Date of Approval: November 29, 2010

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-312

HEXASOL Injection

Oxytetracycline and Flunixin Meglumine
Injectable Solution
Beef and Non-Lactating Dairy Cattle

For the treatment of bacterial pneumonia associated with *Pasteurella* spp. and for the control of associated pyrexia in beef and non-lactating dairy cattle.

Sponsored by:

Norbrook Laboratories, Ltd.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-312
B. Sponsor:	Norbrook Laboratories, Ltd. Station Works Newry BT35 6JP Northern Ireland Drug Labeler Code: 055529 U.S. Agent: Bill Zollers, Ph.D. Norbrook, Inc. 9733 Loiret Blvd. Lenexa, KS 66219
C. Proprietary Name:	HEXASOL Injection
D. Established Names:	Oxytetracycline and flunixin meglumine
E. Pharmacological Categories:	Antimicrobial and non-steroidal anti-inflammatory drug (NSAID)
F. Dosage Form:	Injectable solution
G. Amount of Active Ingredients:	300 mg oxytetracycline and 20 mg flunixin base as flunixin meglumine per mL
H. How Supplied:	100, 250, and 500 mL vials
I. How Dispensed:	Prescription (Rx)
J. Dosage:	13.6 mg oxytetracycline/lb body weight (BW) and 0.9 mg flunixin/lb BW once (equivalent to 1 mL per 22 lb BW)
K. Routes of Administration:	Subcutaneous or intramuscular injection
L. Species/Classes:	Cattle/Beef and non-lactating dairy
M. Indication:	HEXASOL Injection is indicated for the treatment of bacterial pneumonia associated with *Pasteurella* spp. and for the control of associated pyrexia in beef and non-lactating dairy cattle.

II. EFFECTIVENESS:

A. Dosage Characterization:

HEXASOL Injection is a combination product containing oxytetracycline and flunixin meglumine.

The oxytetracycline dose in cattle was selected based upon studies conducted for the approval of oxytetracycline as TETRADURE 300 (NADA 141-143) demonstrating that a dosage of 13.6 mg oxytetracycline/lb body weight (BW) was safe and effective for use in cattle. These studies are described in the FOI Summary for NADA 141-143 dated July 25, 2003.

The flunixin dose in cattle was selected based on the conditions of use for Norbrook Laboratories Limited's HEXASOL LA (oxytetracycline and flunixin meglumine) Solution for Injection for Cattle. HEXASOL LA was approved in the United Kingdom in July 2000 for the treatment of bovine respiratory disease associated with *Mannheimia (Pasteurella) haemolytica* where an anti-inflammatory and anti-pyretic effect is required in cattle, and is administered on a single occasion by intramuscular injection at a dosage of 13.6 mg of oxytetracycline/lb BW and 0.9 mg of flunixin/lb BW.

B. Substantial Evidence:

The effectiveness of HEXASOL Injection (oxytetracycline and flunixin meglumine) was demonstrated using a combination of pharmacokinetic data and a field study. Pharmacokinetic data were used to (1) bridge the oxytetracycline effectiveness data for the respiratory disease indication (at the 13.6 mg/lb BW dosage) from TETRADURE 300 (NADA 141-143, Norbrook Laboratories Limited) to HEXASOL Injection, (2) to demonstrate bioequivalence of the oxytetracycline component of HEXASOL Injection for the two routes of administration (intramuscular (IM) and subcutaneous (SC)), and (3) to bridge the flunixin effectiveness data from the SC route to the IM route.

1. Comparative Pharmacokinetic Study

a. Title: "A Comparative Three-Period Crossover Pharmacokinetic Study in Cattle Following the Subcutaneous and Intramuscular Administration of a Formulation of Oxytetracycline/Flunixin Injection and Subcutaneous Administration of TETRADURE 300 Injection (NADA 141-143)". Study Number 022/04. April 2005 to March 2006.

b. Study Director and Location: Matthew Glenn, B.Sc., B.Agr., Norbrook Laboratories, Research Division, Ballyedmond Castle Farms Limited, Northern Ireland.

c. Study Description:

Twenty-four healthy male cattle of various beef breeds (ages 6 to 9 months, and weighing between 470 to 655 lbs) were used in the study. The objective was to determine the pharmacokinetic profile of oxytetracycline and flunixin in cattle following a single subcutaneous (SC) or intramuscular (IM) injection of HEXASOL Injection (oxytetracycline and flunixin meglumine) or a single SC injection of TETRADURE 300 (oxytetracycline), and to establish bioequivalence of the two products using the criteria of $AUC_{0\text{-last}}$ and C_{max}. This study was conducted in accordance with Good Laboratory Practice (21 CFR part 58) regulations.

The study was conducted as a three-period, three-treatment, three-sequence crossover design, with a 42-day washout period. Animals were randomly assigned to one of three treatment groups (8 animals per group).

Table 2.1: Treatment Groups

Group	Period 1	Period 2	Period 3
Group A	TETRADURE 300 SC	HEXASOL Injection IM	HEXASOL Injection SC
Group B	HEXASOL Injection SC	TETRADURE 300 SC	HEXASOL Injection IM
Group C	HEXASOL Injection IM	HEXASOL Injection SC	TETRADURE 300 SC

Treatments consisted of a single dose of HEXASOL Injection by SC (left neck) or IM (right rump) administration at a dose of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW, or as a single dose of TETRADURE 300 by SC administration (right neck) at a dose of 13.6 mg oxytetracycline/lb BW. The maximum injection volume was 10 mL per site. Blood samples were collected at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 32, 48, 56, 72, 96, 120, 144, 168, 192, 216, and 240 hours post-dose. Plasma samples were analyzed for oxytetracycline using a validated microbiological assay using *Bacillus cereus* ATC 11778 spore suspension as the sensitive test organism and Oxoid Antibiotic Medium No. 1 as the test medium. Plasma samples were analyzed for flunixin using a High Performance Liquid Chromatography (HPLC) method.

d. Results:

1) *Oxytetracycline:* The mean pharmacokinetic parameter values for each of the treatments are provided in Table 2.2. The oxytetracycline component

of the combination product succeeded in meeting the bioequivalence criteria of 80 to 125% (using log-transformed values) for $AUC_{0\text{-last}}$ and C_{max}.

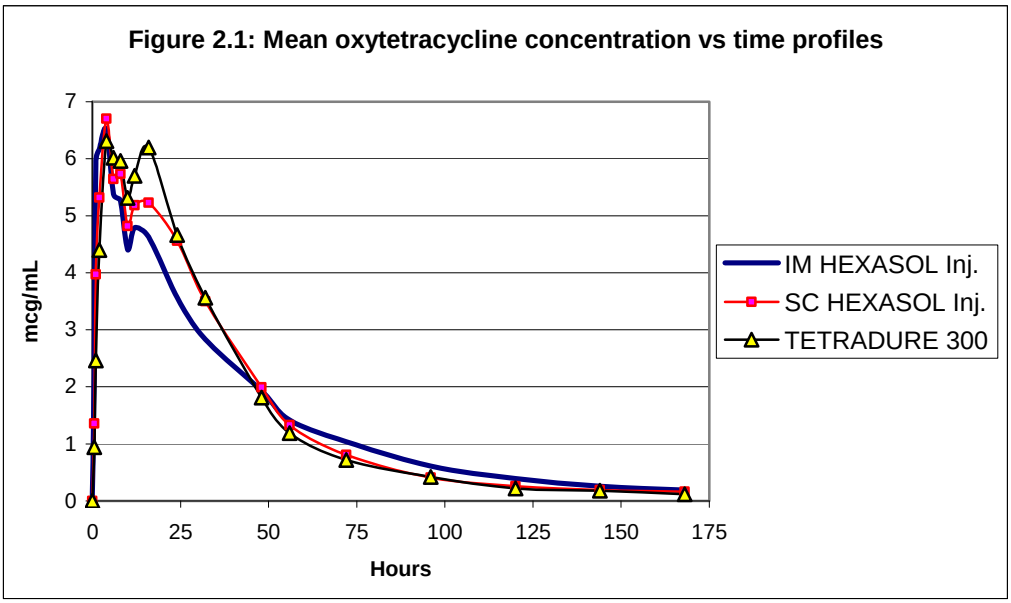
Table 2.2: Bioequivalence Results for the Oxytetracycline Component of HEXASOL Injection (HEX) Compared with TETRADURE 300 (TET).

	HEXASOL Injection				**TETRADURE 300**		**Confidence Interval**		
	IM		**SC**						
Parameter	Mean	%CV[1]	Mean	%CV	Mean	%CV	SC HEX vs. IM HEX	TET vs. IM HEX	TET vs. SC HEX
$AUC_{0\text{-last}}$[2]	261	15.8	261	12.5	262	16.8	96.1 - 103.6	96.0 - 103.6	95.8 - 103.4
C_{max}[3]	7.3	16.6	7.5	17.3	8.0	28.7	97.1 - 113.7	85.9 - 100.6	90.3 - 105.8
T_{max}[4]	3.25	79.7	7.20	86.3	8.80	47.6			
T_{half}[5]	42.9	59.5	32.3	56.7	34.4	48.3			

[1]%CV = Percent coefficient of variation
[2]$AUC_{0\text{-last}}$ = Area under the curve from time zero to the last quantifiable concentrations
[3]C_{max} = Maximum plasma concentration
[4]T_{max} = Time at which maximum plasma concentration is reached
[5]T_{half} = Time required for the concentration of drug in the body to be reduced to one-half

Corresponding mean concentration versus time profiles for these three treatment groups are provided in Figure 2.1.

Figure 2.1: Average plasma concentration of oxytetracycline in cattle following a single IM or SC injection of HEXASOL Injection (at a dose of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW) or a single SC injection of TETRADURE 300 (at a dose of 13.6 mg oxytetracycline/lb BW).



Plasma concentrations of oxytetracycline were measured from 0.5 to 240 hours post-dose and the last time point with quantifiable concentrations in all three treatment groups was at 168 hours. The average peak concentrations of oxytetracycline were observed at 3.3, 7.2, and 8.8 hours post-dose for the HEXASOL Injection IM, HEXASOL Injection SC, and TETRADURE 300 groups, respectively. The average peak concentrations (C_{max}) of oxytetracycline were 7.3, 7.5, and 8.0 µg/mL for the HEXASOL Injection IM, HEXASOL Injection SC, and TETRADURE 300 groups, respectively.

2) *Flunixin:* The mean pharmacokinetic parameter values for flunixin when administered as an IM or SC injection of HEXASOL Injection are provided in Table 2.3. The flunixin component of the combination product did not succeed in meeting the bioequivalence criteria of 80 to 125% (using log-transformed values) for $AUC_{0\text{-last}}$ and C_{max}.

Table 2.3: Bioequivalence Results for the Flunixin Component of HEXASOL Injection Following SC Versus IM Injection.

	IM HEXASOL Injection		SC HEXASOL Injection		Confidence Interval
Parameter	**Mean**	**%CV**	**Mean**	**%CV**	**IM vs. SC**
$AUC_{0\text{-last}}$	7.96	20.6	7.49	33.0	99.7 - 120.1
C_{max}	2.20	29.9	0.79	39.2	257.0 - 322.7
T_{max}	0.52	39.8	3.47	65.9	
T_{half}	4.06	22.2	6.01	31.4	

3) *Injection Site Irritation:* Injection site swelling in the SC HEXASOL Injection group and hardness in both the IM and SC HEXASOL Injection groups were reported. Swelling resolved within 55 days (SC HEXASOL Injection) post-dosing. Hardness resolved by 37 days post-dosing in the IM HEXASOL Injection group and by 55 days post-dosing in the SC HEXASOL Injection group.

e. Adverse Reactions: No adverse reactions were reported.

f. Conclusions: The data demonstrate that the IM and SC routes of administration for the oxytetracycline component of HEXASOL Injection are bioequivalent to each other and to the SC route of administration of TETRADURE 300. Accordingly, this pharmacokinetic bridge demonstrates the effectiveness of oxytetracycline for the treatment of bacterial pneumonia associated with *Pasteurella* spp. and for the control of associated pyrexia in beef and non-lactating dairy cattle.

The data demonstrate that the IM and SC routes of administration for the flunixin component of HEXASOL Injection are not bioequivalent to each other, because the two routes of administration result in different rates of absorption. The SC route resulted in substantially lower flunixin peaks than the IM route (while there was no difference between the two routes in the rate or extent of absorption for the oxytetracycline component). Therefore, the pharmacokinetic study was used to justify the selection of the SC route for the pivotal effectiveness study described below. Because higher flunixin peak concentrations were seen in this study following IM administration compared to SC administration, demonstration of effectiveness for the SC route is considered sufficient to also demonstrate effectiveness for the IM route.

2. Field Study

a. Title: "A Field Clinical Study to Evaluate the Anti-Pyretic Efficacy of a Combination of Oxytetracycline and Flunixin (Oxytetracycline/Flunixin Injection, Norbrook Laboratories Ltd, Product Code P-FLO-020) in Comparison to TETRADURE 300 (Product Code NADA 141-143) or Sterile Saline in Naturally Occurring Respiratory Infections in Cattle". Protocol numbers 006/05, 007/05, 008/05, and 010/05. May 2005 to October 2005.

b. Type of Study: Clinical effectiveness study. The study was conducted according to the current VICH GL9 Guideline for Good Clinical Practices (CVM Guidance for Industry #85).

c. Study Investigators and Locations:

1) Terry TerHune, DVM, Ph.D.
HMS Veterinary Development, Inc., Tulare, CA.

2) Tony Janes, B.S.
J-Bar H Cattle Company, Inc., Amarillo, TX.

3) Kelly Lechtenberg, DVM, Ph.D.
Midwest Veterinary Services, Inc. Oakland, NE.

4) Jenifer Edmonds, DVM, Ph.D.
Johnson Research, Parma, ID.

d. Study Design:

1) *Objective:* To evaluate the antipyretic effectiveness of a combination of oxytetracycline and flunixin (HEXASOL Injection) in comparison to TETRADURE 300 (NADA 141-143) or sterile saline in cattle with naturally occurring respiratory infections associated with bacterial pneumonia.

2) *Test Animals:* A total of 306 beef crossbred or Holstein cattle were enrolled across four sites. Calves ranged in age from 4 months to yearlings, and from 270 to 712 lbs. On arrival, cattle were processed according to standard feedlot procedures at each site. Calves were maintained under normal feedlot husbandry conditions in outdoor feedlot pens. Calves were observed daily for signs of bovine respiratory disease (BRD). Enrollment was permitted for up to 14 days after arrival at each facility.

3) *Experimental Design:* Calf respiratory and attitude scores were recorded based on the following scale:

Respiratory Scores:

0 = normal: respiratory rate, sounds, and effort appropriate for environment;

1 = mild: slightly increased respiratory rate and sound, some roughness in breathing, cough may be present;

2 = moderate: increased respiratory rate and effort, some abdominal breathing, abnormal respiratory sounds and cough may be present;

3 = severe: increased respiratory rate with clear abdominal effort, rales, cough, open mouth breathing or respiratory grunting may be present.

Attitude Scores:

0 = normal: bright, alert, and responsive;

1 = mildly depressed: may stand isolated with its head held down or ears drooping, but responsive and moves readily when stimulated;

2 = moderately depressed: may stand isolated with head down, possible signs of muscle weakness (standing cross-legged or knuckling when walking), may move slowly when stimulated;

3 = severely depressed: recumbent and reluctant to rise under most circumstances; or if standing, isolated and reluctant to move. When animal moves, ataxia, knuckling, or swaying may be evident. Eyes dull, head carried low with ears drooping, and possible excess salivation or lacrimation.

Calves were enrolled if they had a respiratory score of ≥ 2 and/or an attitude score of ≥ 2 and a rectal temperature of ≥ 104.5 °F. All sites used the same scoring criteria. Calves that met enrollment criteria were randomly assigned to one of three treatment groups. Only complete blocks (one animal from each treatment group) were enrolled; calves enrolled in incomplete blocks on any given day were treated with standard feedlot therapy and excluded from the study.

4) *Treatment Groups:* The treatment groups are described in Table 2.4.

Table 2.4: Treatment Groups

	Drug	**Dosage**	**No. of Calves**
A	oxytetracycline/flunixin (HEXASOL Injection)	13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW (equivalent to 1 mL/22 lb BW)	102
B	oxytetracycline (TETRADURE 300)	13.6 mg oxytetracycline/lb BW (equivalent to 1 mL/22 lb BW)	102
C	saline	1 mL/22 lb BW	102

5) *Test Article Administration:* The test article was HEXASOL Injection (300 mg oxytetracycline/mL and 20 mg flunixin/mL). TETRADURE 300 (NADA 141-143, 300 mg oxytetracycline/mL) was used as a reference article. Sterile saline (0.9% sodium chloride) was used as a control article. Treatments were administered as a single subcutaneous injection in the neck at 1 mL/22 lb BW at enrollment (Hour 0). The maximum injection volume was 10 mL per injection site.

6) *Measurements and Observations:* A nasal swab was collected from each calf prior to enrollment. Calves were weighed prior to treatment to determine dosage. Rectal temperature was measured using a calibrated thermometer prior to treatment administration and at 6 hours (± 1 hour) following treatment administration. Temperature data were collected by personnel unaware of treatment assignments.

   The primary variable for determining antipyretic effectiveness was the difference between the pre-treatment and post-treatment (6 hours ± 1 hour) rectal temperatures. This study did not evaluate post-treatment clinical respiratory and attitude scores.

7) *Statistical Analysis:* The difference between the pre-treatment and post-treatment (6 hours ± 1 hour) rectal temperatures was modeled using a mixed effects analysis of variance (ANOVA) model. The treatment group was included in the model as a fixed effect. Terms for site and the treatment-by-site interaction were included in the model as random effects. The HEXASOL Injection treatment group was compared to the saline and TETRADURE 300 treatment groups using two-sided tests and a 5% significance level.

e. Results: The table 2.5 below shows the mean decrease in rectal temperature across the four study sites.

Table 2.5: Mean Decrease in Rectal Temperature from Hour 0 to Hour 6 (± 1 Hour)

Mean Decrease in Rectal Temperature (p-value vs. HEXASOL Injection)	
HEXASOL Injection	2.46 °F ± SEM* 0.09
TETRADURE 300	0.74 °F ± SEM 0.11 ($p < 0.0001$)
saline	0.12 °F ± SEM 0.1 ($p < 0.0001$)

*SEM – Standard Error of Mean

A clinically relevant mean decrease in rectal temperature (2.46 °F) was seen in the HEXASOL Injection-treated group across the four sites. The mean decrease in rectal temperature in the HEXASOL Injection-treated group was statistically significant compared to the saline-treated group (2.46 °F vs. 0.12 °F, $p < 0.0001$) and compared to the TETRADURE 300-treated group (2.46 °F vs. 0.74 °F, $p < 0.0001$).

Mannheimia haemolytica, *Pasteurella multocida*, and *Histophilus somni* were isolated from pre-treatment nasal swabs, confirming that the BRD-associated pneumonia was associated with bacterial organisms.

f. Adverse Reactions: No test article related adverse reactions were reported.

g. Conclusion: The study demonstrates that HEXASOL Injection (oxytetracycline and flunixin meglumine), administered as a single SC dose of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW, was effective for the control of pyrexia in calves with naturally occurring bacterial pneumonia.

III. TARGET ANIMAL SAFETY:

A target animal safety (systemic toxicity) study evaluated HEXASOL Injection administered by intramuscular injection every 3 days for three administrations (3X the intended label duration) at 1X, 3X, and 5X the labeled dose. Pharmacokinetic data were used to justify the use of intramuscular administration in the systemic toxicity study to support both intramuscular and subcutaneous administration. Injection site irritation was evaluated during the pharmacokinetic study and two residue studies conducted for the approval.

A. Systemic Toxicity Study

1. Title: "A target animal safety study in cattle following the intramuscular administration of Oxytetracycline/Flunixin Injection (Norbrook Laboratories Limited, Product Code, P-FLO-020)". Study Number 027/07. June to July 2007.

2. Study Director and Location: Matthew Glenn, B.Sc., B.Agr. and Cormac Caraher, B.Sc., Norbrook Laboratories, Research Division, Ballyedmond Castle Farms Limited, Northern Ireland.

3. Study Design:

   a. *Objective*: To demonstrate the safety of an oxytetracycline/flunixin combination injection following intramuscular administration to cattle at 1X, 3X, and 5X the labeled dose of 13.6 mg oxytetracycline/lb body weight (BW) and 0.9 mg flunixin/lb BW for 3X the proposed duration (three administrations 72 hours apart). This study was conducted in accordance with Good Laboratory Practice (21 CFR part 58) regulations.

   b. *Test Animals*: Twenty-four healthy commercial calves (12 bulls and 12 heifers) of multiple beef and dairy breeds, approximately 3 to 5 months of age, weighing between 220 to 324 lbs at selection, were used in the study. Study animals were penned individually indoors and were acclimated for 15 days prior to treatment. Hay and water were continuously available. The calves also received a 16 % protein calf ration supplement twice a day.

   c. *Test and Control Articles*: The test article was the final intended marketed formulation of HEXASOL Injection, a combination injectable solution containing 300 mg oxytetracycline/mL and 20 mg flunixin (as flunixin meglumine)/mL. The control article was saline (0.9% sodium chloride) injectable solution.

   d. *Experimental Design*: The cattle were randomly divided into four groups of calves (3 males and 3 females each). Each group was administered saline or oxytetracycline/flunixin at 1X, 3X, or 5X the labeled dose of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW by intramuscular injection every 3 days for three administrations (Days 0, 3, and 6). Each animal was dosed based on its individual body weight measured on Day -1. The individuals performing clinical assessments were masked to treatment. The treatment administrator and Study Director were not masked and did not perform clinical observations or record data.

   e. *Treatment Groups*: Animals were randomly assigned to one of four treatment groups (6 animals per group) as shown in Table 3.1.

Table 3.1: Treatment Groups, Study 027/07.

Treatment Group	Treatment Description	Treatment Duration	Number of Animals
Group 1 (1X)	13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW	3 treatments 72 hours apart	6 (3 males, 3 females)
Group 2 (3X)	40.8 mg oxytetracycline/lb BW and 2.7 mg flunixin/lb BW	3 treatments 72 hours apart	6 (3 males, 3 females)
Group 3 (5X)	68.0 mg oxytetracycline/lb BW and 4.5 mg flunixin/lb BW	3 treatments 72 hours apart	6 (3 males, 3 females)
Group 4 (0X)	5 mL saline per 22 lb BW (volume equivalent to 5X dose volume)	3 treatments 72 hours apart	6 (3 males, 3 females)

f. *Measurements and Observations*: The following measurements and observations were made on Days -1, 1, 4, 7, 14, and 21: hematology, serum chemistry, coagulation analysis, urinalysis, and fecal analysis. Clinical observations including physical examinations with temperature, heart rate, and respiration rate were performed daily from Days -1 to 7, and on Days 14 and 21. Body weights were recorded on Days -1, 7, and 21. Animal health observations (including evidence of adverse reactions to treatment), feed consumption, and water consumption were recorded twice daily throughout the study. The injection sites were observed for significant abnormalities (e.g., signs of animal discomfort, severe swelling/inflammation, abscessation, etc.) and recorded daily until the animal was euthanized or until no abnormal observations were recorded for two consecutive days. Two animals from each group were selected for necropsy based on their having the most significant abnormal laboratory changes at Day 1 and/or Day 4, or they were selected by predetermined random allotment if no laboratory abnormalities were found in the group. Organ weights (liver, kidney, spleen, and heart), gross pathology, and histopathology data were obtained from tissues collected at necropsy within 24 to 32 hours after the final administration (Day 7).

g. *Statistical Methods*: When the response variable was measured once, inferential statistics were conducted using an analysis of variance where the model was a completely randomized design structure with a two-way treatment structure, dose and sex. The two-way interaction was included in the model. When the response variable was measured multiple times, inferential statistics were conducted using an analysis of variance where the model was a completely randomized design structure with a three-way treatment structure, dose, sex, and time with repeated measures. All the two-way and the three-way interactions were included in the model. Statistical significance was defined at ≥ 0.05 for the three-way interaction and ≥ 0.10 for main and two-way effects.

4. Results:

   a. *Clinical and Animal Health Observations*: No adverse test article-related effects were observed.

   b. *Injection Sites*: No adverse test article-related effects were observed.

   c. *Body Weights*: No statistically significant adverse test article-related effects were observed. Two female calves in the 5X group demonstrating evidence of kidney toxicity lost weight by Day 7 of the study, but the average for the group was not statistically significantly lower compared to the control group.

   d. *Food and Water Consumption*: No adverse test article-related effects were observed.

   e. *Hematology*: No adverse test article-related effects were observed.

   f. *Coagulation Analysis*: No adverse test article-related effects were observed.

   g. *Serum Chemistry*: Aspartate aminotransferase (AST) in the 1X, 3X, and 5X groups increased up to five times the upper limit of normal in a dose-dependent, statistically significant ($p < 0.0001$) manner until Day 7, then decreased to normal on Days 14 and 21. Although females tended to have higher values, increases were seen in both genders. These findings were not considered clinically relevant because the effects were relatively small, resolved without incident, and no evidence of liver toxicity was found. The increases in AST were considered to be a result of muscle inflammation secondary to intramuscular injection.

      Creatinine and blood urea nitrogen (BUN) were both statistically significantly ($p < 0.0001$) increased in the 5X group compared to the saline group, with creatinine means peaking slightly above normal on Day 1 and BUN means peaking near the high end of the normal range on Day 4. Both parameters returned to pre-treatment levels by Day 14. Although the increases were seen in all the calves in the 5X group, two females had much higher levels of both creatinine and BUN up to Day 7, at which time they were euthanized and necropsied.

   h. *Urinalysis*: The pre- and post-treatment urine specific gravity (USG) results of the 5X group were significantly different than the saline group. On Day -1 the mean 5X group USG was higher than the saline group, but on Days 1 and 4 it was significantly lower ($p < 0.02$). USG in the 5X group increased above the saline group on Day 7 and was lower than but not different from the saline group on Days 14 and 21.

   i. *Fecal Analysis*: No adverse test article-related effects were observed.

j. *Gross and Microscopic Pathology*: In the two females necropsied in the 5X group, the pathologist identified minimal cortical tubular necrosis, minimal to slight tubular casts, slight inflammatory cell infiltrate, slight to moderate basophilic cortical tubules and slight to moderate dilated cortical tubules. No males were necropsied in the 5X group. These findings, in conjunction with the results for creatinine, BUN, and urinalysis, were considered to be evidence of mild renal toxicity associated with the test article in the 5X group. The pathologist found no significant kidney lesions in the saline, the 1X, or the 3X group. No gross lesions were detected in any group.

5. Conclusions**:** This study demonstrates that HEXASOL Injection is safe in cattle when administered once as an intramuscular injection at a dosage of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW.

B. Pharmacokinetic Study:

Results of a three-period cross-over study (Study 022/04, summarized in section II.B.1 above) demonstrated pharmacokinetic bioequivalence between the IM and SC routes of administration for the oxytetracycline component of HEXASOL Injection in cattle. The data also demonstrated that the two routes were not bioequivalent for the flunixin component of HEXASOL Injection; higher flunixin peak concentrations were observed following IM administration compared to SC administration. Therefore, in conjunction with the results of the systemic toxicity study (Study 027/07, summarized in section III.A above), this study demonstrates that HEXASOL Injection is safe in cattle when administered once as an intramuscular or subcutaneous injection at a dosage of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW.

C. Injection Site Irritation Studies:

Injection site irritation was evaluated during the pharmacokinetic study and two residue studies conducted for the approval.

1. During the pharmacokinetic study (Study 022/04, summarized in section II.B.1 above), all injection sites were monitored daily for the first four days following subcutaneous or intramuscular injection of HEXASOL Injection and then twice weekly until the end of the animal phase of the study. At each observation, swelling was measured (length, width, and height), and hardness/softness, signs of discomfort (resentment on palpation), heat, and redness/discoloration were scored. The observers found injection site swelling in the subcutaneous HEXASOL Injection-treated group and hardness in both the subcutaneous HEXASOL Injection-treated group and the intramuscular HEXASOL Injection-treated group. Swelling resolved within 55 days after treatment for the subcutaneous HEXASOL Injection-treated group. Hardness resolved by 55 days after treatment in the subcutaneous HEXASOL Injection-treated groups, and by 37 days in the intramuscular HEXASOL Injection-treated group. No other adverse reactions were reported.

2. During the tissue residue study 027/04 (summarized in section IV.B.1.b below), all injection sites were monitored daily for the first four days following subcutaneous injection of HEXASOL Injection and then twice weekly until reactions were resolved or the animal was euthanized. At each observation, swelling was measured (length, width, and height), and hardness/softness, signs of discomfort (resentment on palpation), heat, and redness/discoloration were scored. At the time of euthanasia, injection sites were examined and photographed. No redness/discoloration or heat was observed during the study. Signs of discomfort were mild and transient, with no signs of discomfort recorded for any animal after Day 3. Swelling and hardness were recorded for all treated animals following injection. The maximum swelling size recorded was 20 x 10 x 3 cm (observed on Day 3). Swelling and hardness reduced over time, with no animals demonstrating measurable swelling after Day 31, and only one animal demonstrating hardness at Day 35. Postmortem examination confirmed that injection site reactions showed evidence of resolving over time. Grossly visible lesions found on postmortem examination included swelling and hemorrhage of subcutaneous tissue, and fibrosis and surface discoloration of surrounding muscle. These lesions were seen in all treated animals euthanized at Day 3, 7, 14, 28, and 35, and in 3 of 4 treated animals at Day 21. No other adverse reactions were reported. This study demonstrates that HEXASOL Injection, when administered subcutaneously at the labeled dose, may cause transient inflammation, including signs of discomfort, swelling, and hardness at the site of injection and surrounding tissues, lasting up to at least 35 days after treatment.

3. During the tissue residue study 028/04 (summarized in section IV.B.1.c below), all injection sites were monitored daily for the first four days following intramuscular injection of HEXASOL Injection and then twice weekly until reactions were resolved or the animal was euthanized. At each observation, swelling was measured (length, width, and height), and hardness/softness, signs of discomfort (resentment on palpation), heat, and redness/discoloration were scored. At the time of euthanasia, injection sites were examined and photographed. No swelling, redness/discoloration, signs of discomfort, or heat were observed during the study. Hardness was recorded for all treated animals following injection. No animals euthanized on Days 14, 21, or 28 had hardness recorded at the time of euthanasia; only one animal euthanized at Day 35 had a hardness score recorded. Postmortem examination confirmed that injection site reactions showed evidence of resolving over time. Grossly visible lesions found on postmortem examination included discoloration of muscle and fibrosis of muscle and surrounding fascia. These lesions were seen in all treated animals euthanized at all time points. No other adverse reactions were reported. This study demonstrates that HEXASOL Injection, when administered intramuscularly at the labeled dose, may cause transient inflammation, including hardness at the site of injection and surrounding tissues, lasting up to at least 35 days after treatment.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this original approval. The FOI Summaries for the original approvals of NADA 141-143 dated July 25, 2003, for oxytetracycline and ANADA 200-308 dated November 17, 2003, for flunixin meglumine, contain summaries of all toxicology studies.

The impact of residues in edible tissues of cattle treated with 300 mg/mL oxytetracycline in combination with 20 mg/mL flunixin as flunixin meglumine (HEXASOL Injection – administered in a single IM or SC dose at a dose rate of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW) on human intestinal flora in consumers of these edible tissues was carefully considered by the Agency. The oxytetracycline component and dosage of the combination formulation is the same as that already approved under NADA 141-143 (TETRADURE 300). The Agency determined that, because there are no significant changes in formulation, dosage, route of administration, or duration of use associated with the oxytetracycline component in this product, the addition of flunixin meglumine to the previously approved 300 mg/mL oxytetracycline should not significantly impact public health. Therefore further evaluation of any impact on human intestinal flora was not necessary at this time.

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Total Residue Depletion Study

1) Title: "A Total Residue Depletion Study of [^{14}C]-Flunixin Residues in Cattle Following a Subcutaneous Injection of HEXASOL (Oxytetracycline/Flunixin) Injectable". Study Number 006-00925. June to July 2008.

A statement is provided describing adherence to Good Laboratory Practices according to 21 CFR part 58.

2) Study Director: John W. Byrd, Ph.D.

3) Study Report Date: July 28, 2009

4) In-Life Facility: Southwest Bio-Labs, Inc., Las Cruces, New Mexico

5) Analytical Laboratory:

Determination of Total Radioactive Residues:	Southwest Bio-Labs, Inc., Las Cruces, New Mexico

Marker Residue Determination: XenoBiotic Laboratories, Inc., Plainsboro, New Jersey

6) Test Material: [^{14}C]-HEXASOL Injection containing [^{14}C]-flunixin with a specific activity of 7.58 µCi/mg and radiochemical purity of 98.49% was used. The final [^{14}C]-HEXASOL Injection dose solution was prepared by adding 497.9 mg of [^{14}C]-flunixin meglumine (equivalent to 300 mg of ^{14}C-flunixin) to 252 mL of HEXASOL Injection solution.

7) Test Animals: Six crossbred cattle (3 steers and 3 heifers) weighing 343 to 429 lbs were used. One steer served as a control animal.

8) Dosing: [^{14}C]-HEXASOL Injection was administered subcutaneously on Study Day 0 at a rate of 0.98 mg [^{14}C]-flunixin/lb BW. The total dose volume was divided into two syringes, so that no more than a maximum of 10 mL was administered in a single injection.

9) Sample Collection: Animals were euthanized at 24 or 48 hours post-dose. At necropsy, the following tissue samples were collected: liver, kidneys, muscle (composite of leg and loin), fat (perirenal and omental fat deposits), and all injection sites.

10) Total Residue Concentration: Kidney, liver, muscle, and injection site samples were assayed for total flunixin equivalent residues by oxidizing samples to ^{14}C-carbon dioxide and counting the radioactivity by LSC.

11) Flunixin Concentration: Flunixin concentrations in liver and injection site #1 samples were determined using the validated HPLC-UV assay for the analysis of flunixin (free acid).

12) Results:

Table 4.1: [^{14}C]-Flunixin Equivalent Residues (ppm ± standard deviation)

Tissue Sample	Withdrawal Period	
	24 hours	**48 hours**
Liver	1.0586 ± 0.361	0.1721 ± 0.022
Kidney	0.7306 ± 0.286	0.137 ± 0.036
Muscle	0.0118 ± 0.002	0.0047 ± 0.0005
Fat	0.0549 ± 0.0026	0.0103 ± 0.003
Injection Site 1	18.871 ± 19.813	3.4926 ± 1.306
Injection Site 2	16.8872 ± 10.143	2.7347 ± 0.863

Table 4.2: Flunixin (free acid) Residues in Liver and Injection Site

Withdrawal Period	Animal No./Sex	Flunixin (Free Acid) Residues (in PPM)	
		Liver	Injection Site #1
24 hours	4811/F	0.4943	3.6428
	4812/M	0.8497	7.8241
	4816/M	0.4316	34.3618
48 hours	4809/F	0.0597	3.2472
	4810/F	0.0683	2.9656
	4814/M	0.0484	1.3482

b. Residue Depletion Study

1) Title: "A tissue residue study to determine levels of oxytetracycline and flunixin in cattle 3, 7, 14, 21, 28 and 35 days following the subcutaneous administration of a formulation of Oxytetracycline/Flunixin Injection." Protocol Number 027/04, April 4, 2006.

A statement is provided describing adherence to Good Laboratory Practices according to 21 CFR part 58.

2) Study Director: Alistair Couper, BVMS, MRCVS

3) Study Location: Ballyedmond Castle Farms Limited, Northern Ireland

4) Objective: The objective of the study was to determine the concentrations of oxytetracycline and flunixin in tissues of cattle sacrificed at 3, 7, 14, 21, 28, and 35 days after a one time subcutaneous injection of 13.6 mg of oxytetracycline/lb BW and 0.9 mg flunixin/lb BW.

5) Test Material: HEXASOL Injection.

6) Test Animals: Twenty-seven cattle representative of U.S. beef breeds (13 males, 14 females) about 7 to 20 months old and weighing 443.12 to

747.36 lbs were used in this study. The study design is shown in Table 4.3.

Table 4.3: Study Design for Study 027/04

Treatment Group	No. Animals (Sex)	Drug Dose*	Route	Sacrifice Time (Days)
A	4 (2M, 2F)	HEXASOL	SC	3
B	4 (2M, 2F)	HEXASOL	SC	7
C	4 (2M, 2F)	HEXASOL	SC	14
D	4 (2M, 2F)	HEXASOL	SC	21
E	4 (2M, 2F)	HEXASOL	SC	28
F	4 (2M, 2F)	HEXASOL	SC	35
G	3 (1M, 2F)	Control	NA	3, 14, 35

*A single SC injection of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW

7) Dosing: Each treatment group animal received a single subcutaneous treatment with HEXASOL Injection. The maximum injection volume was 10 mL and the sites were, sequentially, right neck, left neck cranial, left neck middle, and left neck caudal.

8) Sample Collection: At the respective sacrifice times, groups of animals were euthanized by captive bolt and exsanguination. Following euthanasia, the following tissues were sampled: muscle, liver, kidney (both entire organs), fat, and injection site (right neck, which received the maximum volume administration).

9) Oxytetracycline Residue Analysis: Tissue samples were assayed in triplicate for oxytetracycline content using a cylinder cup microbiological assay technique based upon the U.S. regulatory method published in *Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports and Protocols*, revised October 1968, reprinted December 1974, National Center for Antibiotic and Insulin Analysis, Food and Food and Drug Administration.

10) Flunixin Residue Analysis: Tissue samples were assayed in duplicate for flunixin using the U.S. regulatory determinative HPLC method SOM No.: CRD/FLX/010 (limit of quantification – 15.6 ppb).

Because oxytetracycline has a longer withdrawal period than flunixin, assays for flunixin in muscle, liver, and injection site were performed only at 3 and 7 days.

11) Results: Tables 4.4 and 4.5 summarize the results of the study for oxytetracycline and flunixin, respectively. At 28 and 35 days, all tissues of treated animals contained residues for oxytetracycline at less than

0.1 ppm, the limit of quantitation. For flunixin, all tissues of treated animals contained less than 15.6 ppb, the limit of quantitation.

Table 4.4: Mean Residues of Oxytetracycline (ppm) in Edible Tissues of Cattle after a Single Subcutaneous Injection of 13.6 mg Oxytetracycline and 0.9 mg Flunixin/lb BW.

Treatment Group (Withdrawal in Days)	Muscle	Liver	Kidney	Fat	Injection Site (Right Neck)
Control (3)	<0.1	<0.1	<0.1	<0.1	<0.1
A (3)	0.92	2.04	3.08	0.27 ± 0.02*	271.3
B (7)	0.14**	0.41	1.07	<0.1	40.1
Control (14)	<0.1	<0.1	<0.1	<0.1	<0.1
C (14)	<0.1	<0.1	0.22***	<0.1	22.6
D (21)	<0.1	<0.1	<0.1	<0.1	3.0
E (28)	<0.1	<0.1	<0.1	<0.1	<0.1
Control (35)	<0.1	<0.1	<0.1	<0.1	<0.1
F (35)	<0.1	<0.1	<0.1	<0.1	<0.1

* One value; the other three values were <0.1.
** Two values; the other two values were <0.1.
*** Three values; the other value was <0.1.

Table 4.5: Concentrations of Flunixin (ppb) in Edible Tissues of Cattle after a Single Subcutaneous Injection of 13.6 mg Oxytetracycline and 0.9 mg Flunixin/lb BW.

Treatment Group (Withdrawal in Days)	Muscle	Liver	Injection Site (Right Neck)
Control (3)	<15.6	<15.6	<15.6
A (3)	<15.6	<15.6	<15.6
B (7)	<15.6	<15.6	<15.6

12) Conclusion: The residue depletion data from oxytetracycline in kidney were analyzed using a statistical tolerance limit algorithm for the 99th percentile of the population with a 95% confidence limit, and a 5-day withdrawal period was calculated for a the SC route. However, with regard to injection site residues, we note that even at 14 days withdrawal, two values exceed the allowable injection site residue levels (i.e., 20 ppm, 10X the muscle tolerance of 2 ppm). By 21 days, none of the values at the injection site exceed allowable levels. Therefore, we assign a 21-day withdrawal period for the SC route.

c. Residue Depletion Study

1) Title: "A tissue residue study to determine levels of oxytetracycline and flunixin in cattle 3, 7, 14, 21, 28, and 35 days following the intramuscular

administration of a formulation of Oxytetracycline/Flunixin Injection." Protocol Number 028/04, March 30, 2006.

A statement is provided describing adherence to Good Laboratory Practices according to 21 CFR part 58.

2) Study Director: Matthew Glenn, B.Sc., B.Agr.

3) Study Location: Ballyedmond Castle Farms Limited, Northern Ireland

4) Objective: The objective of the study was to determine the concentrations of oxytetracycline and flunixin in tissues of cattle sacrificed at 3, 7, 14, 21, 28 and 35 days after a one time intramuscular injection of 13.6 mg oxytetracycline and 0.9 mg flunixin/lb BW (equivalent to 1 mL/22 lb BW).

5) Test Material: HEXASOL Injection.

6) Test Animals: Twenty-seven cattle representative of US beef stock (13 males, 14 females) about 6 to 17 months old and weighing 557.76 to 740.75 lbs were used in this study. The study design is shown in Table 4.6.

Table 4.6: Study Design for Study 028/04

Treatment Group	No. Animals (Sex)	Drug Dose*	Route	Sacrifice Time (Days)
A	4 (2M, 2F)	HEXASOL	IM	3
B	4 (2M, 2F)	HEXASOL	IM	7
C	4 (2M, 2F)	HEXASOL	IM	14
D	4 (2M, 2F)	HEXASOL	IM	21
E	4 (2M, 2F)	HEXASOL	IM	28
F	4 (2M, 2F)	HEXASOL	IM	35
G	3 (1M, 2F)	Control	NA	3, 14, 35

*A single IM injection of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW

7) Dosing: Each treatment group animal received a single intramuscular treatment with HEXASOL Injection. The maximum injection volume was 10 mL and the sites were, sequentially, right rump, left cranial rump, left middle rump, and left caudal rump.

8) Sample Collection: At the respective sacrifice times, groups of animals were euthanized by captive bolt and exsanguination. Following euthanasia, the following tissues were sampled: muscle, liver, kidney (both entire organs), fat, and injection site (right rump, which received the maximum volume administration).

9) Oxytetracycline Residue Analysis: Tissue samples were assayed in triplicate for oxytetracycline content using a cylinder cup microbiological assay technique based upon the U.S. regulatory method published in *Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports and Protocols*, revised October 1968, reprinted December 1974, National Center for Antibiotic and Insulin Analysis, Food and Food and Drug Administration.

10) Flunixin Residue Analysis: Tissue samples were assayed in duplicate for flunixin using the U.S. regulatory determinative HPLC method SOM No.: CRD/FLX/010 (limit of qualification – 15.6 ppb).

Because oxytetracycline has a longer withdrawal period than flunixin, assays for flunixin in muscle, liver, and injection site were performed only at 3 and 7 days.

11) Results: Tables 4.7 and 4.8 summarize the results of the study for oxytetracycline and flunixin, respectively. At 28 and 35 days, all tissues of treated animals contained residues for oxytetracycline at less than 0.1 ppm, the limit of quantification. For flunixin, all tissues of treated animals contained less than 15.6 ppb, the limit of quantification.

Table 4.7: Mean Residues of Oxytetracycline (ppm) in Edible Tissues of Cattle after a Single Intramuscular Injection of 13.6 mg Oxytetracycline and 0.9 mg Flunixin/lb BW

Treatment Group (Withdrawal in Days)	Muscle	Liver	Kidney	Fat	Injection Site (Right Rump)
Control (3)	<0.1	<0.1	<0.1	<0.1	<0.1
A (3)	0.80	2.33	2.98	0.18*	513.3
B (7)	0.15**	0.55	1.15	<0.1	43.6
Control (14)	<0.1	<0.1	<0.1	<0.1	<0.1
C (14)	<0.1	0.16***	0.47	<0.1	38.4
D (21)	<0.1	<0.1	<0.1	<0.1	1.5^
E (28)	<0.1	<0.1	<0.1	<0.1	2.85*
Control (35)	<0.1	<0.1	<0.1	<0.1	<0.1
F (35)	<0.1	<0.1	<0.1	<0.1	10.6**

* Two values; the other two values were <0.1.
** One value; the other three values were <0.1.
*** Three values; the other value was <0.1.

Table 4.8: Concentrations of Flunixin (ppb) in Edible Tissues of Cattle after a Single Intramuscular Injection of 13.6 mg Oxytetracycline and 0.9 mg Flunixin/lb BW.

Treatment Group (Withdrawal in Days)	Muscle	Liver	Injection Site (Right Rump)
Control (3)	<15.6	<15.6	<15.6
A (3)	<15.6	<15.6	<15.6
B (7)	<15.6	<15.6	<15.6

12) Conclusion: The residue depletion data from oxytetracycline in liver were analyzed using a statistical tolerance limit algorithm for the 99th percentile of the population with a 95% confidence limit, and an 11-day withdrawal period was calculated for the IM route of administration. However, we note that even at 14 days withdrawal, two values at the injection site exceed the allowable injection site residue levels (i.e., 20 ppm, 10X the muscle tolerance of 2 ppm). By 21 days, none of the values at the injection site exceed allowable levels. Therefore, we will assign a 21-day withdrawal period for the IM route.

2. Target Tissue and Marker Residue Assignment

The marker residue for oxytetracycline in cattle is parent oxytetracycline. A target tissue for oxytetracycline in cattle is not assigned (21 CFR 556.500). The marker residue for flunixin in cattle liver (the target tissue) is flunixin free acid (21 CFR 556.286).

3. Tolerance Assignments

The tolerances for oxytetracycline in edible tissue of cattle are established as 2 ppm in muscle, 6 ppm in liver, and 12 ppm in fat and kidney (21 CFR 556.500). The tolerances for flunixin free acid in edible tissue of cattle are established as 25 ppb in muscle and 125 ppb in liver (21 CFR 556.286).

4. Withdrawal Times

A 21-day pre-slaughter withdrawal period is assigned for the use of 300 mg oxytetracycline/mL and 20 mg flunixin (as meglumine)/mL via the intramuscular or subcutaneous routes of administration in beef cattle, non-lactating dairy cattle, calves and yearlings.

C. Microbial Food Safety:

The impact of the use of 20 mg/mL flunixin meglumine in combination with 300 mg/mL oxytetracycline (HEXASOL Injection – administered in a single IM or SC injection at a dose rate of 13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW) on antimicrobial resistance among bacteria of public health concern in or on

treated cattle was carefully considered by the Agency. The sponsor provided a microbial food safety assessment addressing the use of HEXASOL Injection in cattle for the treatment of bovine respiratory disease associated with *Pasteurella* spp.

The assessment included a *release assessment* to describe the probability that the use of HEXASOL Injection under the proposed conditions of use would result in emergence or selection of resistant *Campylobacter, Salmonella, Escherichia coli*, and *Enterococcus*; an *exposure assessment* to describe the likelihood of human food-borne exposure to *Campylobacter* and *Salmonella* following consumption of ground beef from treated cattle; and a *consequence assessment* to describe potential human health consequences arising from exposure to the defined food-borne pathogens or resistance determinants by considering the human medical importance of tetracyclines.

The Agency determined that the microbial food safety risk associated with proposed use of HEXASOL Injection in cattle is medium (based on an integration of release, exposure, and consequence assessment results of high, medium, and highly important – medium; respectively). This overall risk estimation of medium for the proposed use of HEXASOL Injection in cattle is adequately addressed by the Agency's Category 2 risk management strategies – prescription (Rx) only, injectable, limited number of animals – treated individually, and continued monitoring by the National Antimicrobial Resistance System.

D. Analytical Method for Residues:

1. Analytical Method for Oxytetracycline

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 in *Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports and Protocols*, revised October 1968, reprinted December 1974, National Center for Antibiotic and Insulin Analysis, Food and Food and Drug Administration.

2. Determinative Method for Flunixin

The determinative assay for flunixin is a HPLC method which provides acceptable sensitivity, specificity, accuracy, and precision for the routine monitoring of flunixin residues in bovine liver. Flunixin, present in liver tissue as free, conjugated, or esterified forms, is hydrolytically released, extracted, and purified through the sequential use of silica gel, reversed-phase, and cation exchange column chromatography. The purified solution is analyzed by HPLC using a mobile phase containing an ion pairing reagent. The method was demonstrated to reliably quantitate flunixin residues at levels of 0.01 to 0.20 ppm. No interference was observed from 17 veterinary drugs commonly used in cattle.

3. Confirmatory Method for Flunixin

The confirmatory method utilizes a liquid chromatography/mass spectrum/mass spectrum (LC/MS/MS) methodology applied to the purified solution obtained from the determinative method work-up. Daughter ion (m/z 297) mass spectrometry yielded confirmatory ions at m/z 264, 279 (base peak), and 297.

4. Availability of Method

The method is available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to HEXASOL Injection:

WARNING: Not for use in humans. Keep out of reach of children.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To obtain an MSDS contact Norbrook at 1-866-591-5777.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that HEXASOL Injection, when used according to the label, is safe and effective for the treatment of bacterial pneumonia associated with *Pasteurella* spp. and for the control of associated pyrexia in beef and non-lactating dairy cattle. Additionally, data demonstrate that residues in food products derived from cattle treated with HEXASOL Injection will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

Labeling restricts this drug to use by or on order of a licensed veterinarian. This decision was based on the following factors: (1) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat bacterial pneumonia; and (2) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use that could result in violative tissue residues.

B. Exclusivity:

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.

C. Patent Information:

HEXASOL Injection is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
6,479,473	May 6, 2017

For current information on patents, see the Animal Drugs @ FDA database (formerly the Green Book) on the FDA CVM internet website.