FREEDOM OF INFORMATION SUMMARY
FOR A SUPPLEMENT TO AN ABBREVIATED NEW ANIMAL DRUG APPLICATION

1. GENERAL INFORMATION:

ANADA Number:	200-008
Sponsor:	Boehringer Ingelheim Animal Health, Inc. 2621 North Belt Highway St. Joseph, Missouri 64506
Established Name:	oxytetracycline injection
Trade/Proprietary Names:	OXY-TET™ 200 BIO-MYCIN® 200
Dosage Form:	sterile injectable solution
How Supplied:	100 mL, 250 mL, and 500 mL bottles
Marketing Status:	OTC
Amount of Active Ingredient:	200 mg/mL
Effect of Supplement:	To add the subcutaneous route of administration to the label for cattle.

2. INDICATIONS FOR USE:

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:

BEEF CATTLE AND NONLACTATING DAIRY 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. ROUTE(S) OF ADMINISTRATION AND RECOMMENDED DOSAGE(S):

Route(s) of administration: This supplemental application provides for the addition of the subcutaneous route of administration to cattle in addition to the existing approved recommended intramuscular and intravenous routes. The approved recommended route of administration in swine is intramuscular.

Recommended Dosage:

BEEF CATTLE AND NONLACTATING DAIRY CATTLE

OXY-TET 200 is to be administered by intramuscular, subcutaneous, 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 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*.

OXY-TET 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.

No more than 10 mL should be injected intramuscularly or subcutaneously at any one site in adult beef cattle and nonlactating dairy cattle; rotate injection sites for each succeeding treatment. The volume administered per injection site should be adjusted according to age and body size so that 1 to 2 mL per injection site is injected in small calves.

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.

No more than 5 mL of OXY-TET 200 should be injected intramuscularly per site in adult swine; rotate injection sites for each succeeding treatment.

4. EFFECTIVENESS:

A blood level relative bioavailability study and four clinical end-point bioequivalence studies were conducted to compare the intramuscular and subcutaneous routes of administration of the test product, OXY-TET 200 in cattle.

A. Relative Bioavailability Study

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

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

3) General Design of Investigation:

The study population was comprised of commercial crossbred steers and heifers about 6-12 months of age. The animals were acclimated for 28 days prior to initiation of the study. Selection of the sixteen (16) animals to be used in the study was based on health status, serum chemistry, and hematological values, and body weight uniformity. The animals were ranked within sex by weight to form replicates of two which were then randomly assigned to one of two treatment groups.

The study was conducted as a two-period crossover design using 16 calves divided into two groups. Each calf received single IM or SQ doses of test product at rates of 20 mg oxytetracycline per kg (9 mg/lb) of body weight in each of two crossover test periods that were separated by a 42-day washout interval.

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 or subcutaneous injection in each study period.

4) Results and Conclusions:

The results are given in the following table with L = lower bound on the 90% confidence interval and U = upper bound on the 90% confidence interval for the difference between the IM and SQ formulation product means.

MAJOR PHARMACOKINETIC MEASURES	IM Mean	SQ Mean	Lower	Upper
Maximum observed serum concentration (CMAX) (µg/mL)	5.57	9.27	49.98%	83.11%
Time to CMAX (TMAX) (hrs)	3.13	2.15	-60.10%	-1.89%
Area under the concentration-time curve (AUC)	178.86	197.76	6.38%	14.76%

Area under the curve (AUC), maximum concentration (C_{MAX}), and time to maximum concentration (T_{MAX}) from hour 0 (the start of dosing) to sample hour 108 were analyzed, using confidence intervals, as described in the CVM Bioequivalence Guideline. AUC was the only parameter for which the confidence interval [based on the difference in the mean of the SQ route-mean of IM route], was found to lie within 20% of the IM route mean. The SQ route achieved a higher mean C_{MAX} than the intramuscular route, and the mean time to C_{MAX} was approximately one hour sooner for the SQ route, as compared with the IM route of administration.

The results demonstrated that the extent of absorption of the drug was comparable by the SQ and IM routes of administration, and the SQ route achieved a higher drug concentration than the IM route of administration.

B. Clinical End-point Bioequivalence Study

1) GENERAL STUDY DESIGN

The purpose of the study was to evaluate the relative antibacterial efficacy of the intramuscular and subcutaneous routes of administration of OXY-TET 200 against pneumonia in naturally-infected feedlot cattle, a target species for which the produc intended. For the four combined study sites, four hundred sixty-six (466) commercial crossbred feedlot steers were randomly assigned to one of two groups:

- 232 animals received intramuscular injections
- 234 animals received subcutaneous injections

The following were used as qualifying criteria when accepting an animal into the study:

a. A rectal temperature of ≥104.0˚ F (Study #1) or 104.5˚ F (Studies #2, 3, and 4)
b. An illness index score of ≥2 (0 = normal, 1 = mild depression, 2 = mild to moderate depression, 3 = moderate to severe depression, 4 = severe depression or moribund, 5 = dead)
c. An elevated respiratory rate

At the onset of established symptoms, each steer received either an intramuscular or subcutaneous injection of OXY-TET 200 (oxytetracycline 200 mg/mL injectable solution), at a rate of 20 mg/kg (9 mg/lb), with a subsequent retreatment at 72 hours or before 7 days if clinical signs reoccurred.

As soon as the first animal fulfilled the entrance criteria for treatment, the trial period was initiated. The trial lasted until the required number of animals were treated and each was monitored for 42 days following the initial treatment. For each animal, seventy-two hours or more after the first treatment, if a test animal had a rectal temperature of 104.0˚ F (Study #1) or 104.5˚ F (Studies #2, 3, and 4) or greater, elevated respiratory rate, or an illness score of 3 or greater, the animal was treated again with the same method of administration.

The primary test parameter was the determination of treatment success or failure. The following are the 6 categories of response:

- A - responded by 72 hours - no further treatment needed
- B - responded by 72 hours - retreatment needed before Day 7
- C - no response by 72 hours - retreated - no further treatment needed
- D - no response by 72 hours - retreated - retreatment needed again before Day 7
- E - No response by 72 hours - retreated - sick at 48 hours
- F - died prior to Day 7

Body weight gain, injection site reaction, and nasopharyngeal swabs for microbiologic assessment were also evaluated.

2) STUDY SITES

Study Site #1

Investigator: Dr. David T. Bechtol
Agri-Research Center, Inc.
Canyon, Texas 79105

Statistician: George A. Milliken, Ph.D.
Torrey J. Lumpe
Flint Hills Statistical Consulting Company, Inc.
Manhattan, Kansas

Study Site #2

Investigator: Dr. Ed Johnson
Johnson Research
Parma, Idaho 83660

Statistician: George A. Milliken, Ph.D.
Torrey J. Lumpe
Flint Hills Statistical Consulting Company, Inc.
Manhattan, Kansas

Study Site #3

Investigator: Dr. Jeff Davidson
Health Management Services, Inc.
Tulare, California 93274

Statistician: George A. Milliken, Ph.D.
Torrey J. Lumpe
Flint Hills Statistical Consulting Company, Inc.
Manhattan, Kansas

Study Site #4

Investigator: Dr. Jerry Biwer
Benchmark Beef Research
Imperial, California 92251

Statistician: George A. Milliken, Ph.D.
Torrey J. Lumpe
Flint Hills Statistical Consulting Company, Inc.
Manhattan, Kansas

3) RESULTS:

STUDY SITE #1

TREATMENT RESPONSE: The SQ success rate was 46.84% as compared to a success rate of 43.04% for the calves treated IM as shown in the table below.

Group	Treatment	N	No. of Treatment Successes	No. of Treatment Failures
1	Oxy-Tet 200 20 mg/kg SQ	79	37 (46.84%)	42 (53.16%)
2	Oxy-Tet 200 20 mg/kg IM	79	34 (43.03%)	45 (56.96%)
Total		158*	71	87

*Two animals were not retreated according to the protocol; therefore, their data were not included in the analysis.

BODY WEIGHTS: Weight gains from the 0-28 days and 0-42 days are summarized in the following table.

		Weight, kg			Weight gain, kg	
Group	Treatment	Day 0	Day 28	Day 42	Day 28	Day 42
1	SQ	175.2	196.3	218.7	22.6	44.5
2	IM	178.3	198.3	221.2	20.5	43.5

INJECTION SITES: Injection sites were observed daily for the first 7 days of the study and on Days 28 and 42 at which time the study was terminated. The following table summarizes the results providing the number of animals in each category and the percentage of animals for that group.

	No reaction	Reaction present during first 7 days	Reaction severity SLIGHT	Reaction severity MODERATE	Reaction severity SEVERE	Reaction present at Day 28
SQ	7 (9%)	73 (91%)	15 (19%)	43 (54%)	15 (19%)	9 (11%)
IM	25 (31%)	55 (69%)	16 (20%)	26 (32%)	13 (16%)	4 (5%)

PRE- AND POST-MICROBIOLOGY: The percent of isolates that were resistant or intermediate in sensitivity were 51.8% of the isolates made. There were 110 cultures that isolated respiratory pathogens. Of these, 56 were resistant or of intermediate sensitivity to oxytetracycline (only 5 were intermediate, the remainder were resistant). Of the animals that died and cultures were available, there were 17 cultures of 25 that grew *Pasteurella hemolytica* that was resistant to oxytetracycline.

STUDY SITE #2

TREATMENT RESPONSE: The SQ success rate was 100% as compared to a success rate of 94% for the calves treated IM as shown in the table below.

Group	Treatment	N	No. of Treatment Successes	No. of Treatment Failures
1	Oxy-Tet 200 20 mg/kg SQ	51	51 (100%)	0 (0%)
2	Oxy-Tet 200 20 mg/kg IM	50	47 (94%)	3 (6%)
Total		101	98	3

BODY WEIGHTS: Weight gains from the 0-29 days and 0-42 days are summarized in the following table.

		Avg Weight Gain, lb	
Group	Treatment	Day 0-29	Day 0-43
1	SQ	86.92	128.92
2	IM	86.62	132.4

INJECTION SITES: Injection sites were observed daily for the first 7 days of the study. The following table summarizes the results providing the number of animals in each category and the percentage of animals for that group.

	No reaction	Reaction present during first 7 days	Reaction severity SLIGHT	Reaction severity MODERATE	Reaction severity SEVERE
SQ	0	50 (100%)	4 (8%)	8 (16%)	38 (74%)
IM	2 (4%)	48 (96%)	7 (14%)	14 (28%)	28 (56%)

PRE- AND POST-MICROBIOLOGY: The percent of isolates that were resistant in sensitivity were 15% of the isolates made. There were 67 cultures where respiratory pathogens were isolated. Of these, 10 were resistant to oxytetracycline.

STUDY SITE #3

TREATMENT RESPONSE: Calves with naturally occurring BRD which were treated with 20 mg/kg Oxy-Tet 200 SQ had similar percentages of recoveries (successes - A, B, C) and non-responders (failures - C, D, E) with a success rate of 94.5% as compared to a success rate of 92.4% for the calves treated IM as shown in the table below.

Group	Treatment	N	No. of Treatment Successes	No. of Treatment Failures
1	Oxy-Tet 200 20 mg/kg SQ	54	51 (94.5%)	3 (5.5%)
2	Oxy-Tet 200 20 mg/kg IM	53	49 (92.4%)	4 (7.6%)
Total		107	100	7

BODY WEIGHTS: Weight gains from the 0-29 days and 0-42 days are summarized in the following table.

		Avg Weight Gain, lb	
Group	Treatment	Day 0-29	Day 0-43
1	SQ	55.61	90.28
2	IM	57.81	90.26

INJECTION SITES: Injection sites were observed daily for the first 7 days of the study. The following table summarizes the results providing the number of animals in each category and the percentage of animals for that group.

	No reaction	Reaction present during first 7 days	Reaction severity SLIGHT	Reaction severity MODERATE	Reaction severity SEVERE
SQ	49 (90.7%)	5 (10%)	5 (10%)	0	0
IM	51 (96.2%)	2 (4%)	2 (4%)	0	0

PRE- AND POST-MICROBIOLOGY: The percent of isolates that were resistant to OTC were 47% of all the isolates grown. There were 163 respiratory pathogens isolated. Of these, 77 were resistant to oxytetracycline.

STUDY SITE #4

TREATMENT RESPONSE: The SQ success rate was 69.4% as compared to a success rate of 70.5% for the calves treated IM as shown in the table below.

Group	Treatment	N	No. of Treatment Successes	No. of Treatment Failures
1	Oxy-Tet 200 20 mg/kg SQ	49	34 (69.4%)	15 (30.6%)
2	Oxy-Tet 200 20 mg/kg IM	51	36 (70.5%)	15 (29.5%)
Total		100	70	30

BODY WEIGHTS: Weight gains from the 0-29 days and 0-43 days are summarized in the following table.

		Avg Daily Weight Gain, lb	
Group	Treatment	Day 0-29	Day 0-43
1	SQ	1.36	1.76
2	IM	1.19	1.44

INJECTION SITES: Injection sites were observed daily for the first 7 days of the study. The following table summarizes the results providing the number of animals in each category and the percentage of animals for that group.

	No reaction	Reaction present during first 7 days	Reaction severity SLIGHT	Reaction severity MODERATE	Reaction severity SEVERE
SQ	10 (20%)	38 (79%)	28 (57%)	6 (12%)	4 (8%)
IM	27 (53%)	20 (39%)	17 (33%)	2 (4%)	1 (2%)

PRE- AND POST-MICROBIOLOGY: The percent of isolates that were resistant in sensitivity were 51.2% of the isolates made. There were 80 isolates of respiratory pathogens. Of these, 41 were resistant to oxytetracycline.

4) RESULTS AND CONCLUSIONS

Data from all four of the clinical end-point bioequivalence studies were pooled for the purposes of analysis. The following table provides the results combined.

Route of administration	# of Cases	# of Treatment Successes	# of Treatment Failures
IM	232	166	67
SQ	234	173	60
TOTAL	466	339	127

Using a 90% confidence interval method there was no significant difference between the SQ and IM routes of administration of OXY-TET 200 in feedlot cattle. The 90% confidence interval on the difference between success probabilities for the IM and SQ routes was calculated as (-0.1002, 0.0354). This confidence interval contains 0.0 and implies that there is no significant difference between these routes of administration.

To corroborate the 90% confidence interval method, the 90% confidence interval on the odds ratio of the two different routes of administration was calculated. The odds of success for the SQ route of OXY-TET 200 in feedlot cattle was slightly better than the IM route, 1.1776 to 1.0. The 90% confidence interval on the odds ratio of the two routes of administration was calculated as (0.8359, 1.6589). This confidence interval contains 1.0 and implies that there is no significant difference between these routes of administration. In this study, the lower bound 0.8359 is contained within this interval, while the upper bound 1.6589 is not contained which implies that the SQ route of administration is slightly more effective than the IM route.

The studies demonstrated comparable clinical efficacy for the subcutaneous and intramuscular routes of administration for OXY-TET 200.

6. HUMAN FOOD SAFETY:

Tolerance

The tolerance for oxytetracycline is 0.1 ppm in uncooked edible tissues of cattle (21 CFR 556.500).

Withdrawal Time

Study Establishing the Withdrawal Period for the SQ Route in Cattle

The purpose of the study was to determine the tissue residue profile for an oxytetracycline 200 mg/mL solution administered subcutaneously for the maximum allowable duration of 1 time at 20 mg/kg (9 mg/lb) using production type beef cattle, a target species and class for which the product is intended. The investigator was Bill C. Clymer at CRC-CAVL, Amarillo, TX. The statistician was Thomas J. Keefe at EnviroStat Associates, Fort Collins, CO.

Twenty production type beef calves (10 steers and 10 heifers) approximately 6 to 10 months of age, weighing between 214 and 267 kilograms were used. All animals were administered the test product by subcutaneous injection one time at 20 mg/kg (9 mg/lb) on Day 0. Animals were assigned to 4 serial groups by weight and sex, with 2 steers and 3 heifers, or 3 steers and 2 heifers in each serial for sacrifice at 2, 5, 8, or 11 days post-injection. Kidney fat, kidney, liver, longissimus dorsi muscle and trapezius muscle at the injection site were assayed for oxytetracycline residues.

Mean* Oxytetracycline Residue Concentrations (in ppm) in Cattle Injected Once Subcutaneously with 20 mg/kg Body Weight of Oxytetracycline as OXY-TET 200

Days Post-Injection	Fat	Muscle	Liver	Kidney	Injection Site
2	0.177	1.273	3.751	7.994	512.19
5	0.000	0.192	0.424	1.048	51.96
8	0.000	0.073	0.075	0.270	4.00
11	0.000	0.030	0.042	0.308	3.89

*Geometric mean residue; detected but nonquantifiable residues in muscle tissue were set to the detection limit of 0.075 ppm. for purposes of statistical analysis

The depletion of oxytetracycline from injection site tissue was evaluated by the fitted linear model obtained via resistant regression analysis. Although injection site residues are initially very high, they deplete rapidly leaving kidney residues which deplete more slowly to the tolerance to be used to establish the withdrawal time for this product.

The fitted linear regression equation for residues in kidney was used to estimate, with 95% confidence, the time at which 99% of the calves would have residues in kidney at or below the tolerance of 0.1 ppm oxytetracycline. Residues in kidney did not vary significantly between male and female calves ($p=0.253$) but did vary significantly among the four post-withdrawal sampling times ($p<0.001$). Although the linear decrease in log-residues of oxytetracycline in kidney was highly significant, the test for departure from linearity was also highly significant ($p < 0.001$ for each). Consequently, the fitted linear equation for log-residue versus time was based on data from 5 through 11 days post-withdrawal (i.e., excluding the data at day 2 post-withdrawal). Based on the fitted linear model and using a statistical tolerance limit for the 99th percentile of the population with 95% confidence, a withdrawal time of 36 days was assigned for cattle administered one subcutaneous injection of 20 mg/kg body weight of oxytetracycline as OXY-TET 200.

Regulatory Method:

The validated microbiological method with minor modifications was used to measure antimicrobial activity of oxytetracycline in cattle tissues (Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports, and Protocols, FDA, 1968). The method is on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.

Tissue Irritation Evaluation:

The data for this evaluation were derived from observations made during the Tissue Residue Depletion Study, as described above.

Investigator: Bill C. Clymer
CRC-CAVL
Amarillo, Texas

Pathologist: Jim Sheldon
CAVL, Inc.
Amarillo, Texas

A. General Design of the Study:

This portion of the study was to evaluate injection site tissue irritation following a subcutaneous 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. The drug was administered once on day 0.

Twenty (20) commercial beef type calves (10 heifers and 10 steers), weighing between 214 and 267 kilograms and approximately 6 to 10 months of age.

The clinical parameters evaluated were heat at the injection site, swelling, hardness (increased tissue density), pain, and measurement of the site with a caliper . Direct injection site irritation observations were made from tissue samples of the right trapezius muscle from the five euthanized animals on each of the following study days: 2, 5, 8, and 11. The selected area was grossly described and photographed. Histopathological examination was done on a 4 cm long x 2 cm deep x .5 cm wide section.

B. Results:

Diameter or area size at the injection site proved to be the most significant of all the palpation observations. Pain at the injection site was greatest between 3 and 8 days

post injection, but appeared to decrease by Day 11. Hardness increased for the first 4 observation periods (up to Day 4) then fluctuated for the remainder of the study. There was no distinguishable pattern for temperature. Swelling continued to increase for the first 3 observation periods and then began a slight decrease for the remainder of the study.

SUMMARY OF ANTEMORTEM OBSERVATIONS ON 20 CALVES INJECTED SUBCUTANEOUSLY WITH A 20 mg/kg DOSE OF OXY-TET 200

Day of Study		Temp[a]	Swelling[b]	Hardness[c]	Pain[d]	Size[e]
4 hrs post-dose	mean	0.13	1.20	1.30	0.00	53
	SD	0.33	0.61	0.60	0.00	22
Day 2	mean	0.20	1.77	2.00	1.33	10505
	SD	0.41	0.43	0.00	0.55	3658
Day 3	mean	0.13	1.87	2.03	1.80	9657
	SD	0.35	0.51	0.41	0.76	2411
Day 4	mean	0.00	1.80	2.80	1.90	9729
	SD*	0.00	0.42	0.42	0.32	2070
Day 5	mean	0.40	1.70	2.60	1.70	7678
	SD	0.50	0.47	0.60	0.80	2213
Day 8	mean	0.10	1.65	2.75	1.95	6431
	SD	0.31	0.49	0.55	0.89	2343
Day 11	mean	0.00	1.40	2.60	1.00	4153
	SD*	0.00	0.52	0.52	1.15	1459

Scoring Codes:

a 0 = Normal 1 = Warm 2 = Hot

b 0 = Normal 1 = Slight 2 = Moderate 3 = Severe

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

d 0 = None 1 = Slight 2 = Moderate 3 = Severe

e Diameter measured in mm at 4 hours and by area mm^2 at other times

Gross Lesions:

At all times examined post-injection, up to and including eleven days post injection, there was tissue discoloration at the injection sites.

Microscopic Summary:

This product was administered at a consistent dose per kg of body weight and a consistent amount per injection site. With SQ administration, muscle necrosis is evident in all sections. Fibroplasia, fat replacement, initial scarring, and even a suggestion of abscess formation is seen. A scoring of 4 confirms necrosis, muscle replacement, scarring, and a tract-like pattern with fibroplasia extending beyond the injection site. All 20 samples scored 4 which is obvious evidence of irreversible tissue destruction. This includes necrosis, abscess formation, scarring, and a tract-like fibroplasia which would extend into and between adjacent fibers.

C. Conclusions:

The clinical observations on the external injection sites showed that most clinical parameters were nearly normal by Day 11, however, a trim-out statement will be necessary on the label due to the tissue discoloration in all animals up to Day 11 post-treatment.

7. AGENCY CONCLUSIONS:

The data submitted in support of this supplemental ANADA comply with the requirements of section 512 of the Act and demonstrate that OXY-TET 200 and BIO-MYCIN 200 Injectable (oxytetracycline) 200 mg/mL for subcutaneous injection in beef cattle and non-lactating dairy cattle, is safe and effective for the indications stated on the product labeling.

For cattle the tolerance of residues for oxytetracycline are as specified in 21 CFR 556.500. A tolerance of 0.1 ppm is established in the uncooked edible tissues. A tissue residue study was conducted to determine the tissue residue profile for an oxytetracycline 200 mg/mL solution administered subcutaneously for the maximum allowable duration of 1 time at 20 mg/kg (9 mg/lb) using production type beef cattle, a target species and class for which the product is intended. Based on the fitted linear model and using a statistical tolerance limit for the 99th percentile of the population with 95% confidence, a withdrawal time of 36 days was assigned for cattle administered one subcutaneous injection of 20 mg/kg body weight of oxytetracycline as OXY-TET 200. The withdrawal time is 36 days for the subcutaneous injection route in cattle (21 CFR 522.1660). A trim-out statement is necessary due to the tissue discoloration present at injection sites examined up to 11 days posttreatment.

The original approval of OXY-TET 200 and BIO-MYCIN 200 Injectable (oxytetracycline) 200 mg/mL 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.

ATTACHMENTS:

The following labeling is attached.

The facsimile bottle label, insert, and carton for OXY-TET™ 200/BIO-MYCIN® 200, oxytetracycline injection 200 mg/mL (100 mL bottles only)

Facsimile hang tag to be used temporarily on product inventory to show SQ route

Approved original bottle label and carton for OXY-TET™ 200/BIO-MYCIN® 200, oxytetracycline injection 200 mg/mL (500 mL bottles only)