Date of Approval: July 26, 2013

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-360

EQUISUL-SDT

Sulfadiazine/Trimethoprim

Oral Suspension

Horses

For the treatment of lower respiratory tract infections in horses caused by susceptible strains of *Streptococcus equi* subsp. *zooepidemicus*

Sponsored by:

Aurora Pharmaceutical, LLC

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-360

B. Sponsor

Aurora Pharmaceutical, LLC
1196 Highway 3 South
Northfield MN 55057-3009

Drug Labeler Code: 051072

C. Proprietary Name

EQUISUL-SDT

D. Established Name

Sulfadiazine/Trimethoprim

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Oral Suspension

G. Amount of Active Ingredient

400 mg/mL combined active ingredients
(333 mg/mL sulfadiazine and 67 mg/mL trimethoprim)

H. How Supplied

150 mL amber glass bottle containing 135 mL of EQUISUL-SDT
950 mL amber glass bottle containing 900 mL of EQUISUL-SDT

I. Dispensing Status

Rx

J. Dosage Regimen

Administer 24 mg combined active ingredients per kg body weight (10.9 mg/lb) twice daily for 10 days. EQUISUL-SDT can be administered by volume at 2.7 mL per 45.4 kg (2.7 mL/100 lb) body weight.

K. Route of Administration

Oral

L. Species/Class

Horses

M. Indication

EQUISUL-SDT is indicated for the treatment of lower respiratory tract infections in horses caused by susceptible strains of *Streptococcus equi* subsp. *zooepidemicus.*

II. EFFECTIVENESS

A. Dosage Characterization

As a class, the effectiveness of potentiated sulfonamides is most closely related to drug concentration time above minimum inhibitory concentration (MIC). A pilot study was conducted to investigate the relationship between administered dose, systemic exposure, and clinical outcome in horses with lower respiratory tract infections. Since the effect of the drug is time-dependent, the dose that resulted in a positive clinical outcome and provided drug concentrations above the MIC_{90} for at least 80% of the dosing interval was chosen for further investigation.

In a pilot dose determination study (146013-E-11.0-2007), horses with clinical signs of respiratory disease were administered placebo (n=6), 20 mg/kg (n=7), 24 mg/kg (n=6), or 30 mg/kg (n=6) EQUISUL-SDT twice daily for 7 days. Infection with *S. equi* subsp. *zooepidemicus* was confirmed by semi-quantitative culture of transtracheal washes collected prior to treatment. Pharmacokinetic (PK), microbiologic, and clinical data were collected. In the 24 mg/kg group, 5/6 horses were considered to be a clinical cure by Day 7 and all horses demonstrated alleviation of clinical signs of lower respiratory tract disease by Day 14. Four out of six horses demonstrated microbial success based on absence of *S. equi* subsp. *zooepidemicus* on post-treatment transtracheal wash culture. The median C_{max} was observed within 2 to 8.5 hours for both trimethoprim (TMP) and sulfadiazine (SDZ) following administration of a single dose of EQUISUL-SDT oral suspension. The median half-life across the doses (20-30 mg/kg) ranged between 3 to 3.78 hours for TMP and 6.90 to 8.25 hours for SDZ. Both TMP and SDZ reached steady state by Day 3 (see Figures 1 and 2). It appears from the PK data (Tables 1 and 2) and the mean plasma profiles (Figures 1 and 2) that the TMP/SDZ concentrations at steady state remain above the MIC_{90} for *S. equi* subsp. *zooepidemicus* (TMP/SDZ: 0.25/4.75) for most of the dosing interval. The combination of TMP with other sulfonamides (e.g. sulfamethoxazole or SMX) have shown MIC_{90} values of 0.25/4.75 for TMP/SMX (*S. equi* subsp. *zooepidemicus*) with the majority being below 0.12/2.4[1]. Further, the activity of TMP/SMX against organisms defined for this combination is comparable to the TMP/SDZ combination.

A dose of 24 mg/kg combined active ingredients was selected for further evaluation in the field effectiveness study based on the positive outcome of horses in the 24 mg/kg group and the presence of free drug concentrations that

[1] Bade D, Sibert GJ, Hallberg J, Portis ES, Boucher J, Bryson L. 2009. Ceftiofur Susceptibility of *Streptococcus equi* subsp *zooepidemicus* Isolated From Horses in North America Between 1989 and 2008. Vet Ther. 10(4):E1-7.

exceeded the MIC_{90} of the targeted pathogen for the entire 24 hour dosing interval.

Table 1. Median (range) of sulfadiazine pharmacokinetics parameters following repeat dosing of 20, 24, and 30 mg/kg EQUISUL-SDT twice daily for 7 days to horses in fed condition

Dose (mg/kg)	n	T_{max} (hr)	C_{max} (mcg/mL)	$AUC_{0-12(last\ dose)}$ (hr*mcg/mL)	$T_{1/2}$ (hr)
20	7	2.50 (1.00-10.00)	20.46 (9.16-27.18)	194.79 (94.79-258.79)	8.25 (5.77-11.68)
24	6	4.75 (1.00-12.00)	17.63 (10.10-31.15)	159.35 (73.90-282.54)	7.80 (6.78-10.39)
30	6	2.00 (1.00-3.00)	15.21 (11.56-21.42)	157.97 (82.21-219.48)	6.90 (6.17-14.09)

Table 2. Median (range) of trimethoprim pharmacokinetics parameters following repeat dosing of 20, 24, and 30 mg/kg EQUISUL-SDT twice daily for 7 days to horses in fed condition

Dose (mg/kg)	n	T_{max} (hr)	C_{max} (mcg/mL)	$AUC_{0-12(last\ dose)}$ (hr*mcg/mL)	$T_{1/2}$ (hr)
20	7	2.00 (0.50-10.00)	0.83 (0.43-1.53)	5.54 (2.35-8.20)	3.78 (3.19-5.23)
24	6	8.50 (0.50-12.00)	0.78 (0.60-1.14)	5.47 (3.31-10.91)	3.00 (2.31-4.96)
30	6	7.00 (1.00-12.00)	0.96 (0.39-1.35)	7.35 (3.48-13.4)	3.66 (3.02-5.70)

Figure 1. Mean concentration-time profile for sulfadiazine in plasma for 3 dosing groups

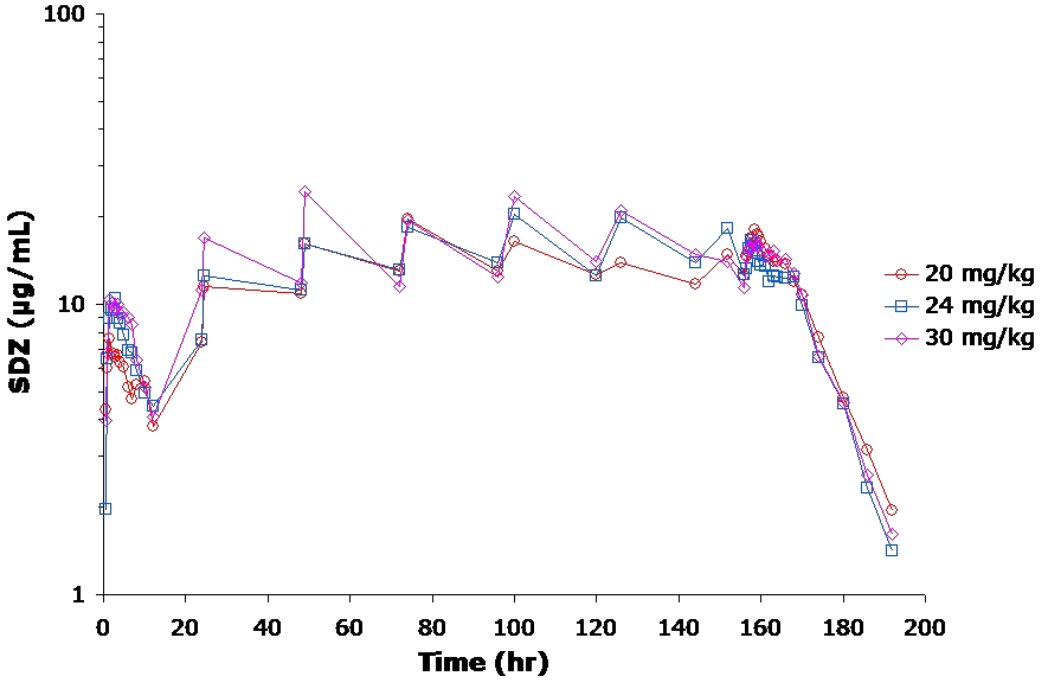
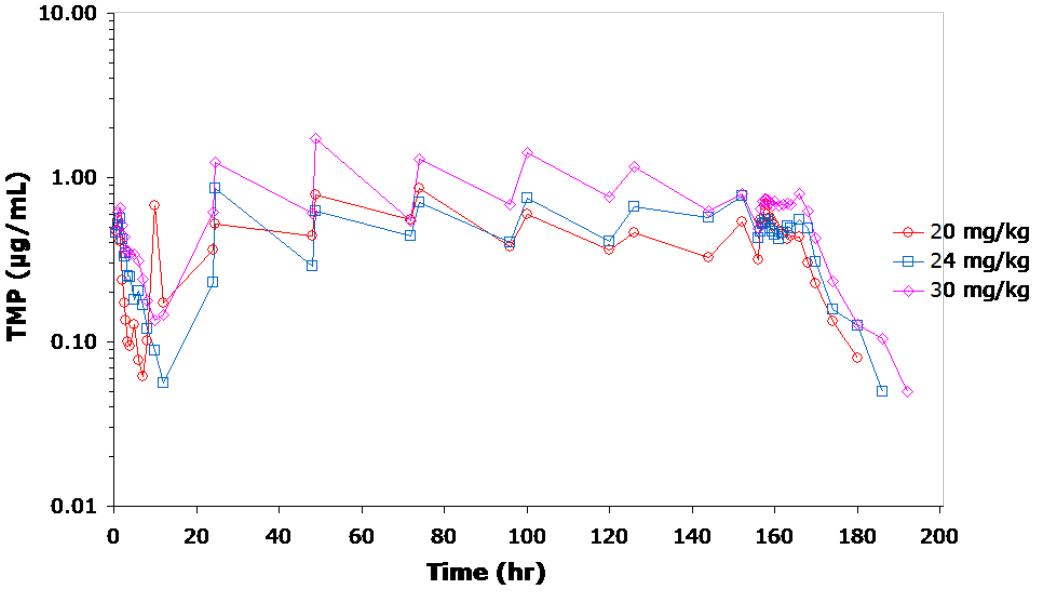


Figure 2. Mean concentration-time profile for trimethoprim in plasma for 3 dosing groups



B. Substantial Evidence

1. Dose Confirmation Study

a. Title: A Negative-Control Field Efficacy Study of Trimethoprim and Sulfadiazine Oral Suspension in Purpose Acquired Horses with Lower Respiratory Infections Caused by *Streptococcus equi* subsp. *zooepidemicus*. Study No. 146013-E-9.1-2009.

b. Investigators:

Table 3. Investigators

Investigator name	Location
Scott McClure, DVM, PhD	Boone, Iowa
Kent Haden, DVM	Mexico, Missouri
Breck Hunsaker, DVM, PhD	Preston, Idaho
Craig R. Reinemeyer, DVM, PhD	Rockwood, Tennessee
Gary W. White, DVM	Sallisaw, Oklahoma

c. Study Design:

(1) *Objective*: The study objective was to confirm effectiveness and field safety of EQUISUL-SDT administered twice daily for 10 days at a dose of 24 mg/kg body weight for the treatment of lower respiratory tract infections in horses caused by *Streptococcus equi* subsp. *zooepidemicus*.

(2) *Study Dates*: June 2010-March 2011

(3) *Study Animals*: 270 male and female purpose bought horses, co-mingled at each site, were randomly assigned to receive either 24 mg/kg EQUISUL-SDT or a saline control at the equivalent volume by body weight, twice daily for 10 days. Multiple pure and mixed breeds were represented, with the majority of animals categorized as Quarter Horse, Paint, or Grade. Study animals ranged in age from 1 year to 25 years, with the average age of 3 years.

(4) *Experimental Design*: Upon meeting the clinical inclusion criteria, horses were randomly allocated to treatment group (2 EQUISUL-SDT: 1 saline). The horses were required to exhibit all of the following clinical signs of lower respiratory tract infection within an 8-hour observation period to qualify for initial enrollment:

- Fever (≥101.0°F)
- Increased respiratory rate (>24 breaths per minute)
- Intermittent or sustained coughing
- Abnormal lung sounds upon auscultation (i.e. wheezing, crackles or diminished lung sounds)

A mid-cervical transtracheal wash was performed on every study horse prior to treatment. Only horses culturing ≥ 100 colonies of *Streptococcus equi* subsp. *zooepidemicus* from the transtracheal wash sample in semi-quantitative culture were included in the final effectiveness analysis. Treatment failures that had significant presence (≥ 100 colonies) of bacteria other than *Streptococcus equi* subsp. *zooepidemicus* in the transtracheal wash culture performed at the time of removal were not included in the effectiveness analysis.

(5) *Treatment Groups*: Horses were assigned to one of two treatment groups as follows:

Table 4. Treatment groups

Treatment group	Dose mg/kg	Number of horses enrolled (evaluable)
Saline	0 mg/kg	88 (61)
EQUISUL-SDT	24 mg/kg	182 (112)

(6) *Drug Administration*: The test article (EQUISUL-SDT) and control article (saline at an equivalent volume to the test article) were administered orally by dosing syringe twice daily for 10 days.

(7) *Measurements and Observations*:

Each horse was given a complete physical examination by a veterinarian, and assessed for clinical signs of respiratory infection (fever, increased respiration, cough, abnormal lung sounds) on Days 0, 5, 10, and 17. Blood samples for hematology, chemistry, and coagulation determinations were collected prior to treatment and at study exit. Samples for microbial analysis were collected by transtracheal wash prior to treatment and again at study exit on all evaluable horses and were cultured to confirm the presence or absence of *Streptococcus equi* subsp. *zooepidemicus*. Clinical observations for general health, mental attitude, fecal consistency, appetite, and any adverse reactions were performed twice daily throughout the ten days of treatment and for an additional seven days following the final dose. All individuals making clinical observations were masked to treatment group.

Improvement in clinical signs of lower respiratory tract infection was considered the primary measure of treatment success, and was evaluated according to the scoring key below:

Rectal Temperature
0) <101 ºF
2) ≥101 ºF

Respiratory Rate
0) ≤ 24 Breaths per minute
2) > 24 Breaths per minute

Respiratory Sounds on Auscultation
0) Normal
2) Abnormal: Crackles, Wheezes, or Reduced Lung Sounds

Coughing
0) No cough elicited by laryngeal palpation
1) Cough elicited by laryngeal palpation
2) Intermittent spontaneous coughing
3) Sustained coughing without stimulus

A clinical score sign of at least 2 for each parameter was required for enrollment in the study. Horses having clinical sign scores for rectal temperature less than two, and a coughing score below three on Day 10 were conditionally considered treatment successes, pending confirmation on Day 17. Horses were required to exhibit clinical sign scores below 2 for each of the four designated clinical signs of lower respiratory infection on Day 17 to be considered an overall treatment success.

d. Statistical Methods:

Clinical success or failure was analyzed through generalized linear mixed model analysis with binary distribution on the single outcome (success or failure for each subject) and logit link. The model included the fixed effect treatment "group." Study site and site by treatment interaction were included as a random effect. The saline control group was compared to the EQUISUL-SDT group and the difference in clinical success was considered significant if the p value was less than 0.05.

e. Results:

A total of 270 horses with lower respiratory tract infection met the clinical enrollment criteria (182 EQUISUL-SDT and 88 saline). Of these, 173 horses (112 EQUISUL-SDT and 61 saline) were evaluable as determined by both clinical and microbial criteria.

At Day 10, 100 of 112 (89%) horses treated with EQUISUL-SDT and 30 of 61 (49%) horses treated with saline met the initial (Day 10) success criteria. Overall, 66 of 112 (59%) horses treated with EQUISUL-SDT and 9 of 61 (15%) horses treated with saline met the final (Day 17) criteria for success. The statistical test for significance is based on overall success, which required horses to be considered a success at both Days 10 and 17.

The observed success rates are 58.9% (66/112) and 14.8% (9/61) for the EQUISUL-SDT and saline treated groups, respectively. Table 5 summarizes the statistical analysis results on the overall success rate.

Table 5. Overall clinical effectiveness results

	EQUISUL-SDT	Saline	P value*
Least Square Means	61%	13.1%	0.0123
* P-value and estimated success rates are based on back-transformed mean estimates from the statistical analysis.			

f. Adverse Reactions:

Adverse reactions reported for all horses treated with either EQUISUL-SDT (n=182) or with a saline control (n=88) are summarized in Table 6. At least one episode of loose stool of varying severity was observed in 69 of 182 (38%) of the EQUISUL-SDT treated horses, and 29 of 88 (33%) saline control horses. Of those animals experiencing loose stool, 2 of 182 (1.1%) of the EQUISUL-SDT treated horses and 0 of 88 (0%) placebo-treated horses were removed from the study due to diarrhea (defined as at least one episode of watery stool). Both cases of diarrhea in this study were self-limiting and resolved without treatment within 5-10 days after discontinuation of EQUISUL-SDT.

One EQUISUL-SDT treated horse with signs of colic was removed from the study for treatment of colic. This horse was treated medically and recovered within 12 hours. In the remaining horses with signs of colic, clinical signs resolved quickly with medical treatment, and these horses remained in the study.

One EQUISUL-SDT treated horse with swollen lymph nodes during the treatment phase of the study was observed to have a 10 cm, firm, sub-mandibular swelling at Day 17; however, the horse otherwise met the clinical criteria for success.

Table 6. Number of horses with adverse reactions

Adverse reactions	EQUISUL-SDT (n=182)	Saline control (n=88)
Loose stool (including diarrhea)	69 (38%)	29 (33%)
Colic	3 (1.6%)	2 (2.2%)
Diarrhea	2 (1.1%)	0 (0%)

g. Clinical Pathology:

There were no clinically significant changes in clinical pathology parameters related to the administration of EQUISUL-SDT.

h. Microbiology:

EQUISUL-SDT is a potentiated sulfonamide. Potentiated sulfonamides sequentially inhibit enzymes in the folic acid pathway, thereby inhibiting bacterial thymidine synthesis. The sulfonamide blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid (DFA), and

trimethoprim blocks the conversion of DFA to tetrahydrofolic acid by inhibiting dihydrofolate reductase.

The minimum inhibitory concentrations of trimethoprim/sulfadiazine among pre-treatment isolates of *S. equi* subsp. *zooepidemicus* recovered from horses in the EQUISUL-SDT group were determined using the methods described in the Clinical and Laboratory Standards Institute document M31-A3.

Table 7. Trimethoprim/sulfadiazine minimum inhibitory concentration (MIC) values[a] of *Streptococcus equi* subsp. *zooepidemicus* isolates recovered from horses with lower respiratory tract infections treated with EQUISUL-SDT in this study. (2010-2011)

Treatment outcome	Number of isolates	Time of sample collection	MIC_{50}[b] (mcg/mL)	MIC_{90}[b] (mcg/mL)	MIC range (mcg/mL)
Success	65[c]	Pre-Treatment	0.25/4.75	0.25/4.75	0.12/2.4 to 0.5/9.5
Failure	46	Pre-Treatment	0.25/4.75	0.25/4.75	0.12/2.4 to 0.5/9.5

[a] The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
[b] The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.
[c] One isolate of *S. equi* subsp. *zooepidemicus* was not tested.

The results demonstrate that the populations of *S. equi* subsp. *zooepidemicus* among horses prior to treatment had a similar distribution of susceptibility to trimethoprim/sulfadiazine.

i. Conclusion: This study supports the effectiveness of EQUISUL-SDT administered to horses at the dose of 24 mg/kg body weight twice daily for 10 days for the treatment of lower respiratory tract infections caused by susceptible stains of *Streptococcus equi* subsp. *zooepidemicus*.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety Study:

1. Title: A Margin of Safety Study of Pharmaceutical Solution Inc.'s Trimethoprim and Sulfadiazine Oral Suspension in Horses. Study No. 146013-E-7.2-2008

2. Type of Study: Laboratory study

3. Study Dates: January 2009 to March 2009

4. Study Director: Robbin Koenig, PhD
North Little Rock, AR

5. Study Location: Rockwood, TN

6. Study Design:

a. *Objective:* To evaluate the safety of EQUISUL-SDT when administered orally at 0 (0X), 24 (1X), 72 (3X), and 120 (5X) mg/kg twice daily for 30 days.

b. *Study Animals:* Thirty-two healthy horses (17 geldings, 1 stallion, 18 non-pregnant, non-lactating mares) of various breeds, 2-12 years of age, weighing between 329 and 484 kg.

c. *Treatment Group and Drug Administration:*

Horses received 0X, 1X, 3X, or 5X the maximum recommended dose (24 mg/kg) of EQUISUL-SDT administered orally by dosing syringe twice daily for 30 days.

Table 8. Treatment groups

Treatment group	EQUISUL-SDT dose, twice daily	Number (male/female)
0X	0 mg/kg*	4/4
1X	24 mg/kg	4/4
3X	72 mg/kg	4/4
5X	120 mg/kg	4/4

* Control horses were administered saline at a volume equivalent to the 1X dose volume.

d. *Inclusion/Exclusion Criteria:* Healthy horses based on physical exam, clinical pathology, and urinalysis, were included in the study. Pregnant mares were excluded from the study.

e. *Measurements and Observations:*

General health observations were recorded twice daily during the treatment phase and once daily during acclimation. General health observations included an evaluation of fecal consistency which was scored as normal, formed pellets, mixture of pellets and liquid, unformed/cowpile, or watery/diarrhea. Physical examinations were performed on Days -1, 6, 13, 20, and 29. Body weights were recorded prior to acclimation and again on Days -1, 6, 13, 20, and 29. Feed, hay, and water consumption were measured daily from acclimation until necropsy. Hematology, coagulation, and clinical chemistry were evaluated once during acclimation and on Days 6, 13, 20, and 29. Urinalysis and fecal evaluations (fecal flotation and hemoccult analysis) were performed when possible once during acclimation and on Days 6, 13, 20, and 29. Gross necropsy and histopathology were performed post-mortem.

f. *Statistical Analysis:*

Body weights, hematology, coagulation, and clinical chemistry parameters were analyzed using repeated measures analysis of covariance with terms for treatment group, study day, and group by day interaction, using the baseline value as covariate and a compound symmetric structure for the covariance matrix. Relative organ weights (organ weight/body weight

ratio) were analyzed for group difference using one-way analysis of variance. Tests were performed at the 0.10 level of significance.

7. Results:

a. *Clinical Observations:*

The most common abnormal observation in all EQUISUL-SDT treated groups was loose stool defined as a mixture of pellets with liquid and/or unformed/cow pile stool. Fecal consistency scores were significantly higher (more watery) in the 3X and 5X groups as compared to the control group. Fifteen horses treated with EQUISUL-SDT had loose stool on 37 occasions during the study as compared to 3 control horses on 3 occasions. The incidence of loose stool was dose dependent with five 5X, seven 3X, three 1X, and three 0X horses experiencing episodes of loose stool. All episodes of loose stool were self-limiting and did not require treatment. No horses experienced episodes of loose stool categorized as watery/diarrhea, the most severe fecal consistency score.

Table 9. Number of horses with loose stool

Treatment group	Number of horses	Total observations
0X	3	3
1X	3	5
3X	7	16
5X	5	16

Mean body weights demonstrated a statistically significant increase for horses treated with EQUISUL-SDT as compared to control horses. Mean body weights for the 1X, 3X, and 5X groups were 423.4 kg, 423.9 kg, and 424.1 kg, respectively, compared to 411.6 kg for the control group.

b. *Clinical Pathology:*

Clinical pathology evaluations demonstrated significantly higher mean creatinine concentrations in all EQUISULT-SDT treated groups as compared to the control group. The 1X and 5X EQUISUL-SDT groups had significantly higher mean absolute neutrophil counts and mean serum gamma glutamyl transferase (GGT) concentrations as compared to the control group. The 3X and 5X EQUISUL-SDT groups had significantly higher mean albumin concentrations than the control group, and all EQUISUL-SDT treated groups had lower mean fibrinogen concentrations as compared to the control group. Individual animal creatinine, GGT, and albumin concentrations remained within the reference range. Individual animal elevations in absolute neutrophil counts ranged up to 7.09 x 10^3/mcL (reference range: 1.96-5.31 x 10^3/mcL).

c. *Pharmacokinetics:*

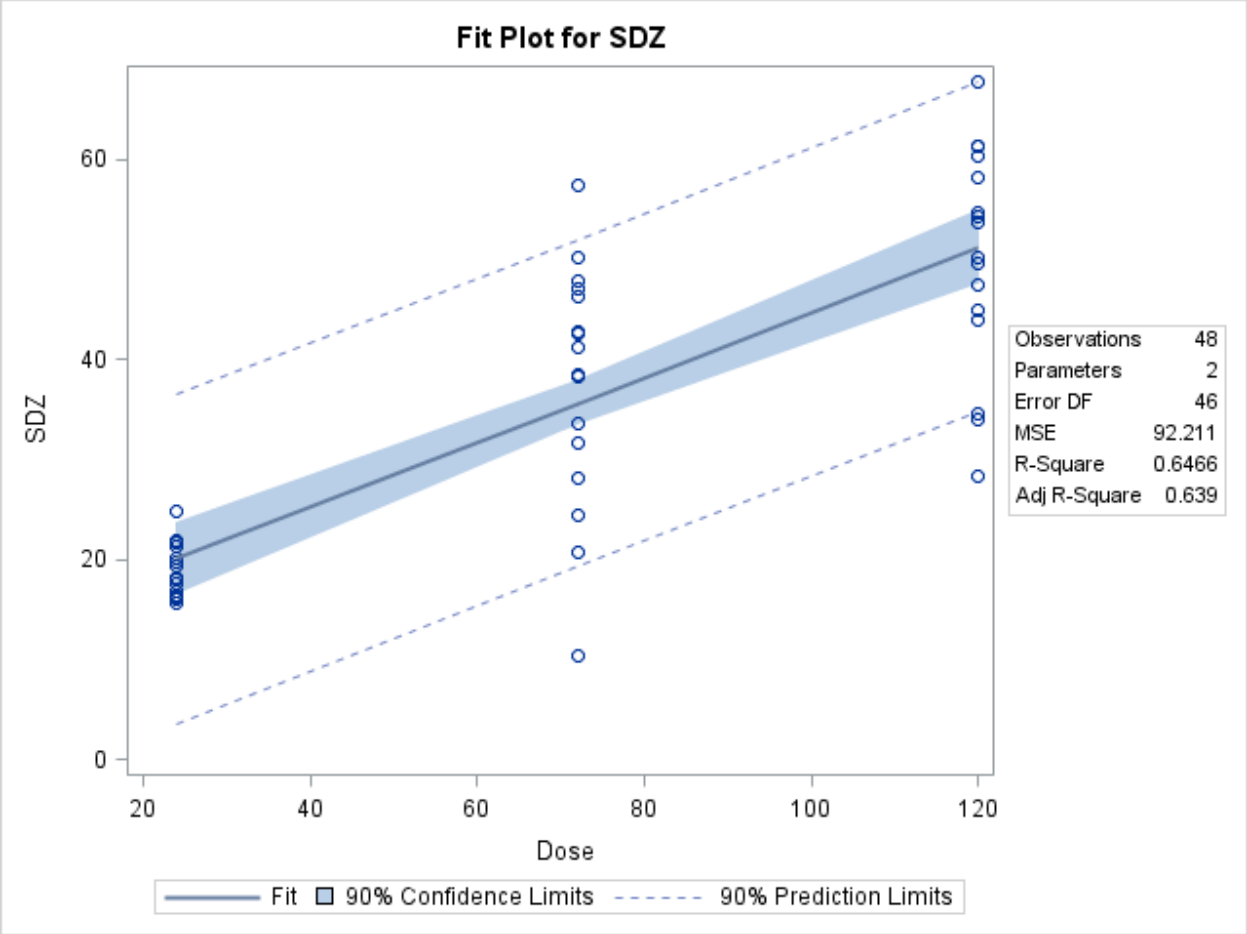
On Days 0, 14, and 29, blood samples were collected at three time points (0, 2, and 12 hours following the AM dose) for the analysis of plasma drug concentrations. This information was used to describe: (1) the exposure associated with the various doses, (2) the magnitude of accumulation with repeated administrations, and (3) the blood levels of horses experiencing

any adverse reactions. Samples were analyzed for sulfadiazine (SDZ) and trimethoprim (TMP) in horse plasma using a validated LC-MS/MS assay method.

Some drug accumulation was observed following repeated twice daily administrations across all EQUISUL-SDT dose groups. For both SDZ and TMP, the magnitude of accumulation varied across the 3X and 5X dose groups, with some animals having drug concentrations lower than that seen after dose 1 following repeated administrations, and others exhibiting more than a 2-fold increase in drug concentrations at steady state. For the 1X dose group, drug concentrations were far less variable (as seen in Figures 3 and 4 below), with the steady state accumulation expressed as concentrations relative to that seen at hour 2 on Day 1 being 1.25 for SDZ and 1.47 for TMP.

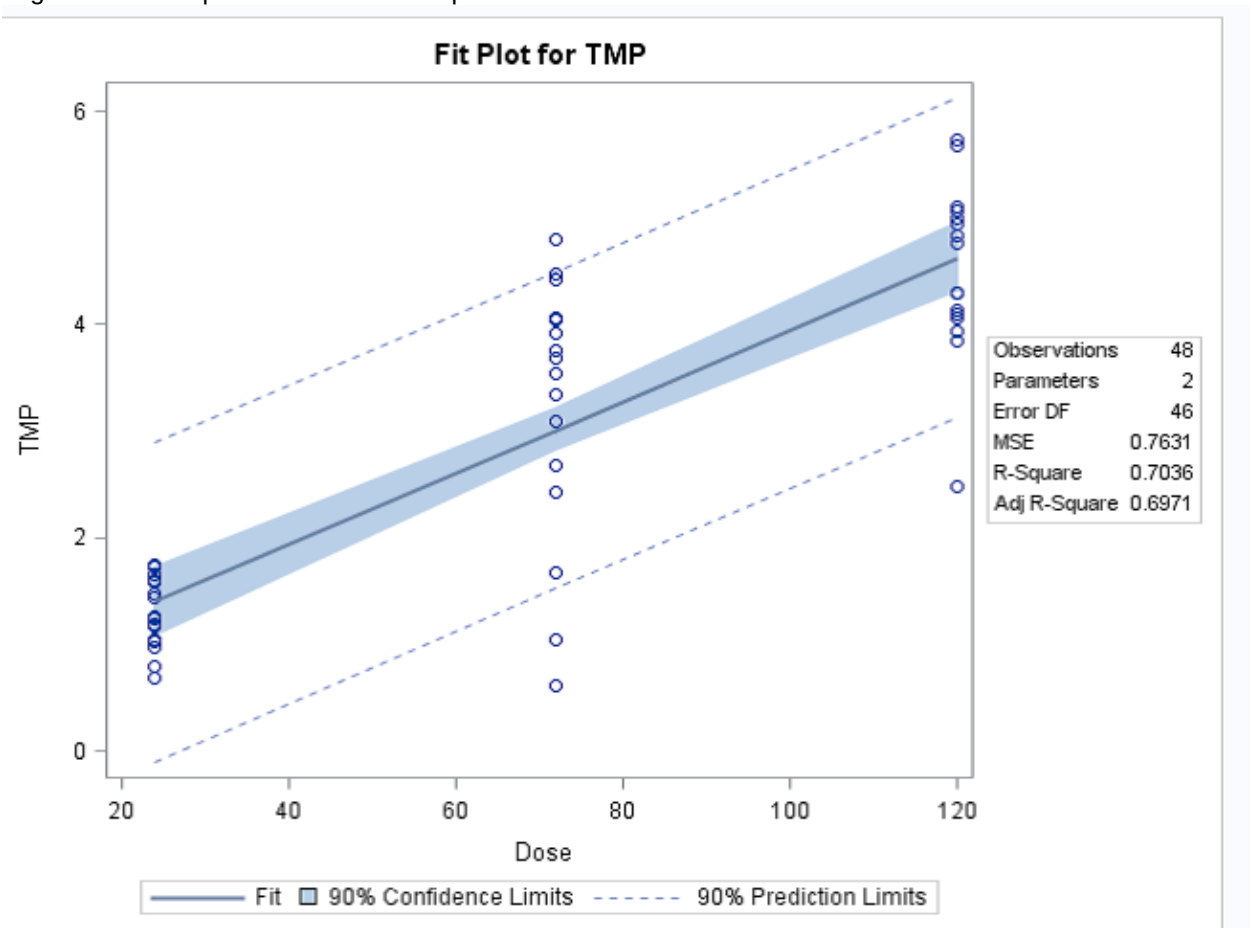
The relative increase in plasma sulfadiazine and trimethoprim concentrations was not dose-proportional. Furthermore, there was very large variability between subjects across dose groups, resulting in large overlaps in drug exposure, despite the exaggerated doses that were administered. An example of the individual hour 2 blood levels of sulfadiazine and trimethoprim (as measured on Days 14 and 29) are provided in the figures below. Hour 2 was selected as the point of comparison because it approximated the estimated expected time of T_{max}. Similar results were obtained when the hour 12 time point was compared across treatment groups. The acceptability of pooling the data across study days was determined by confirming the comparability of individual subject Days 14 and 29 steady state blood levels.

Figure 3. Fit plot for sulfadiazine



In Figure 3, the individual observations for sulfadiazine concentrations at hour 2 (an approximation of peak concentrations on Days 14 and 29) are plotted for each EQUISUL-SDT dose group. The concentrations of sulfadiazine (Y axis, mcg/mL) are plotted as a function of the EQUISUL-SDT mg/kg dose (X axis). The important point to note is the very large between subject variability and the large overlap in the individual subject concentrations across the three dosing groups.

Figure 4. Fit plot for trimethoprim



In Figure 4, the individual observations for trimethoprim concentrations at hour 2 (on Days 14 and 29) are plotted for each EQUISUL-SDT dose group. The concentrations of trimethoprim (Y axis, mcg/mL) are plotted as a function of the EQUISUL-SDT mg/kg dose (X axis). The important point to note is the very large between subject variability and the large overlap in the individual subject concentrations across the three dosing groups.

8. Conclusion: This study supports the safety of EQUISUL-SDT when administered to horses at a dose of 24 mg/kg twice a day for 10 days. Treatment with EQUISUL-SDT was associated with a dose dependent increase in the incidence of self-limiting episodes of loose stool.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in horses. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

The product labeling contains the following Warning statement: Do not use in horses intended for human consumption.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to EQUISUL-SDT:

Not for use in humans. For use in animals only. Keep this and all drugs out of reach of children. Consult a physician in the case of accidental human exposure.

Antimicrobial drugs, including sulfonamides, can cause mild to severe allergic reactions in some individuals. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Persons with a known sensitivity to trimethoprim or sulfonamides should avoid exposure to this product. If an allergic reaction occurs (e.g., skin rash, hives, difficulty breathing, facial swelling) seek medical attention.

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 EQUISUL-SDT, when used according to the label, is safe and effective for the treatment of lower respiratory tract infections in horses caused by susceptible strains of *Streptococcus equi* subsp. *zooepidemicus.*

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is needed in the diagnosis and treatment of lower respiratory tract infections in horses, and for monitoring for possible adverse reactions of the drug.

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:

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