I. GENERAL INFORMATION

A. File Number

NADA 097-452

B. Sponsor

Boehringer Ingelheim Animal Health, Inc.
2226 North Belt Highway
St. Joseph, Missouri 64506

C. Proprietary Name

OXYJECT® 100

D. Established Name

oxytetracycline hydrochloride

E. Dosage Form

OXYJECT® 100 is a sterile solution of oxytetracycline hydrochloride containing 100 mg of oxytetracycline base per milliliter and is available in 500-mL vials.

F. Dispensing Status

OTC

G. Dosage Regimen

The approved dosage of OXYJECT® 100 in all indicated classes of swine and cattle is 3 to 5 mg per pound for a period not to exceed 4 consecutive days.

H. Route of Administration

OXYJECT® 100 is approved for administration by the intravenous, intramuscular, and subcutaneous routes in cattle, and the intravenous and intramuscular routes in swine.

I. Indication

OXYJECT® 100 is indicated for the following:

BEEF CATTLE, BEEF CALVES, NON-LACTATING DAIRY COWS, AND DAIRY CALVES
Treatment of pneumonia and shipping fever complex caused by *Pasteurella* sp., *Haemophilus* sp., and *Klebssiella* sp.
SWINE
Treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli*; pneumonia caused by *Pasteurella multocida*; leptospirosis caused by *Leptospira pomona*
SOWS
Aid in the control of porcine colibacillosis (baby pig scours) caused by *Eschericia coli*

J. Effect of Supplement

This supplemental NADA provides for the subcutaneous route of administration and the application of new tolerances (61 FR 67435) to the approved product, Oxyject® 100.

II. EFFECTIVENESS

A. In Vivo Bioequivalence Study

1. Investigators:

   Susan Rogers and Steve Stroh
   Fermenta Animal Health Research Center
   1512 Webster Court
   Fort Collins, Colorado 80524

2. Study Design:

   The relative bioavailability of OXYJECT® 100 administered by intramuscular (I.M.) and subcutaneous (S.C.) injections at 5 mg per pound was compared in a two-way crossover design study with 8 crossbred, yearling calves weighing 450 to 520 pounds. Serum concentration versus time profiles associated with the two routes of administration were determined with the use of a microbiologic method.

3. Results:

   Areas under the serum concentration versus time curves (AUC), the maximum concentration (Cmax) and the time to reach maximum concentrations (Tmax) were calculated for each calf. Results are summarized in Table 4.1.

   Table 4.1. Means of the area under the serum concentration profile curve (AUC), concentration maximum (Cmax) and time to maximum concentration (Tmax) of Oxyject® 100, administered at 5 mg per pound, by the intramuscular (i.m.) and subcutaneous (s.c.) routes.

Injection Route	AUC (mg * hr/mL)	Cmax (mg/mL)	Tmax (hours)
I.M.	108.71	4.01	6.1
S.C.	107.01	3.97	8.75

   Individual AUC and Cmax values were Log normalized and the 90% confidence intervals for the difference in means for AUC and Cmax were calculated. The estimate and the standard error of the estimate derived from the analysis of variance were used to calculate 90% confidence intervals for the difference in means for AUC and Cmax (see Table 4.2).

Table 4.2. The confidence interval of subcutaneous versus intramuscular routes of administration for Oxyject® 100. The upper and lower confidence intervals for the log of the serum concentration profile curve (AUC) and concentration maximum (Cmax) is presented.

Confidence interval*	LnAUC	LnC_{max}
Upper confidence interval	104.3%	112.4%
Lower confidence interval	92.5%	89.1%

*Acceptable Range (80-125%)

The confidence intervals for both AUC and Cmax fall in the range of 80 to 125% for both parameters. No adverse reactions to OXYJECT® 100 occurred during the study.

4. Conclusion:

   Intramuscular and subcutaneous routes of administration of OXYJECT® 100 are bioequivalent.

III. TARGET ANIMAL SAFETY

A. Tissue Injection Site Reaction Study

1. Investigators:

   Susan Rogers and Steve Stroh
   Fermenta Animal Health Research Center
   1512 Webster Court
   Fort Collins, Colorado 80524

2. Study Design:

   The amount of tissue irritation and damage in cattle tissue resulting from I.M. and S.C. administration of OXYJECT® 100 were compared in eight yearling calves. Each calf received 10 mL I.M. and 10 mL S.C. on the left side. Seven days later each calf received 10 mL I.M. and 10 mL S.C. on the right side. Individual dosages fell in the range of 3 to 5 mg oxytetracycline per pound body weight in accordance with product labeling. The goal of this study was to evaluate the maximum volume of drug deposited at a single site and not the dose.

   Daily observations were conducted. Injection site swelling was observed and documented from both routes of injection. Calves were sacrificed 13 and 20 days after the last injection. These sacrifice times resulted in examining tissue reactions at 13, 20, and 27 days post injection. Injection site observations and gross pathology were documented, and color photographs taken.

3. Results:

   Study results are indicated in Table 5.1 and Table 5.2.

Table 5.1. Frequency of injection site findings of cattle administered 5 mg per pound of Oxyject ® 100 by the subcutaneous (s.c.) and intramuscular (i.m.) routes of administration.

Route	Observations	Days after injection of site		
		13 days	20 days	27 days
I.M.	total injection sites	4	8	4
	necrosis	4	7	4
	discoloration	3	4	0
	edema	0	0	0
	hemorrhage	1	0	0
	fibrous infiltration	1	4	4
S.C.	total injection sites	4	8	4
	necrosis	3	1	0
	discoloration	2	6	2
	edema	1	2	1
	hemorrhage	0	0	0
	fibrous infiltration	0	0	0

As these data demonstrate, necrosis and white fibrous infiltration persists through 27 days after site injection following I.M. and S.C. administration of OXYJECT® 100 and will necessitate trimming of the injection site(s) muscle during the dressing procedure. This results in measurable defects at slaughter in some cattle.

At 20 and 27 days following drug administration, S.C. administration was associated with less weight of injection site trim necessary to remove the lesions as compared to I.M. injection (see Table 5.2).

Table 5.2. Mean muscle trim-out associated with subcutaneous (s.c.) and intramuscular (i.m.) injection of 5 mg per pound Oxyject® 100 in cattle.

Days after injection	Mean trim weight (kg)	
	I.M.	S.C.
13	0.544	0.108
20	0.384	0.063
27	0.381	0.034

4. Conclusions:

The S.C. route of administration is safe and is associated with reduced trim, but a trim-out statement is necessary.

IV. HUMAN FOOD SAFETY

A. Tissue Residue Depletion Study - Subcutaneous Administration

1. Investigators:

Susan Rogers and Steve Stroh
Fermenta Animal Health Research Center
1512 Webster Court

Fort Collins, Colorado 80524

2. Study design and methods:

Twenty-five healthy, uniform, crossbred calves, weighing approximately 520 pounds, were randomly assigned to one of five sacrifice groups. Two herdmates were used as a source of control tissue. Calves were dosed S.C. for four consecutive days at a rate of 5 mg oxytetracycline base per pound with OXYJECT® 100.

Groups were sacrificed at 1, 3, 5, 7, and 9 days after the fourth injection. Skeletal muscle beneath the marked fourth S.C. injection site, and both kidneys were collected from each animal and analyzed for oxytetracycline residues by microbiological assay.

3. Results:

Results are summarized in Table 6.1.

Table 6.1. Mean concentration of oxytetracycline in kidney and the injection site in cattle administered 5 mg per pound Oxyject® 100 subcutaneously. Data are presented as the mean ± standard deviation.

	Oxytetracycline concentration (ppm)	
Day of Collection	**Kidney**	**Injection site**
1	39.3 ± 8.9	19.3 ± 15.5
3	3.5 ± 1.2	0.7 ± 0.7
5	1.1 ± 0.3	0.3
7	0.6 ± 0.1	*
9	0.3 ± 0.1	*
Assay Limit of Quantitation	0.2	0.2

** Concentration below Limit of Quantitation

Statistical analysis was not appropriate for evaluation of oxytetracycline residue data collected from skeletal muscle beneath the S.C. injection site. Oxytetracycline levels were above the quantitative limit at only two of the five post-treatment time points.

A chi-square test was used to determine if the variance at each sacrifice time was constant for the kidney tissues. Analysis of variance was used to test linearity. The withdrawal time was determined from the calculated tolerance limit.

4. Withdrawal Period:

On the basis of a tolerance of 12 ppm in kidney (61 FR 67435), the withdrawal period for OXYJECT® 100 (oxytetracycline HCl, 100 mg/mL), administered via the subcutaneous route, was calculated using kidney residue data from Collection Days 3 to 9. Using a statistical tolerance limit approach with a 95% confidence level on the 99th percentile, the withdrawal period calculated was 2 days.

B. Tissue Residue Depletion Study - Intramuscular/Intravenous Administration

1. Investigators:

   Dr. Charles Deyhle
   Clarendon Veterinary Hospital
   Clarendon, Texas 79226

2. Study design and methods:

   Twelve healthy beef calves, weighing 450 to 1050 lbs were assigned to four sacrifice groups. Two herd mates were used as the source of control tissue. Calves were dosed intramuscularly for four consecutive days at a rate of 5 mg oxytetracycline base per pound with OXYJECT 100. Two different sites were used and no site received more than 10 mL of the test material.

   Groups were sacrificed at 15, 18, 21, and 24 days, respectively, following the fourth injection. Both kidneys, the entire liver, abdominal fat, noninjection site muscle, and injection site muscle were collected from each animal and analyzed by microbiological assay for oxytetracycline residues.

3. Results:

   Results are summarized in Table 6.2.

   Table 6.2. Mean concentration of oxytetracycline in liver, muscle, fat and the injection site kidney and muscle in cattle administered 5 mg per pound Oxyject® 100 intramuscularly. Data are presented as the mean ± standard deviation.

Day(s) of Collection	Oxytetracycline concentration (ppm)				
	Kidney	Liver	Muscle	Fat	Injection Site
15	0.65 ± 0.1	0.183 ± 0	<0.095 ± 0	0.21 ± 0.1	0.18 ± 0.1
18	0.354 ± 0.1	0.068 ± 0	<0.095 ± 0	0.127 ± 0	0.140 ± 0
21	<0.065 ± 0	<0.060 ± 0	<0.095 ± 0	0.080 ± 0	0.080 ± 0
24	<0.065 ± 0	<0.060 ± 0	<0.095 ± 0	0.080 ± 0	0.080 ± 0

4. Withdrawal Period:

   On the basis of the linearity determination, the withdrawal period for OXYJECT® 100 (oxytetracycline HCl, 100 mg/mL), administered via the intramuscular and intravenous routes, was calculated using kidney residue data from Collection Days 15 to 21. Using a statistical tolerance limit approach with a 95% confidence level on the 99th percentile, a withdrawal period of 13 days was calculated.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FFDCA) and Part 514 of the implementing

regulations (Title 21), and demonstrate that OXYJECT® 100 administered by the subcutaneous route is bioequivalent to administration by the intramuscular route in cattle.

The sponsor demonstrated via residue depletion studies, using approved regulatory methods, that the depletion characteristics of the marker residue for OXYJECT® 100 (oxytetracycline) when administered subcutaneously depleted more rapidly than when administered intramusculary or intravenously. Based on the foregoing, it was not necessary to reevaluate the underlying toxicity tests supporting the original approval, or to require additional metabolism and depletion studies.

Using a tolerance of 12 ppm in kidney (61 FR 67435), a pre-slaughter withdrawal period for cattle of 2 days has been established for the use of this drug when administered subcutaneously and 13 days when administered by the intramuscular or intravenous routes at 3 to 5 mg per pound. These restrictions are based on statistical analysis of depletion data, using the upper tolerance limits containing 99 percent of the population with a 95 percent confidence limit.

According to the Center's supplemental approval policy, 21 CFR 514.106(b)(2)(iv) & (x), this is a Category II change that did not require a reevaluation of the safety and effectiveness data in the parent application.

Adequate directions for use of this product by lay persons have been clearly written, and there is reasonable certainty that the conditions of use, stated on the label can and will be followed by the user. The Agency is not aware of any reason why the approval of the additional route of administration would require restriction of the product to prescription use.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action is categorically excluded under 21 CFR 25.24(d)(1)(i) from the requirement to prepare an environmental assessment. The categorical exclusion applies to this action since the animal drug is to be marketed under the same conditions of the original approval. The data available to the Agency do not establish that, at the expected exposure level, the substance may be toxic to organisms in the environment.

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 approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the added route of administration for which the supplement was approved.

VI. ATTACHMENTS

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

1. Oxyject 100 (oxytetracycline) 500 mL carton label
2. Oxyject 100 (oxytetracycline) 500 mL vial label
3. Oxyject 100 (oxytetracycline) 500 mL Package Insert

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

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.