

INTERDEPARTMENTAL CORRESPONDENCE

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TO: W. Hartman, Study Sponsor

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SUBJECT Dog Bioavailability Study with
AND Pentagastrin - Pepto-Bismol with
STUDY #: Simethicone - PBDB# 14

SUMMARY

The purpose of this study was to establish blood salicylate profiles on dogs dosed with Pepto-Bismol with and without simethicone to determine if the simethicone interferes with the absorption of salicylate in the bloodstream. Two formulations of Pepto-Bismol with simethicone were evaluated in this study. Pentagastrin was used to stimulate gastric acid secretions in the dogs to make the dog gastric pH similar to that in humans.

There were no statistical differences between dogs dosed with regular Pepto-Bismol or Pepto-Bismol with simethicone in serum salicylate levels up to 8 hours after dosing. Serum salicylate levels from the treatments were almost identical throughout the study (see attached graph, individual sample times, Lag Time, Time-to-Peak, Peak Concentration, and Duration of Effect Measurements).

These results indicate that the addition of simethicone as an anti-gas agent to Pepto-Bismol liquid will not affect the bioavailability of salicylates in Pepto-Bismol.

OBJECTIVE

One major stomach discomfort for which Pepto-Bismol does not have an indication is gas. Adding simethicone (an anti-gas active used by many antacids) to Pepto-Bismol is a possible way to pursue an anti-gas indication.

After in vitro foam-reduction testing, some formulations of Pepto-Bismol with simethicone performed almost identical as the pure emulsion of simethicone, suggesting that BSS does not interfere with the foam-reducing capacity of the simethicone active. Conversely, we must determine if the simethicone interferes with the performance of the BSS active. One measure involves conducting in vivo tests for blood salicylate levels in pentagastrin-stimulated dogs.

The purpose of this study was to establish blood salicylate profiles on pentagastrin-stimulated dogs dosed with Pepto-Bismol with and without simethicone to determine if the simethicone interferes with the absorption of salicylate in the bloodstream. Pentagastrin was used to stimulate gastric acid secretions in the dogs to make the dog gastric pH similar to that in humans.

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MATERIAL AND METHODS:

Experimental Design:

Type of Study: Bioavailability / Gastric pH

Species: Canine

Strain: Beagle

Source: Hazleton/LRE Research Animals, Kalamazoo, Michigan

Sex: Male

Initial Weight/Age: 12 Kg (average - all dogs over 11.0 kg) / Adult

Total Number of Animals Used: 29

Number of Animals per Group: *

- 1) Pepto-Bismol Control - 7 dogs
- 2) Pepto-Bismol with simethicone - Formulation A - 9 dogs
- 3) Pepto-Bismol with simethicone - Formulation B - 9 dogs
- 4) Water - 4 dogs

* Nine dogs were originally slated to be run in the Pepto-Bismol group. Two dogs had to be eliminated from the group because the product ran out.

Means of Animal Identification: Cage tag, Collar and tag, Ear tattoo

Housing: Off-Study: Individual chain link and concrete runs
During Study: Sling-type cots and individual stainless steel holding cages

Site and/or Location: BETF 790 Building, C Building, Room C-202

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Test Substances:

- 1) Pepto-Bismol Liquid Positive Control
Dose Form: Liquid
Total Dose per Animal: 34.7 mls
Dose Level of Active: 510 mg - bismuth subsalicylate, 14.7 mg/ml
Code or Lot Number/Expiration Date: HH-0736-18I
Special Handling Requirements: Room Temperature
Category: Drug/Food X Non-Food/Non-Drug ___ Both ___
- 2) Pepto-Bismol with AF Simethicone
Dose Form: Liquid
Total Dose per Animal: 26.42 mls
Dose Level of Active: 510 mg bismuth subsalicylate, 19.3 mg/ml
Code or Lot Number/Expiration Date: HH-0736-18D
Special Handling Requirements: Room Temperature
Category: Drug/Food X Non-Food/Non-Drug ___ Both ___
- 3) Pepto-Bismol with AF Simethicone
Dose Form: Liquid
Total Dose per Animal: 28.33 mls
Dose Level of Active: 510 mg bismuth subsalicylate, 18 mg/ml
Code or Lot Number/Expiration Date: HH-0736-18G
Special Handling Requirements: Room Temperature
Category: Drug/Food X Non-Food/Non-Drug ___ Both ___
- 4) Deionized Water - Negative Control
Dose Form: Liquid
Total Dose per Animal: 30 mls
Special Handling Requirements: Room Temperature
Category: Drug/Food ___ Non-Food/Non-Drug X Both ___

Route of Exposure: The water treatments were dosed by oral gavage via a foal feeding tube, 60 cc syringe, and plastic mouthpiece

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Test Methods:

Prior to the Study

On 2/10/92 (the day before the study), blood samples were taken from 10 of the dogs in this study for serum iron, hematocrit, hemoglobin, red blood cells, white blood cells, platelets, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin content analysis. Blood samples were collected from the same dogs three weeks later (on 3/9/92) for the same analyses. The purpose of this testing was to monitor the health of the dogs and to determine if blood levels return to normal in between multiple blood-sampling studies. This was done at the request of the Institutional Animal Care and Use Committee.

The blood samples were collected via jugular venipuncture into one 7 ml EDTA tube, and one 9.5 ml SST tube. The samples were delivered un-refrigerated to MVL and analyzed by the clinical pathology laboratory. The results will be discussed in a separate report.

PBDB# 14

Adult male dogs weighing over 11.0 kg were randomly allocated into 4 treatment groups. Four to six dogs were tested each day. The dogs were food-fasted for approximately 24 hours, and water-fasted for approximately 3 hours prior to being on-study. Baseline endoscopic examinations were done to ensure that the dogs have empty stomachs prior to dosing. Excess gastric fluid and mucus was removed from the dog stomachs during the baseline endoscopy to prevent the interference of these materials with pentagastrin-stimulated gastric secretions and product activity.

After the baseline endoscopy, the dog's necks were clipped and surgically scrubbed with Xenodyne^R (iodine-toned surgical scrub solution). Intravenous catheters were placed in the jugular veins, baseline blood samples were taken, and injection caps were used to close the tops of the catheters. Saline was used to keep the catheters free of blood clots during the experiment (approximately 1/2 cc injected into the catheter through the injection cap after every blood draw). The catheters were kept in place by taping the neck area with 2" adhesive bandage.

The dogs were placed into Pavlov-type sling coats (immediately after placement of the catheters) to facilitate pentagastrin infusion, gastric fluid collection and blood collection. Peptavlon^R pentagastrin (Ayerst Laboratories - Lot # 3910398, Exp. 1/93) was mixed with 500 mls 0.9% injectable sodium chloride solution (Abbott Laboratories) and administered to the dogs by subcutaneous infusion at 8 mcg/kg/hour (Abbott Venoset 60 infusion sets and 20g needles).

Gastric fluid samples were drawn 30 minutes after pentagastrin infusion was begun and every 5-15 minutes thereafter until the gastric pH dropped to baseline levels (pH < 2.0). The samples were collected using a 60cc syringe, size 14Fr Levin stomach tube, foal feeding tube, and plastic mouthpiece. Approximately 5 mls of gastric fluid was drawn from the stomach at each sample time. The fluid was discarded after pH measurement. A Radiometer American pH meter (Model PHM84) and Radiometer Copenhagen combined electrode (Model GK2713C) were used to measure pH on the gastric fluid samples.

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When the gastric pH reached baseline levels, the dogs were dosed once orally (via gavage) with the test substances. All treatments were given by oral gavage (foal feeding tube, 60 cc syringe, and plastic mouthpiece).

Blood samples were taken from the dogs at 15, 30, and 45 minutes, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, and 8 hours after dosing, for a total of 17 samples (including baseline). Approximately 6.5 cc blood was collected at each sample time (total approximately 110.5 mls). The first 1/2 cc fluid from the catheter (from each sample) was discarded to prevent the interference of the saline flush with salicylate results. The samples were collected from the catheters using 6 cc syringes and the blood was poured into 9.5 ml Vacutainer serum separator tubes (SST tubes).

The blood samples were centrifuged for approximately 15 minutes and then refrigerated until delivery to the diagnostic laboratory at Jewish Hospital, Cincinnati, Ohio. The samples were analyzed at Jewish Hospital for serum salicylate levels using an enzyme immuno assay methodology.

Pentagastrin infusion was continuous for the first 4 hours of the study. The dogs were kept in the Pavlov-type sling coats during the infusion period and then placed into holding cages for the remainder of the study. Subcutaneous "pockets" of the pentagastrin solution created by the infusion provided continuous administration of the pentagastrin for the rest of the study. (A previous study, PBDB# 11, showed that the gastric pH remains < 2.0 for at least up 6 hours after the infusion period.)

At the completion of the study (after the 8-hour blood sample was taken), the dogs were returned to their runs and fed.

The serum salicylate results were analyzed by the Newman-Keuls method of statistical analysis at the Biological Efficacy Testing Facility (BETF). The results are listed and discussed on the following pages.

RESULTS

Table 1

Summary of Serum Salicylate Levels (X mg/dl)

Treatment	Base- line	15 Min	30 Min	45 Min	1 Hr	1.25 Hrs	1.5 Hrs	1.75 Hrs	2 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	5 Hrs	6 Hrs	7 Hrs	8 Hrs	
Water	0.8	0.8	0.7	0.8	0.6	0.7	0.9	0.6	0.5	0.4	0.7	0.7	0.4	0.7	0.4	0.5	0.7	n=4
HM 0736 180	0.7	3.9	5.0	5.6	5.7	6.0	6.0	5.8	5.8	5.5	5.2	5.0	4.5	4.2	3.6	3.1	2.8	n=9
HM 0736 18G	0.8	4.6	5.8	6.0	6.2	6.4	6.6	6.1	6.1	5.8	5.3	5.2	4.6	4.2	3.4	3.1	2.9	n=9
Pepto Control	0.8	4.1	5.8	5.7	6.0	6.1	6.1	6.4	5.9	5.7	5.3	5.0	4.6	4.0	3.6	3.2	2.9	n=7

Treatment means within brackets are significantly different from those outside at α 0.05.

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Serum Salicylate Bioavailability

Tables I and II summarize the bioavailability of the products, as measured by serum salicylate levels in the bloodstream. The results are discussed below. The individual dog serum salicylate levels are listed in Attachment I and depicted in the attached graph.

Baseline

As seen in Table I, and the individual dog serum salicylate levels in Attachment I, there were no statistical differences in salicylate levels between any of the groups at baseline. All baseline serum salicylate levels were 0.7 - 0.8 mg/dl, indicating insignificant levels of salicylate in the bloodstream.

15 Minutes through 8 Hours Post-Dosing

As seen in Table I, and the individual dog serum salicylate levels in Attachment I, dogs, dosed with regular Pepto-Bismol liquid and the Pepto-Bismol/simethicone formulations produced significantly higher serum salicylate levels than dogs dosed with water between 15 minutes and 8 hours after dosing.

There were no statistical differences between the Pepto-Bismol treatments with and without simethicone in serum salicylate levels between 15 minutes and 8 hours after dosing in this study.

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The bioavailability of salicylates in the bloodstream after dosing with these products is summarized in Table II below. The individual dog results are listed in Attachment II. Bioavailability was determined by lag time, time-to-peak, peak concentration and duration-of-effect measurements.

Table II
 Summary of Serum Salicylate Bioavailability Results

\bar{X} Lag Time, Time-to-Peak, Peak Concentration, Duration-of-Effect Values

Treatment	Lag Time (Minutes)	Time-to-Peak (>3.0 mg/dl) (Hours)	Peak Salicylate Concentration (mg/dl)	Duration-of-Effect (>3.0 mg/dl) (Hours)
Water	480.0] +	8.0] +	1.1]	0.0] +
HH-0736-18D	15.0]	1.4]	6.2]	6.4] +
HH-0736-18G	15.0]	1.3]	6.9]	6.5] +
Pepto Control	15.0]	1.3]	6.6]	6.6] +

Treatment means within brackets are significantly different from those outside at $\alpha < 0.05$.

+ = minimum

Lag Time - Lag time is the length of time after dosing until significant (therapeutic) concentrations of salicylate are seen in the bloodstream (> 3.0 mg/dl). This measurement indicates the rate of bismuth subsalicylate (BSS) hydrolysis - the process by which bismuth and salicylate are released from the product to become bioavailable (absorbed into the bloodstream).

As seen in Table II above, the individual dog serum salicylate levels in Attachment I, and the individual lag time results in Attachment II, none of the dogs in the water group had significant serum salicylate levels (>3.0 mg/dl) during the study; therefore, their lag time values were equal to the length of the study - 480 minutes.

Dogs dosed Pepto-Bismol with and without simethicone exhibited significant levels of salicylate in the bloodstream within 15 minutes after dosing. There were no statistical differences between any of the Pepto-Bismol treatments (with or without simethicone) in the length of time it took for significant levels of salicylate to appear in the bloodstream.

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Time-to-Peak - Time-to-peak is the length of time it takes for salicylate levels to reach peak and significant (> 3.0 mg/dl) levels in the bloodstream.

As seen in Table II on the previous page, the individual dog serum salicylate levels in Attachment I, and the individual dog time-to-peak measurements in Attachment II, the dogs dosed with water did not exhibit significant levels of salicylates at any time during the study. Therefore, the time-to-peak values for the dogs dosed with water were equal to the length of the study (8 hours), and were significantly longer than those from any of the other products.

Salicylate levels in dogs dosed with Pepto-Bismol with and without simethicone peaked between 1.3 and 1.4 hours after dosing. There were no statistical differences between regular Pepto-Bismol and the two Pepto-Bismol treatments with simethicone in the time-to-peak values in this study.

Peak Concentration - Peak concentration is the highest level of serum salicylate found in the bloodstream over a course of time of interval sampling.

As seen in Table II on the previous page, the individual dog serum salicylate levels in Attachment I, and the individual dog peak salicylate levels in Attachment II, serum salicylate levels from dogs dosed with water remained in the baseline range (< 2.0 mg/dl) throughout the study. The peak serum salicylate levels from dogs dosed with water were significantly lower (1.1 mg/dl) than peak levels from all of the other dogs in the study.

Peak serum salicylate levels in dogs dosed with Pepto-Bismol with and without simethicone were 6.2 - 6.9 mg/dl, with no statistical differences between the treatments.

Duration-of-Effect - Duration-of-Effect is the length of time blood salicylate levels remain at significant (therapeutic) levels in the bloodstream (equal to or greater than 3.0 mg/dl) after dosing.

As seen in Table II on the previous page, the individual dog serum salicylate levels in Attachment I and the individual dog duration-of-effect results in Attachment II, none of the dogs in the water group had significant serum salicylate levels (>3.0 mg/dl) during the study; therefore, their duration-of-effect measurements were 0 hours.

The Pepto-Bismol treatments with and without simethicone produced significantly longer duration-of-effect values than dogs in the water group (at least 6.4 - 6.6 hours after dosing). There were no statistical differences between the regular Pepto-Bismol treatment or the Pepto-Bismol/simethicone groups in the duration-of-effect results in this study.

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DISCUSSION

Serum salicylate levels from the treatments were almost identical throughout the study. A statistical analysis of salicylate levels up to 8 hours after dosing the dogs showed that there were no significant differences ($\alpha 0.05$) between the Pepto-Bismol and Pepto-Bismol/simethicone treatments at the following measurements:

- at the individual sample times (15, 30, 45 minutes, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, and 8 hours after dosing - see Table I)
- in the speed of salicylates into the bloodstream (significant levels of salicylate were evident within 15 minutes of dosing in all of the dogs dosed with Pepto-Bismol with or without simethicone - see Lag Time values, Table II)
- in the length of time it took for salicylate levels to reach peak levels in the blood (salicylate levels in dogs dosed with Pepto-Bismol with and without simethicone peaked between 1.3 and 1.4 hours after dosing - see Time-to-Peak values, Table II)
- in the actual peak salicylate levels in the blood (peak salicylate levels in dogs dosed with Pepto-Bismol with and without simethicone ranged from 6.2 - 6.9 mg/dl - see Peak Concentration values, Table II)
- in the length of time salicylates remained at significant levels (> 3.0 mg/dl) in the bloodstream (salicylate remained at significant levels for at least 6.4 - 6.6 hours after dosing in dogs given Pepto-Bismol with and without simethicone - see Duration-of-Effect results, Table II)

CONCLUSION

Serum salicylate levels from Pepto-Bismol treatments with and without simethicone were almost identical throughout the study. These results indicate that the addition of simethicone (as an anti-gas agent) to Pepto-Bismol liquid will not affect the bioavailability of salicylates in Pepto-Bismol.

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Attachments

Graph - Serum Salicylate Levels

Attachment I - Individual Dog Serum Salicylate Levels

Attachment II - Individual Dog Lag Time, Time-to-Peak, Peak Concentration and Duration of Effect Measurements

cc. R. C. Lijana
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pedb#14re/10

ATTACHMENT I

PODS# 14 INDIVIDUAL DOG SERUM SALICYLATE LEVELS (mg/dl)

Treatment and Dog#	Base-line	15 Min	30 Min	45 Min	1 Hr.	1.25 Hrs.	1.5 Hrs.	1.75 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	4 Hrs.	5 Hrs.	6 Hrs.	7 Hrs.	8 Hrs.
A) Pepto-Bismol Positive Control (n=7)																	
1	0.5	<u>3.2</u>	4.7	4.5	5.3	5.0	4.9	<u>6.3</u>	5.7	5.6	5.3	4.9	4.9	4.2	3.3*	2.9	2.6
12	0.9	<u>3.6</u>	<u>3.8</u>	3.0	3.2	3.4	3.9	<u>4.3</u>	3.0	3.1	3.7	3.5*	2.4	2.6	1.6	1.3	1.7
17	0.7	<u>4.9</u>	<u>6.7</u>	6.0	6.3	6.2	6.0	6.3	5.8	5.9	5.4	4.0	4.8	4.0	3.7	3.3*	2.6
21	0.6	<u>3.7</u>	6.3	6.8	7.1	<u>7.4</u>	7.1	7.1	7.1	6.3	5.5	5.9	6.0	4.4	4.5	4.3	3.6
25	0.7	<u>6.6</u>	6.5	<u>6.8</u>	6.5	6.6	6.5	<u>6.6</u>	6.5	5.7	5.1	5.0	4.6	3.8	3.4*	2.7	2.6
30	1.3	<u>3.6</u>	5.6	5.8	6.5	<u>7.0</u>	7.0	<u>7.4</u>	6.4	6.6	6.2	6.1	4.2	3.9	3.8	3.6	3.1
34	0.7	<u>3.6</u>	6.7	7.2	7.3	<u>7.6</u>	7.1	7.1	7.1	7.0	5.8	5.9	5.4	5.0	4.9	4.4	4.1
X=	0.8	4.1	5.8	5.7	6.0	6.1	6.1	6.4	5.9	5.7	5.3	5.0	4.6	4.0	3.6	3.2	2.9
	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7	n=7
B) Pepto-Bismol with AF Simethicone HH-0736-18D (n=9)																	
2	0.5	<u>3.9</u>	4.4	4.4	5.0	<u>5.2</u>	4.7	4.9	5.0	4.3	4.5	4.2	3.4	3.1*	2.6	2.1	1.6
8	0.6	<u>4.0</u>	5.8	<u>6.2</u>	5.5	<u>6.1</u>	6.2	6.1	5.7	5.8	5.6	5.3	3.9	3.4*	2.7	2.1	2.7
13	1.1	<u>3.2</u>	7.4	7.8	8.2	<u>9.3</u>	9.0	8.3	<u>8.8</u>	7.6	8.0	7.8	6.3	6.3	5.0	4.5	5.0
18	0.8	<u>3.2</u>	4.7	6.3	6.9	6.7	6.9	7.1	<u>7.2</u>	<u>6.3</u>	5.7	6.0	5.8	4.9	4.7	4.3	3.6
22	0.6	<u>3.6</u>	3.2	4.6	4.8	4.7	5.1	5.1	5.1	<u>5.2</u>	4.7	4.1	4.2	3.1*	2.7	2.4	1.9
26	0.6	<u>3.1</u>	3.9	4.3	4.5	4.7	<u>4.8</u>	4.7	4.6	4.2	3.8	3.5	3.7	3.2*	2.8	2.7	2.2
35	0.8	<u>4.6</u>	<u>5.4</u>	5.1	4.8	5.2	5.1	4.9	4.7	5.0	4.6	4.7	4.3	4.5	4.3	3.6	3.1
37	0.7	<u>3.4</u>	4.9	<u>5.5</u>	5.4	5.0	5.0	5.1	4.5	4.9	4.4	4.5	4.3	4.3	3.7	3.1*	2.5
41	0.8	<u>4.0</u>	5.5	6.4	6.2	6.8	<u>6.9</u>	6.4	6.4	6.3	5.7	5.3	5.0	4.6	3.5	3.4*	2.9
X=	0.7	3.9	5.0	5.6	5.7	6.0	6.0	5.8	5.8	5.5	5.2	5.0	4.5	4.2	3.6	3.1	2.8
	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9
C) Pepto-Bismol with AF Simethicone HH-0736-18G (n=9)																	
3	0.7	<u>5.1</u>	5.9	<u>6.2</u>	5.9	5.7	5.8	6.0	5.9	5.4	5.2	4.9	4.3	4.0*	2.7	2.3	1.9
9	1.0	<u>5.7</u>	7.4	<u>7.2</u>	6.8	6.6	7.1	6.7	5.4	4.7	5.3	4.8	3.9	3.7*	2.0	2.0	2.6
15	1.0	<u>3.6</u>	5.0	4.6	5.3	6.6	<u>6.9</u>	5.3	6.4	5.5	5.7	5.5	4.8	4.5	3.1	3.2	3.3
19	0.8	<u>5.1</u>	5.3	5.2	<u>5.9</u>	5.6	5.6	5.8	5.3	<u>4.5</u>	3.9	3.9	3.7	3.0*	2.7	2.0	1.9
28	0.6	<u>3.3</u>	4.8	5.3	5.8	6.4	<u>6.8</u>	6.8	6.8	<u>7.9</u>	6.9	6.7	5.2	4.7	4.3	3.9	3.3
29	1.3	<u>4.2</u>	5.9	5.6	5.9	5.7	<u>6.4</u>	5.7	6.0	5.3	4.6	4.1*	2.8	2.6	2.5	2.0	1.7
36	0.6	<u>3.4</u>	5.1	5.9	6.0	6.2	<u>6.3</u>	6.1	6.1	6.3	5.7	5.5	5.3	5.0	4.7	3.9	3.7
39	0.8	<u>5.5</u>	8.4	8.7	<u>8.8</u>	8.6	<u>8.2</u>	6.0	7.5	6.9	6.1	6.6	6.0	5.7	5.5	4.9	4.4
62	0.4	<u>3.1</u>	4.6	5.0	<u>5.2</u>	5.8	<u>6.2</u>	6.2	5.6	5.5	4.2	4.8	5.1	5.0	3.3	3.4	3.2
X=	0.8	4.6	5.8	6.0	6.2	6.4	6.6	6.1	6.1	5.8	5.3	5.2	4.6	4.2	3.4	3.1	2.9
	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9	n=9
D) Deionized Water (n=9)																	
6	0.8	0.8	0.8	<u>1.2</u>	0.8	1.0	<u>0.6</u>	0.5	0.8	0.5	0.7	0.7	0.3	0.5	0.3	0.2	0.2
11	0.9	1.0	1.1	<u>1.1</u>	0.5	0.5	<u>1.3</u>	1.1	0.2	0.3	1.0	1.1	0.4	0.6	0.2	0.5	0.7
16	0.9	<u>1.0</u>	0.6	0.6	0.5	1.0	1.0	0.2	0.1	0.3	1.0	1.0	0.1	0.7	0.2	0.2	0.7
20	0.6	<u>0.5</u>	0.2	0.2	0.6	0.2	0.5	0.7	0.7	0.6	0.2	0.9	0.8	0.8	0.9	<u>1.0</u>	1.0
X=	0.8	0.8	0.7	0.8	0.6	0.7	0.9	0.6	0.5	0.4	0.7	0.7	0.4	0.7	0.4	0.5	0.7
	n=6	n=4	n=4	n=4	n=4	n=4	n=4	n=4	n=4								

Levels > 3.0 mg/dl are considered significant (therapeutic levels). Peak levels are circled.

Levels > 3.0 mg/dl are used for Lag Time, Time-to-Peak and Duration of Effect Measurements.

— Lag Time ○ Time-to-Peak ○ Peak Concentration * Duration-of-Effect

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ATTACHMENT II

Individual Dog Lag Time, Time-to-Peak, Peak Concentration and Duration of Effect Measurements *

Treatment and Dog#	Lag Time (Minutes)	Time-to-Peak over 3.0 mg/dl (Hours)	Peak Concentration (mg/dl)	Duration of Effect over 3.0 mg/dl (Hours)
A) Pepto-Bismol Positive Control (n=7)				
1	15.0	1.8	6.3	6.0
12	15.0	1.8	4.3	3.5
17	15.0	0.5	6.7	7.0
21	15.0	1.3	7.4	8.0 +
25	15.0	0.8	6.8	6.0
30	15.0	1.8	7.4	8.0 +
34	15.0	1.3	7.4	8.0 +
X=	15.0	1.3	6.6	6.6 +
B) Pepto-Bismol with AF Simethicone (MN-0736-18D) (n=9)				
2	15.0	1.3	5.2	5.0
8	15.0	1.0	6.2	5.0
13	15.0	1.3	9.3	8.0 +
18	15.0	2.0	7.2	8.0 +
22	15.0	2.5	5.2	5.0
26	15.0	1.5	4.8	5.0
35	15.0	0.5	5.4	8.0 +
37	15.0	0.8	5.5	7.0
41	15.0	1.5	6.9	7.0
X=	15.0	1.4	6.2	6.4 +
C) Pepto-Bismol with AF Simethicone (MN-0736-18G) (n=9)				
3	15.0	0.8	6.2	5.0
9	15.0	0.8	7.6	5.0
15	15.0	1.5	6.9	8.0 +
19	15.0	1.0	5.9	5.0
28	15.0	2.5	7.9	8.0 +
29	15.0	1.5	6.4	3.5
36	15.0	1.5	6.3	8.0 +
39	15.0	1.0	8.8	8.0 +
62	15.0	1.5	6.2	8.0 +
X=	15.0	1.3	6.9	6.5 +
D) Deionized Water (n=4)				
6	480.0 +	8.0 +	1.2	0.0
11	480.0 +	8.0 +	1.3	0.0
14	480.0 +	8.0 +	1.0	0.0
20	480.0 +	8.0 +	1.0	0.0
X=	480.0	8.0 +	1.1	0.0

* See report for category explanations
+ = minimum time

- Pepto-Bismol Control
- HH-0736-18D
- ▲ HH-0736-18G
- + Deionized Water

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