. Study Number: 089/96

3. Investigator: Mr. A. Carragher, B.Sc.
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. Study Design: The study was conducted parallel to a target animal safety study involving calves treated at 1, 2, and 4 times the recommended dose of 13.6 mg/lb. The results obtained from the 1x and 2x groups are included. Animals were randomly assigned to treatment group. Tissue irritation was appraised via clinical observation of the calves after treatment with the test article administered in the neck region. Additionally, a portion of the animals were sacrificed, and the injection site (in the neck area) was removed and examined for gross pathological changes. The study was conducted in accordance with the Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.

   a. Purpose: To assess injection site irritation of the test article administered at the highest recommended volume in the neck region of calves.

   b. Test Animals: Four (4) animals (2 male and 2 female) approximately 7.5 to 9 months of age and weighing 520 to 560 pounds.

   c. Control: None applicable

   d. Dosage form: 300 mg/mL injectable

   e. Route of administration: Intramuscular injection in the neck, rump and leg musculature

f. Dose: 13.6 and 27.2 mg/lb with a maximum injection volume of 10 mL per site administered on three occasions 72 hours apart. Injections in the neck area were made at the first and third administrations.

g. Test duration: 21 days

h. Pertinent parameters measured: The injection sites were monitored throughout the study for gross signs of reaction and also immediately prior to sacrifice for swelling, hardness/softness, heat, redness and pain. Additionally, the animals were sacrificed 21 days after the initial injection (15 days after the final injection), and the injection sites were excised and examined for gross pathological changes.

5. Results: No injection site reactions were recorded at any of the neck sites. Post-mortem examination of the injection sites revealed lesions consisting of necrotic and fibrotic tissue, hemorrhage that appeared to be resolving with fewer lesions noted after 21 days than after 15 days.

6. Conclusions: Intramuscular injection of the test article into the neck muscles of cattle at a volume of 10 mL per site results in some amount of localized tissue necrosis that resolves with time, but may still be present at 21 days post-injection.

E. Irritation Monitoring During Residue Study (Cattle)

1. Title: A Tissue Residue Study of Oxytetracycline in Cattle Following Intramuscular Administration of OXYTET 30.

2. Study Number: 011/96 (Injection site irritation was monitored as part of the residue depletion study supporting human food safety).

3. Investigator: Norbrook Laboratories, Research Division
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. Study Design: Calves were randomly assigned to five groups sacrificed at various intervals to determine the residue depletion profile based on tissue concentrations of oxytetracycline. Injection site irritation was also assessed during the study. The study was conducted in accordance with Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.

a. Purpose: To assess injection site irritation of the test article administered at the highest recommended volume in the rump region of calves.

b. Test Animals: Twenty animals (10 male and 10 female) approximately 9 months to 2 years of age and weighing 620 to 795 pounds.

c. Control: None applicable to injection site irritation assessment.

d. Dosage form: 300 mg/mL injectable

e. Route of administration: Intramuscular injection

f. Dose: 5 mg/lb with a maximum injection volume of 10 mL per site administered for four consecutive days. Sites of administration included both sides of the rump and neck regions. The site of the final injection was the right rump musculature.

g. Test duration: 28 days

h. Parameters measured: The injection sites were monitored for up to 18 days after initial administration of the test article and also immediately prior to sacrifice. This involved assessment of swelling, hardness/softness, heat, redness and pain at the injection sites. Following sacrifice, injection sites at the final site of administration were excised, examined for gross lesions, and photographed.

5. Results:

a. Clinical Observations: Transient reactions of swelling and/or hardness were noted at the rump injection sites of 14/20 animals. Two of these animals also exhibited swelling at the neck injection sites. The severity of swelling reactions ranged from mild (only notable on careful palpation) to severe (visible). No sloughing occurred, and all reactions resolved without need for veterinary intervention. The time to resolution of the clinical signs ranged from 2 to 16 days post-treatment. No systemic reactions, lameness, or other significant adverse reactions were recorded during the animal phase of the study.

b. Gross Pathology Observations: Post mortem examination of the injection sites revealed lesions consisting of necrotic and fibrotic tissue, hemorrhage, and very small cystic areas. The severity of the lesions decreased with time. By Day 28 only very small areas of fibrotic and necrotic tissue were observed.

6. Conclusions: The amount of tissue irritation at the injection sites of TETRADURE 300, administered by intramuscular injection to cattle, is acceptable from an animal safety perspective. Intramuscular injection of TETRADURE 300 at volumes up to 10 mL per site results in transient swelling and tissue damage at the injection site. The lesions resolve quickly, but small amounts of abnormal muscle tissue may remain at the end of the 28-day withdrawal period.

F. Irritation Monitoring During Residue Study (Swine)

1. Title: A Tissue Residue Study of Oxytetracycline in Pigs Following Intramuscular Administration of OXYTET 30.

2. Study Number: 010/96 (Injection site irritation was monitored as part of the residue depletion study supporting human food safety).

3. Investigator: Norbrook Laboratories, Research Division

Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. Study Design: Pigs were randomly assigned to one of five groups sacrificed at various intervals to determine the residue depletion profile based on tissue concentrations of oxytetracycline. Injection site irritation was also assessed during the study. The study was conducted in accordance with Good Laboratory Practices (GLP) Regulations 21 CFR Part 58.

   a. Purpose: To assess injection site irritation of the test article administered at the highest recommended volume in the rump region of pigs.

   b. Test Animals: Twenty animals (10 male and 10 female) approximately 14 to 18 weeks of age and weighing 114 to 157 pounds.

   c. Control: None applicable to injection site irritation assessment.

   d. Dosage form: 300 mg/mL injectable

   e. Route of administration: Intramuscular injection

   f. Dose: 5 mg/lb with a maximum injection volume of 5 mL per site administered for four consecutive days. Sites of administration included both sides of the rump and neck regions. The site of the final injection was the right rump musculature.

   g. Test duration: 21 days

   h. Parameters measured: The injection sites were monitored daily until the animals were sacrificed or until all reactions had resolved. Assessments included swelling, hardness/softness, heat, redness and pain at the injection sites. Following sacrifice, injection sites at the final site of administration were excised, examined for gross pathological changes, and photographed.

5. Results:

   a. Clinical Observations: Transient reactions characterized by swelling and/or hardness were noted at the rump injection sites of 12/20 animals. Six animals exhibited swelling at the neck injection site. The severity of swelling reactions was characterized as mild (only notable on careful palpation). No sloughing occurred, and all reactions resolved without need for veterinary intervention. The time to resolution of the clinical signs was 2 or 3 days post-treatment. No systemic reactions, lameness, or other clinically significant adverse reactions were recorded during the animal phase of the study.

   b. Gross Pathology Observations: Post mortem examination of the injection sites revealed lesions consisting of necrotic and fibrotic tissue and hemorrhage. The severity of the lesions decreased with time and by Day 21 only a small area of

fibrotic and necrotic tissue along with a small degree of hemorrhage was noted.

6. Conclusions: Intramuscular injection of this product results in transient swelling and tissue damage at the injection site. The lesions resolve quickly, but small amounts of abnormal muscle tissue may remain at the end of the 21 day withdrawal period. The product labeling will require a "trim out" statement.

G. Irritation Monitoring During PK Study (Cattle)

1. Title: A Comparative Study of Plasma Levels of Oxytetracycline in Cattle Following Intramuscular and Subcutaneous Administration of OXYTET 30 (Norbrook Laboratories Limited).

2. Study Number: 058/97

3. Investigator: Mr. A. Carragher
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. Study Design:

a. Purpose: Effectiveness determination by comparison of plasma pharmacokinetics of the sponsor's oxytetracycline 300 mg/mL injection product administered intramuscularly or subcutaneously at the recommended dosage in a cross-over design bioequivalence study.

b. Test Animals: Twenty-four mixed breed, beef-type calves consisting of 12 males and 12 females weighing 910 to 1020 pounds were evaluated in the study.

c. Control (reference): Norbrook oxytetracycline 300 mg/mL injectable.

d. Dosage form: 300 mg/mL injectable.

e. Route of administration: Intramuscular or subcutaneous injection.

f. Dose: Single treatment per period with 13.6 mg oxytetracycline per pound of body weight with a maximum of 10 mL administered in one site. Subcutaneous injections were made in the neck area and intramuscular injections were made in the muscles of the rump.

g. Test duration: 53 days (42 day washout period).

h. Pertinent parameters measured: Swelling, hardness/softness, heat, redness and pain at injection sites were evaluated during the study.

5. Results: Injection site reactions of swelling and hardness were noted at all sites with mild or moderate pain associated with the subcutaneous sites only. Complete resolution of the swelling and hardness associated with the intramuscular sites

entailed 14 to 35 days. Complete resolution of the swelling and hardness associated with the subcutaneous injection sites required a minimum of 38 days and sometimes exceeded 101 days. No systemic reactions or any other significant adverse reactions related to either subcutaneous or intramuscular treatment were recorded.

6. Conclusions: Both intramuscular and subcutaneous administration of TETRADURE 300 produced varying degrees of swelling and transient pain in treated animals. Subcutaneous injection has the potential to cause a transient local tissue reaction that may result in trim-loss of edible tissue at slaughter. Consequently, product labeling will need to include statements regarding the potential occurrence of injection site swelling/discomfort in treated animals and the possibility of trim-loss of edible tissues at slaughter due to lesions/discoloration associated with injection sites(s).

H. Irritation Monitoring During Residue Study (Cattle)

1. Title: A Tissue Residue Study of Oxytetracycline and Injection Site Irritancy Evaluation in Cattle, Following the Subcutaneous Administration of OXYTET 30.

2. Study Number: 010/98

3. Investigator: Norbrook Laboratories, Research Division
Ballyedmond Castle Farms Limited
101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

4. General Design:

a. Test Animals: Twenty-three beef-type steers and heifers approximately 7 months to 2 years of age weighing approximately 605 to 765 pounds were used. Three of the animals served as untreated controls to demonstrate lack of background oxytetracycline.

b. Route, Time and Duration of Drug Administration: A nominal dose of 5 mg oxytetracycline per pound of body weight once daily for 4 consecutive days was administered subcutaneously limiting the volume per injection site to 10 mL. This dose regimen represents the highest volume of product to be administered for all proposed indications. Additionally, one group of calves was administered a single subcutaneous injection at a nominal dose of 13.6 mg/lb limiting the volume per injection site to 10 mL.

c. Pertinent Parameters Measured: Gross observations of swelling, hardness/softness, heat, redness and pain at injection sites (in the area of the neck) were made during the study.

5. Results: Injection site reactions of swelling, hardness, and pain were noted at all injection sites, in absence of heat, softness, and redness. Most injection sites tended to decrease in size and magnitude with time. However, reactions at sites associated with the maximum dose volume tended to be more pronounced and persisted throughout the entire 28-day observation period. Complete resolution was only reported for some low volume administration sites.

   Post-mortem examination of the injection sites revealed lesions consisting of fibrotic tissue with some necrosis and hemorrhage reducing in severity but persistent through the 28-day study period. No cystic lesions were noted.

   Histopathology examinations revealed inflammatory changes at a majority of the injection sites with a reduction in severity evident by 28 days.

6. Conclusions: Subcutaneous administration of this 300 mg/mL oxytetracycline injectable product produced varying degrees of swelling and pain in treated animals. Fibrotic and necrotic tissues were evident through the 28-day period. This will require a "trim out" statement on the labeling.

4. HUMAN SAFETY:

A. Microbial Food Safety:

CVM evaluated microbial food safety information for oxytetracycline dihydrate (TETRADURE 300) at a dose rate of 13.6 mg/lb body weight for the control of bovine respiratory disease (BRD) in cattle at high risk of developing respiratory disease associated with *Pasteurella* spp. This risk assessment procedure involved conducting: 1) a release assessment to describe the probability that the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the food animal under proposed conditions of use; 2) an exposure assessment to describe the likelihood of human exposure to the resistant bacteria or resistance determinants through consumption of edible products from treated animals, specifically, beef; and 3) a consequence assessment to describe the potential human health consequences of exposure to the defined resistant bacteria or resistance determinants by considering the human medical importance of tetracyclines in the treatment of human infectious disease.

It was determined that the risk associated with the use of this product is MEDIUM. An overall risk of MEDIUM is compatible with the proposed conditions of use for TETRADURE 300, *i.e.*, a dose rate of 13.6 mg/lb body weight for the control of bovine respiratory disease (BRD) in cattle at high risk of developing respiratory disease associated with *Pasteurella* spp.

B. Toxicity:

Oxytetracycline

It was concluded that this drug has low toxicity at therapeutic doses. The animal studies summarized in the submission, the summary paper on the human toxicity of oxytetracycline and the long history of use of this antibiotic were stated to be enough to alleviate concerns on the toxicity of oxytetracycline.

According to current requirements, CVM evaluated the safety of oxytetracycline residues present in the edible tissues of food animals on the intestinal flora of the consumer. This assessment was performed following a pathway approach proposed by CVM in the draft Guidance #52 *Assessment of the Effects of Antimicrobial Drug Residues from Food Animal Origin on the Human Intestinal Flora* published for comments in December of 2001. The pathway approach considered the microbiological activity of the drug on relevant bacteria of the human intestinal flora, the possibility of the drug residues reaching the human colon, the amount of residues remaining active in the colon environment, and the effects that the microbiological active residues could have on the intestinal flora.

It is concluded that oxytetracycline residues present in edible tissues of cattle treated with TETRADURE 300 at a dose level of 13.6 mg/lb would have no adverse impact on the intestinal flora of the consumer. The ADI calculated based on the amount of

residues present in edible cattle tissues, the concentration of microbiologically active residues reaching the human colon, human data on effect of tetracycline on human intestinal flora, and *in vitro* data from test systems containing human fecal flora, is similar to the codified ADI of 1.5 mg/person/day for all tetracyclines when 60% adsorption is applied. The amount of residues ingested in the total meal basket is lower than the codified ADI for all tetracyclines. The ADI is partitioned as follows: 40% for tissues and 60% for milk.

Glycerol Formal

Studies submitted to address the toxicity of glycerol formal were found adequate.

C. Safe Concentration of Residues:

Oxytetracycline

Safe concentrations of residues of oxytetracycline, following partitioning of the ADI, are: 2 ppm in muscle, 6 ppm in liver, and 12 ppm in kidney and fat (61 FR 67453).

Glycerol Formal

Residue and metabolism data for glycerol formal, plasma pharmacokinetic data for oxytetracycline and glycerol formal, and calculations estimating exposure to glycerol formal resulting from the consumption of meat derived from treated animals were presented. These data reference studies were originally submitted under NADA 128-409.

An ADI of 0.01 mg/kg is calculated for glycerol formal. For a 60-kg person, this is equivalent to an acceptable daily intake of 0.6 mg/person/day. On the basis of muscle residues being below the LOD for the method at 5 days post-dosing, the sponsor calculates a maximum daily intake of 25 µg glycerol formal/person. For a 60-kg person, this represents an actual intake of 0.4 µg glycerol formal/kg body weight/day. A 24X safety margin between the ADI and actual daily intake (0.6 mg/person/day divided by 25 µg/person/day) on the basis of tissue residues 5 days post-dosing is calculated.

D. Residue Depletion Studies:

Oxytetracycline residue depletion studies were conducted (in cattle and swine) at the 5 mg/lb dose administered for 4 consecutive days on the premise that this is the highest labeled dose intended (total of 20 mg/lb). The studies were conducted administering product via the intramuscular and subcutaneous routes in cattle and the intramuscular route in swine.

Oxytetracycline

1. Title: A Tissue Residue Study of Oxytetracycline in Cattle Following the Intramuscular Administration of OXYTET 30

   Conducted by: Norbrook Laboratories, Research Division
   Ballyedmond Castle Farms Limited

101 Killowen Road
Rostrevor
Co. Down, BT34 3AG
Northern Ireland

Test Animals**:** Twenty-three (23) beef-type steers and heifers approximately 1 to 2 years of age weighing approximately 620 to 795 pounds were used. Three of the animals served as untreated controls to demonstrate lack of background for oxytetracycline.

Route, Time, and Duration of Drug Administration: A nominal dose rate of 5 mg oxytetracycline per pound of body weight once daily for four consecutive days was administered intramuscularly limiting the volume per injection site to a volume of 10 mL. This dose regimen represents the highest volume of product to be administered for all proposed indications.

Table 4.1. Oxytetracycline Residues in Tissues of Cattle Treated with OXYTET 30

Withdrawal Time (Days)	Oxytetracycline Residues (µg/g)			
	Muscle	Kidney	Liver	Fat
5	0.163 ± 0.015*	1.020 ± 0.064	0.482 ± 0.082	<0.1
8	0.109 ± 0.004	0.518 ± 0.185	0.266 ± 0.079	<0.1
11	<0.1	0.263 ± 0.071	0.146 ± 0.027	<0.1
21	<0.1	<0.1	<0.1	<0.1
28	<0.1	<0.1	<0.1	<0.1

*Mean ± SEM

A statistical analysis of the depletion data using an upper 99th percentile tolerance limit with a 95% confidence interval resulted in calculated withdrawal times of 21 and 25 days in liver and kidney samples, respectively. Thus, the residue depletion data are consistent with the assignment of a 28-day pre-slaughter withdrawal period.

2. Title: A Tissue Residue Study of Oxytetracycline in Swine Following Intramuscular Administration of OXYTET 30

   Conducted By: Norbrook Laboratories, Research Division
   Ballyedmond Castle Farms Limited
   101 Killowen Road
   Rostrevor
   Co. Down, BT34 3AG
   Northern Ireland

   Test Animals: Twenty-three (23) pigs, castrated males and females approximately

14 to 18 weeks of age weighing approximately 114 to 157 pounds were used. Three of the animals served as untreated controls to demonstrate lack of background for oxytetracycline.

Route, Time, and Duration of Drug Administration: A nominal dose rate of 5 mg oxytetracycline per pound of body weight once daily for four consecutive days was administered intramuscularly. This dose regimen represents the highest volume of product to be administered for all proposed indications.

Table 4.2. Oxytetracycline Residues in Tissues of Swine Treated with OXYTET 30

Withdrawal Time (Days)	Oxytetracycline Residues (µg/g)			
	Muscle	Kidney	Liver	Fat
2	0.421 ± 0.096*	1.903 ± 0.502	0.581 ± 0.106	0.128 ± 0.009
5	0.133 ± 0.016	0.682 ± 0.053	0.176 ± 0.055	<0.1
8	<0.1	0.188 ± 0.083	<0.1	<0.1
11	<0.1	0.138 ± 0.062	<0.1	<0.1
21	<0.1	<0.1	<0.1	<0.1

*Mean ± SEM

A statistical analysis of the depletion data, using an upper 99th percentile tolerance limit with a 95% confidence interval resulted in calculated withdrawal times of 18 days in kidney samples. These depletion data are consistent with the assignment of a 28-day preslaughter withdrawal period.

3. Title: A Tissue Residue Study of Oxytetracycline and Injection Site Irritancy Evaluation in Cattle Following Subcutaneous Administration of OXYTET 30

   Conducted by: Norbrook Laboratories, Research Division
   Ballyedmond Castle Farms Limited
   101 Killowen Road
   Rostrevor
   Co. Down, BT34 3AG
   Northern Ireland

   Test Animals: Twenty-three (23) beef-type steers and heifers approximately 7 months to 2 years of age weighing approximately 605 to 765 pounds, were used. Three of the animals served as untreated controls to demonstrate lack of background oxytetracycline.

   Route, Time, and Duration of Drug Administration: A nominal dose rate of 5 mg oxytetracycline per pound of body weight once daily for four consecutive days was administered subcutaneously limiting the volume per injection site to 10 mL. This dose regimen represents the highest volume of product to be administered for all proposed indications. Additionally, one group of calves was administered a single subcutaneous injection at a nominal dose rate of 13.6 mg/lb limiting the volume per

injection site to 10 mL.

Design: The calves were euthanized at designated intervals (7, 10, 14, and 28 days) and muscle, kidney, liver, and fat samples were collected for oxytetracycline residue analysis using a validated microbiological agar diffusion method. Injection sites were evaluated during the study and at post mortem examination as described above in the Target Animal Safety section of this FOI Summary.

Table 4.3. Oxytetracycline Residues in Tissues of Cattle Treated with OXYTET 30 (Dose rate 5 mg/lb/day for 4 days)

Withdrawal Time (Days)	Oxytetracycline Residues (µg/g) Tissues				Oxytetracycline Residues (µg/g) Injection Sites			
	Muscle	Liver	Kidney	Fat	Site 1	Site 2	Site 3	Site 4
7	0.190 ± 0.012*	0.574 ± 0.137	0.873 ± 0.094	<0.1	15.938 ± 26.450	0.482 ± 0.180	461.25 ± 139.62	13.102 ± 16.402
10	0.142 ± 0.033	0.383 ± 0.108	0.568 ± 0.188	<0.1	1.267 ± 1.143	0.494 ± 0.221	436.000 ± 142.75	8.002 ± 7.286
14	0.123 ± 0.018	0.332 ± 0.184	0.509 ± 0.207	<0.1	31.475 ± 30.056	0.173 ± 0.043	265.725 ± 256.756	3.302 ± 4.342
28	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.145 ± 0.009	<0.1

*Mean ± SEM

Table 4.4. Oxytetracycline (Dose Rate 13.6 mg/lb)

Withdrawal Time (Days)	Oxytetracycline Residues (µg/g) Tissues				Oxytetracycline Residues (µg/g) Injection Sites							
	Muscle	Liver	Kidney	Fat	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8
14	<0.1	0.168 ± 0.01*	0.418 ± 0.03	<0.1	177 ± 33.54	1.37 ± 0.16	268.7 ± 45.15	3.56 ± 0.97	170.6 ± 73.38	1.99 ± 0.74	246.3 ± 85.06	1.95 ± 0.33

*Mean ± SEM

Withdrawal Period Calculation

The residue depletion data from the multidose residue study were analyzed using a statistical tolerance limit algorithm for the 99th percentile of the population with a 95% confidence limit. The residue depletion data are consistent with the pre-slaughter assignment of a 28-day withdrawal period.

Although not analyzed statistically, the 14-day residue data from the single dose residue study are comparable to the 14-day residue data from the multidose study. Thus, it is consistent with the public health to assign a 28-day withdrawal for the single dose treatment regime as well.

Glycerol Formal

Residue and metabolism data for glycerol formal originally provided under NADA 128-409, plasma pharmacokinetic data for oxytetracycline and glycerol formal, and calculations estimating exposure to glycerol formal resulting from the consumption of meat derived from treated animals were presented.

Depletion characteristics of oxytetracycline and glycerol formal demonstrated that plasma residues of glycerol formal will deplete more rapidly than residues of oxytetracycline (a half-life of approximately 4 hours *vs*. a half-life of approximately 27 - 35 hours). It is concluded that residues of glycerol formal will not present human food safety concern at the withdrawal period anticipated for the active ingredient, oxytetracycline (i.e. 28 days).

E. Tolerance:

Tolerances of 2 ppm in muscle, 6 ppm in liver, 12 ppm in kidney, and 12 ppm in fat are codified for the uncooked edible tissues of beef cattle, non-lactating dairy cattle, and swine under 21 CFR 556.500.

F. Withdrawal Time:

A 28-day pre-slaughter withdrawal period is assigned for the use of oxytetracycline 300 mg/mL, via the intravenous, intramuscular, or subcutaneous routes of administration in beef cattle and non-lactating dairy cattle and via the intramuscular route of administration in swine.

G. Regulatory Method for Residues:

The regulatory analytical method for detection of residues of the drug is a cylinder plate diffusion microbiological assay using *Bacillus cereus* var. *mycoides* (ATCC 11778). The method is published by the Food and Drug Administration, "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocols", Revised October 1968, reprinted December 1974. The method is available from the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

5. AGENCY CONCLUSIONS:

The data submitted in support of this original NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that OXYTETRACYCLINE INJECTION 300 mg/mL and TETRADURE 300 INJECTION(Oxytetracycline) are safe and effective for use in cattle and swine for the approved indications, when administered as indicated in the product labeling at the approved dose.

Tolerances of 2 ppm in muscle, 6 ppm in liver, 12 ppm in kidney, and 12 ppm in fat are codified for the uncooked edible tissues of beef cattle, non-lactating dairy cattle, and swine under 21 CFR 556.500.

OXYTETRACYCLINE INJECTION 300 mg/mL is labeled for over-the-counter (OTC) use. Routine injection of cattle and swine is a widely accepted and recommended practice performed by the lay person for this product. Additionally, adequate directions for use have been written for the layman and the conditions for use prescribed on the label are likely to be followed in practice.

TETRADURE 300 INJECTION is restricted to use by or on the order of a licensed

veterinarian because professional veterinary expertise is required to determine when cattle are at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*, and to monitor the animals for signs of adverse reactions when the drug is administered at higher doses than those recommended for other indications.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. This marketing exclusivity applies only to the increase in formulation concentration to 300 mg/mL; and to the veterinary prescription use of the product in cattle for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*, and for a dosage range of 9 to 13.6 mg/lb for the treatment of bacterial pneumonia caused by *Pasteurella* spp. (shipping fever) in calves and yearlings and infectious bovine keratoconjunctivitis (pinkeye) caused by *Moraxella bovis*, for which new data were required.

Oxytetracycline is under U.S. patent number 6,110,905 and 6,310,053, which expire August 29, 2020 and October 30, 2021, respectively.

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

100, 250 and 500 mL vial labels for the Rx and OTC product
100, 250 and 500 mL carton labels for the Rx and OTC product
Package insert for the Rx and OTC product