

HEALTH AND PERSONAL CARE DIVISION CLINICAL STUDY REPORT
CLINICAL OPERATIONS & BIOMETRICS -- HEALTH PROJECTS

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November 11, 1987

MAXIMUM-STRENGTH PEPTO-BISMOL
CROSSOVER BIOAVAILABILITY STUDY
(PB-118 -- ORC Study No. 996)

Test Materials

Maximum-Strength Pepto-Bismol Liquid, D-0471
(alias: Extra-Strength, Pepto-Bismol Concentrate)
Regular Strength Pepto-Bismol Liquid, D-0368

Investigators

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Key Findings

As indicated by post-dosing urinary bismuth excretion, the total amount of bismuth absorbed from the the Regular Strength and Maximum-Strength Pepto-Bismol formulations were found to be equivalent. Moreover, comparing urinary bismuth excretion to bismuth ingestion, less than 0.005% of the ingested bismuth was absorbed.

With regard to salicylate absorption, significantly more salicylic acid was found in the plasma and significantly more salicylic acid and salicyluric acid were voided in the urine after dosing with Regular Pepto-Bismol than after dosing with the Maximum-Strength formulation. The observed differences are similar in magnitude to the difference in total salicylate content (including excipients) of the two formulations. Salicylate recovery was 78% for Regular and 81% for Maximum-Strength.

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Protocol Abstract

An 8-day bioavailability study comparing the plasma and urine salicylate profiles and the blood and urine bismuth profiles of two bismuth subsalicylate formulations was conducted among 16 healthy, male volunteers. The study was conducted at Quincy Research Center between September 23, 1985 and November 18, 1985 according to a randomized, crossover design. Following an overnight fast, each subject was administered either 8 doses (30 mL/dose) of regular Pepto-Bismol Liquid at half-hour intervals, or 4 doses (30 mL/dose) of Maximum-Strength Pepto-Bismol Liquid at one-hour intervals. Both regimens resulted in a total intake of 4.2 g of bismuth subsalicylate. Blood bismuth (Bi) concentrations were determined in whole blood samples taken over the 36 hours following initial medication ingestion. The amount of Bi absorbed was determined from consecutive 12-hour or 24-hour pooled collections of urine taken over 8 days following ingestion. Similarly, salicylic acid (SA) concentrations were determined in plasma samples collected over 36 hours, and total salicylate (salicylic acid and salicyluric acid) absorbed was determined from pooled urine collections over 8 days following ingestion. A 6-day washout period followed the 8-day collection period for the first medication before dosing the second medication. Further details of the study logistics can be obtained from the Investigator's Final Report or the PB-118 Protocol, both in Appendix I.

Protocol Deviations

As discussed on page 10 of the Investigator's Final Report (Appendix I), there were three logistic departures from the protocol. First, three subjects were entered into the study whose body weights were 1-2 kg below the specified minimum. Second, due to subject withdrawals, a total of 18 rather than 16 subjects participated in the study. Third, three blood samples were collected five or more minutes later than specified. These departures are deemed minor and are judged unlikely to affect the bioavailability comparison.

In addition, due to samples being lost in transit or lost during the assay procedure, SA/SU concentrations were not measured in five plasma samples and in three urine samples (identified in the table below). Loss of these individual values is also judged unlikely to affect the bioavailability comparison.

<u>Sample</u>	<u>Medication</u>	<u>Subj Number</u>	<u>Time</u>
Plasma	Maximum-Strength	9	0.5 hr
	Regular Strength	13	Baseline
	Maximum-Strength	13	1.0, 1.5, 2.0 hr
Urine	Maximum-Strength	1	6, 7, 8-day

Clinical Supplies

The Maximum-Strength formulation used in this study was manufactured by The Procter & Gamble Company, Cincinnati, Ohio; the Regular Strength formulation was manufactured by Norwich Eaton Pharmaceuticals Inc., Norwich, New York. The formulations were prepared to be as identical as possible in color and flavor and were packaged in identical amber, glass bottles. Subject number assignments to the medication orders were randomly determined (in blocks of two) by a computer program. Each subject was assigned one sixteen-ounce bottle of each formulation for use during the study.

Subject Accountability

Eighteen (18) subjects participated in this study with only 16 completing the entire trial. One subject withdrew for personal reasons after the 6-hour blood draw on day 1 of the first medication (Regular Pepto-Bismol); the other subject withdrew for unknown personal reasons on day 6 post-dosing of the second medication (Maximum-Strength Pepto-Bismol). Therefore, side effects associated with Regular Pepto-Bismol were evaluated in 18 subjects, and side effects associated with Maximum-Strength Pepto-Bismol were evaluated in 17 subjects. The withdrawals are also documented on page 10 of the Investigator's Final Report (Appendix I), but the times of the mid-study withdrawals are incorrectly described as "between treatment periods."

Clinical Complaints

As documented on page 11 and in Appendix M of the Investigator's Final Report (Appendix I of this report), several subjects reported clinical symptoms during the trial. All but three complaints were judged by the investigators to have no relationship to the test medications. These three are summarized in the following table.

<u>Subj</u>	<u>Symptom</u>	<u>Medication</u>	<u>Onset</u>		<u>Duration</u>	<u>Relationship</u>
			<u>Day</u>	<u>Time</u>		
4	Heartburn	Regular	1	2400	5 hrs	Possible
8	Nausea	Maximum	3	1820	6 hrs	Possible
10	Wozy	Maximum	2	2150	6.5 hrs	Remote

The following quote from page 15 of the Investigator's Final Report (Appendix I) gives the Investigator's interpretation of the relevance of these complaints.

"...none of the symptoms were felt to be clinically significant and none warranted medical intervention or early termination from study participation."

Analytical Techniques

Bismuth (Bi)

All Bi assays were performed at The Procter & Gamble Company using an HGAAS (Hydride Generation Atomic Absorption Spectroscopy) technique. Instructions for sampling, storage and shipping the blood and urine specimens used for Bi analysis are given in Appendix III. Whole blood samples were obtained using Vacutainer Trace Metal Tubes (Navy-colored stoppers) containing sodium heparin. Assay method sensitivity was 5 ppb in blood and 1 ppb in urine. The statistical analysis results were reported in terms of ppb (ng/ml) of Bi in the blood, and total mcg of Bi voided in the urine. A value of 0 was used in the statistical analysis for all samples yielding non-detectable concentrations.

Salicylate (SA and SU)

All salicylate assays (both SA and SU) were performed at Kansas City Analytical Services using an HPLC (High Pressure Liquid Chromatography) technique. Plasma samples were obtained using Vacutainers (Gray-colored stoppers) containing potassium oxalate and sodium fluoride. Assay results for both plasma and urine were reported in terms of mcg/ml; the method sensitivity was 5.00 mcg/ml for SA in plasma, 0.50 mcg/ml for SA in urine and 2.00 mcg/ml for SU in urine. A value of 0 was used in the statistical analysis for all samples yielding non-detectable concentrations. Listings of the raw data, standard curve summaries and other associated analytical data are given in Appendix IV.

Data Handling

Only the 16 subjects who completed the entire study were included in the statistical analysis of the bioavailability parameters. Statistical treatment of the data was performed using Release 5.08 of SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC) at The Procter & Gamble Company. IBM SAS data files were constructed and used for storage of all information.

Statistical Analysis

The following parameters were analyzed using both conventional Analysis of Variance techniques for crossover designs and

nonparametric Wilcoxon 2-sample tests. Statistical significance was defined as a two-sided p-level of 0.05 or less. Due to occasional missing assay values in the analyses, the results are reported using the LSMeans (Least Squares Means) which adjust for the imbalance.

Bismuth (Bi)

Whole Blood: Since no bismuth was detected in any blood samples collected after subjects were dosed with the test medications, these data were not statistically analyzed. (Two bismuth levels above the detection limit were found, however, in the pre-dose blood samples.)

- Urine:
- 1) Total Bi voided during the 8-day (192-hour) post-dose sampling period.
 - 2) Amount of Bi voided during the -12-0 hr pre-dose period and during each of the following pooled collection periods: 0-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 and 168-192 hrs.

Salicylic Acid (SA)

- Plasma:
- 1) AUC 0-36: Area under the concentration-time curve through the first 36 hours after initial medication ingestion.
 - 2) Cmax: maximum observed concentration.
 - 3) Tmax: time of Cmax.
 - 4) Plasma concentrations at each sampling time point.

- Urine:
- 1) Total SA voided during the 8-day (192-hour) post-dose sampling period.
 - 2) Amount of SA voided during the -12-0 hr pre-dose period and during each of the following pooled collection periods: 0-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 and 168-192 hrs.

Salicyluric Acid (SU)

- Urine:
- 1) Total SU voided during the 8-day (192-hour) post-dose sampling period.
 - 2) Amount of SU voided during the -12-0 hr pre-dose period and during each of the following pooled collection periods: 0-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 and 168-192 hrs.

Results

> Bismuth (Bi)

Whole Blood: Table 1 presents summary statistics for the whole blood Bi assays. As stated above, no statistical analysis of these data was performed.

Urine: Table 2a displays summary statistics for the urine Bi assays. Although the amount of Bi voided with the Maximum-Strength formulation is greater than the Regular Strength formulation (in total and during most of the individual collection periods), the differences are not statistically significant. Further investigation reveals three subjects (#6, #1003 and #1004) who exhibited large differences in Bi excretion values between the two test medications. This can be seen in the table below.

<u>Subject</u>	<u>Total Bi Voided (mcg)</u>			<u>Average</u>	<u>Percentage*</u>
	<u>Max. Str.</u>	<u>Regular</u>	<u>Difference</u>		
2	119	73	46	96	48%
3	60	30	30	45	67%
4	89	38	51	63.5	80%
5	116	88	28	102	27%
6	55	188	-133	121.5	109%
7	88	61	27	74.5	36%
8	37	55	- 18	45.5	40%
9	46	69	- 23	57.5	40%
10	85	86	- 1	85.5	1%
11	79	141	- 62	110	56%
12	83	50	33	66.5	50%
13	47	42	5	44.5	11%
14	57	82	- 25	69.5	36%
16	50	70	- 20	60	33%
1003	311	47	264	179	147%
1004	296	79	217	187.5	116%

* Percentage = difference/average Bi voided x 100%

The following procedures were undertaken to investigate these three subjects. First, the testing facility was contacted to determine if there was a possible dosing error, but all dosing records indicate this was not the case. Second, the plasma and urine salicylate measurements for these subjects were inspected and found to be comparable to the other subjects (also indicating correct dosing). Next, the raw data from the Bi assays were investigated and, again, nothing was found which accounts for the suspect

values. The samples in question were analyzed at the same time as samples from several other subjects whose values do not appear aberrant.

One common condition among these three subjects, however, was found. The drug administration schedule (Appendix H of the Investigator's Final Report) shows that they were the only ones participating on October 30, 1985. This time corresponds to the test period for Maximum-Strength Pepto-Bismol for subjects 1003 and 1004 and Regular Strength Pepto-Bismol for subject 6 (the three suspect values in the table above). Nothing else in the study records was found, however, which explains why the "off-phase" participation would account for the apparent inconsistency.

Although no definitive reasons for deleting the suspect data were uncovered, summary statistics on the urine Bi assays without subjects 6, 1003 and 1004 were calculated to determine the extent of their influence on the results. These data are presented in Table 2b and show a numerically negligible as well as statistically non-significant difference in the total amount of Bi voided in the urine after dosing with the two test medications. Although statistically significant differences were observed between the formulations on days 4 and 6, the isolated nature of these differences makes interpretation difficult.

The average Urine Bi excretion values and the range of observed values are presented graphically in Figures 1 and 2 for the entire data set, and in Figures 3 and 4 for the supplemental data base excluding subjects 6, 1003 and 1004.

Salicylic Acid (SA)

Plasma: Results of the plasma SA analyses comparing AUC 0-36 hr, Cmax and Tmax values are given in Table 3a. These analyses indicate that these pharmacokinetic parameters are not statistically different after dosing with either of the two test medications. The area under the concentration-time curve for Regular Pepto-Bismol is "directionally" greater than the area under the curve for Maximum-Strength Pepto-Bismol. The difference of 6.1% between the AUC values is likely due to differences in the total salicylate content between the formulations. There was approximately 15% more salicylate administered with the Regular Strength formulation than with the Maximum-Strength formulation tested in this study.

Results of the analyses comparing the plasma SA concentrations at each sampling time point are given in Table 3b and shown graphically in Figure 5. These analyses indicate that dosing with the Regular Strength formulation produces greater plasma SA concentrations than does dosing with the Maximum-Strength formulation. The concentration is significantly ($p < 0.05$) greater at the 3-hr and 4-hr sampling times, and "directionally" ($p < 0.10$) greater at the 2-hr, 5-hr and 10-hr sampling times. Again, these differences are likely attributable to the 15% difference in total salicylate between the two formulations.

Urine: Results of the analyses comparing the total SA voided during the 192-hour observation period and the amount of SA voided during each sampling interval and are summarized in Table 4. These results show that more SA was voided in the urine after dosing with the Regular Strength formulation than after dosing with the Maximum-Strength formulation. Statistically significant ($p < 0.05$) differences are observed a) throughout the study (0-192 hours) and b) during the first 12 hours after ingestion. These differences (14% and 19%, respectively) are similar to the 15% difference in total salicylate content between the formulations.

Salicyluric Acid (SU)

Urine: Results of the analyses comparing the total SU voided during the 192-hour observation period and the amount of SU voided during each sampling interval and are summarized in Table 5. Although the results show that more SU was voided in the urine after dosing with the Regular Strength formulation than after dosing with the Maximum-Strength formulation, the differences are not statistically significant ($p < 0.05$). As with the SA, however, the observed differences (9% to 12%) are similar to the 15% difference in total salicylate content between the formulations.

Discussion

As indicated by post-dosing urinary bismuth excretion, the total amount of bismuth absorbed from the the Regular Strength and Maximum-Strength Pepto-Bismol formulations were found to be equivalent. Moreover, when the greatest total urinary bismuth excretion value (101 mcg for Maximum Strength) is compared to the 2.46 g of bismuth administered, less than 0.005% of the ingested bismuth was absorbed.

With regard to salicylate absorption, significantly more SA was found in the plasma and in the urine while directionally more SU was found in the urine after dosing with Regular Pepto-Bismol than after dosing with the Maximum-Strength formulation. The observed differences are similar in magnitude to the difference in total salicylate (including excipients) between the two formulations. Salicylate recovery was 78% for Regular Strength (397 mg SA and 1239 mg SU versus 2104 mg administered), and 81% for Maximum-Strength (341 mg SA and 1127 mg SU versus 1816 mg administered).

Prepared by: T. K. Balm 11/13/87
T. K. Balm

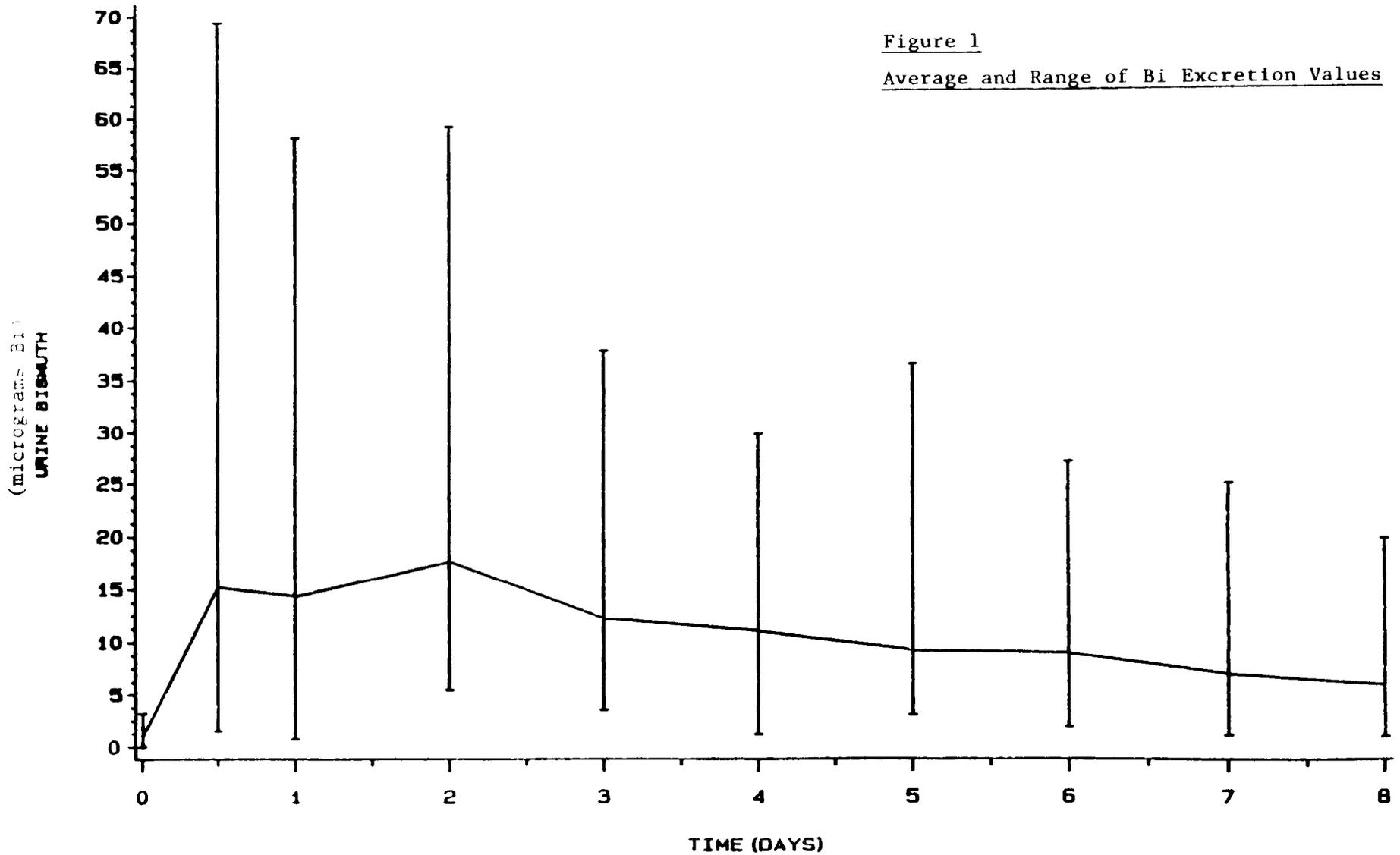
Approved by: J. B. Lucas, M.D. 11/23/87
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Approved by: D. Ws. Bierer 11/23/87
D. Ws. Bierer

PB116 BIOAVAILABILITY STUDY
AVERAGE URINARY BISMUTH CONCENTRATION
TRT-MAX STRENGTH

Figure 1

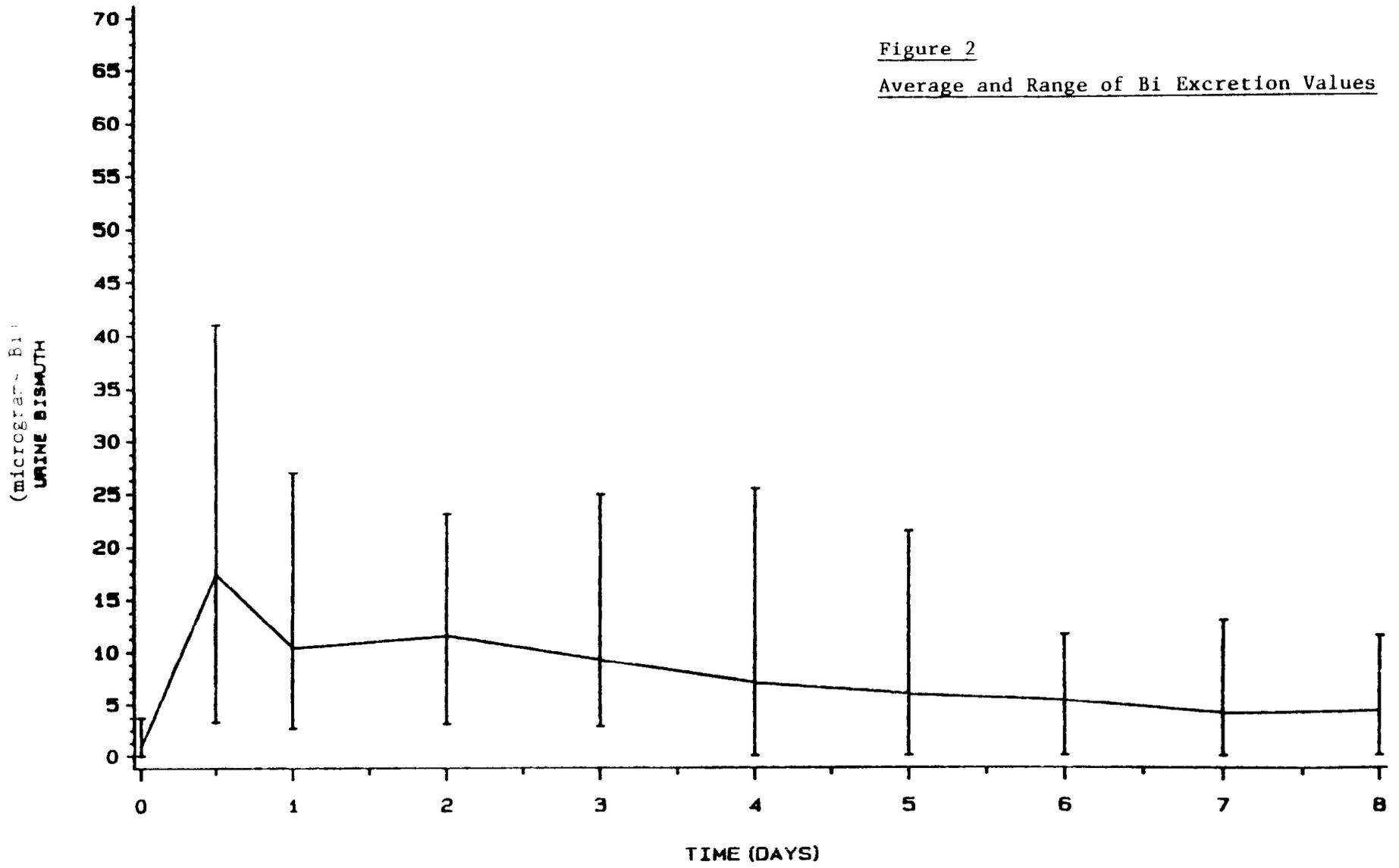
Average and Range of Bi Excretion Values



PB118 BIOAVAILABILITY STUDY
AVERAGE URINARY BISMUTH CONCENTRATION
TRT-REG STRENGTH

Figure 2

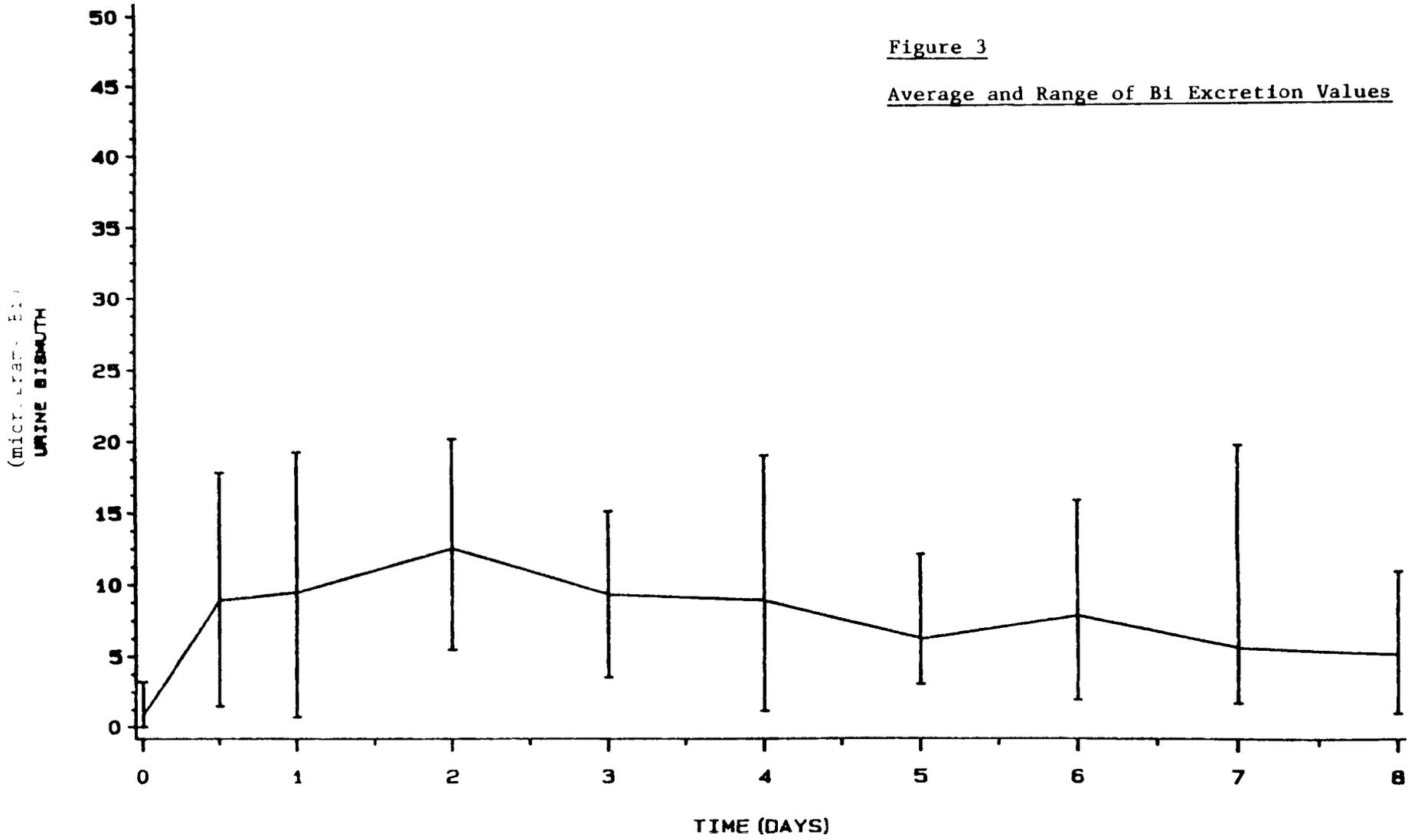
Average and Range of Bi Excretion Values



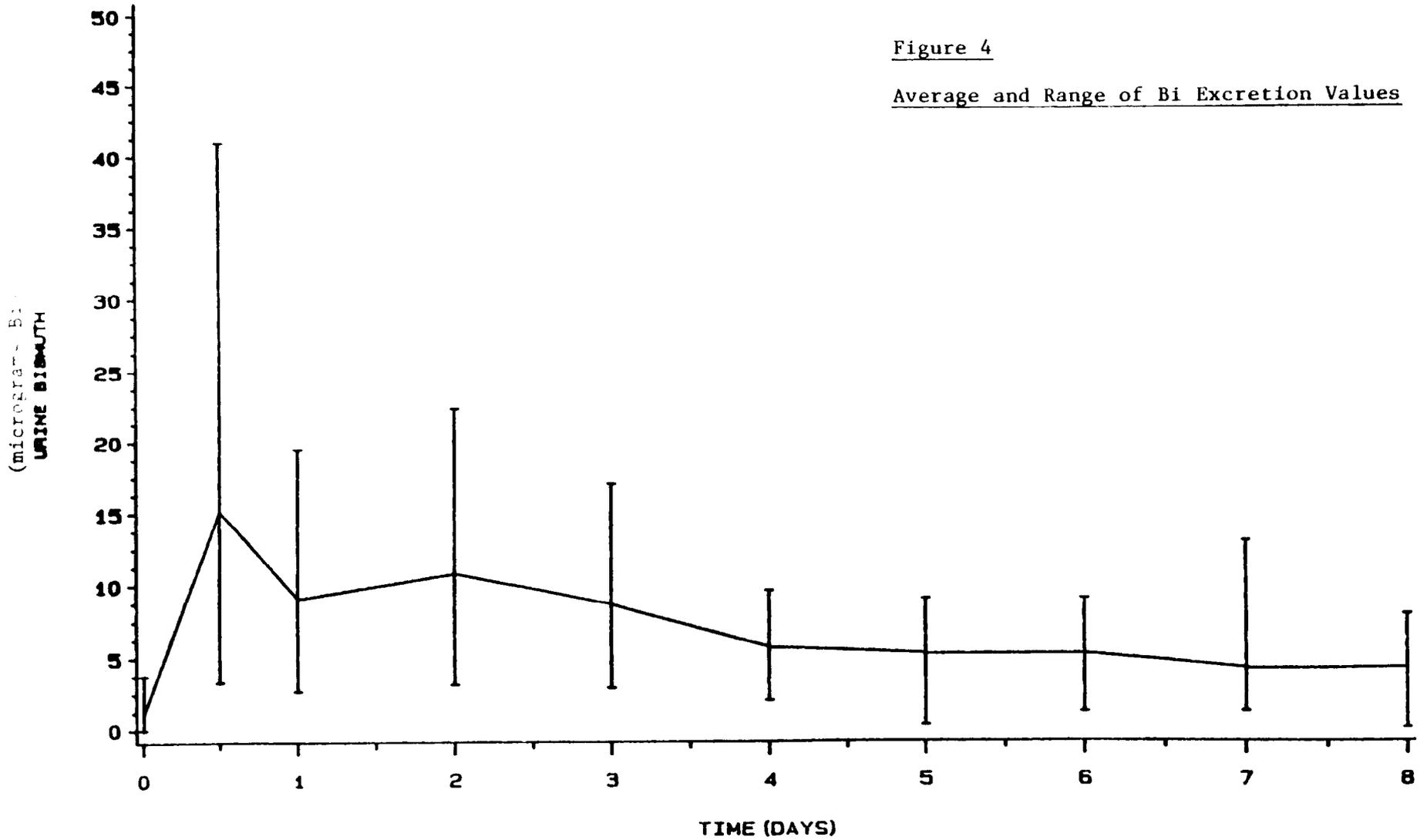
PB118 BIOAVAILABILITY STUDY
AVERAGE URINARY BISMUTH CONCENTRATION
DELETING SUBJECTS 6, 1003, 1004
TRT-MAX STRENGTH

Figure 3

Average and Range of Bi Excretion Values



**PB118 BIOAVAILABILITY STUDY
AVERAGE URINARY BISMUTH CONCENTRATION
DELETING SUBJECTS 6, 1003, 1004
TAT-REG STRENGTH**



PB118 BIOAVAILABILITY STUDY
AVERAGE PLASMA SALICYLIC ACID CONCENTRATION

Figure 5

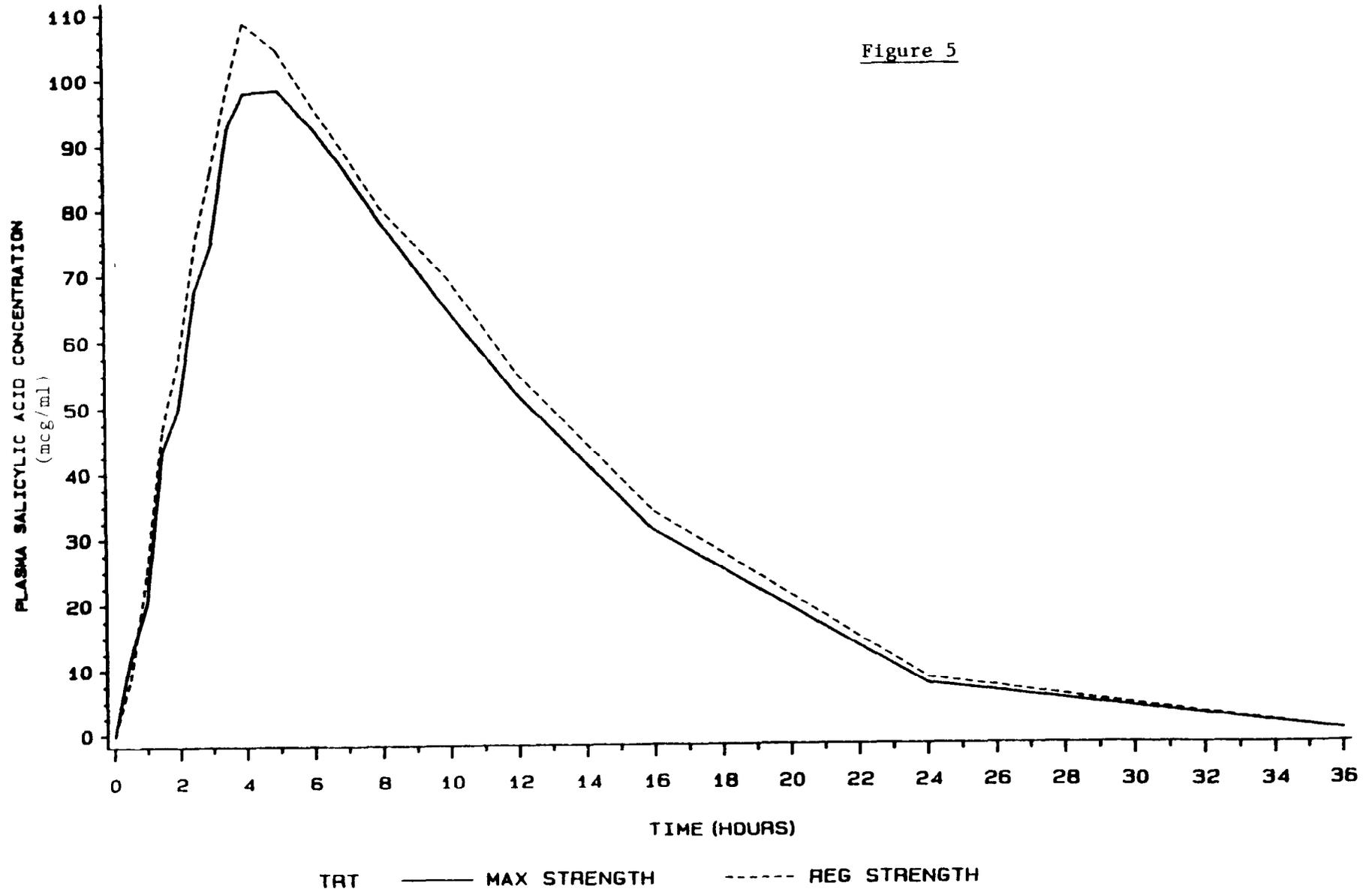


Table 1
Results of Whole Blood Bi Assays

<u>Sample Time</u>	<u>Treatment</u>	<u>Sample Size</u>	<u>Subjects with Detectable Bi Concentration</u>	<u>Concentrations (ppb)</u>		
				<u>Maximum</u>	<u>Median</u>	<u>Average</u>
0-hr	Max. Str.	16	2	9	<5	0.8
	Regular	16	0	<5	<5	0.0
4-hr	Max. Str.	16	0	<5	<5	0.0
	Regular	16	0	<5	<5	0.0
8-hr	Max. Str.	16	0	<5	<5	0.0
	Regular	16	0	<5	<5	0.0
12-hr	Max. Str.	16	0	<5	<5	0.0
	Regular	16	0	<5	<5	0.0
36-hr	Max. Str.	16	0	<5	<5	0.0
	Regular	16	0	<5	<5	0.0

Note: To compute average concentrations, a value of 0 was used for all assays below the detection limit of 5 ppb.

Table 2a
Results of Urine Bi Assays

<u>Sample Period</u>	<u>Treatment</u>	<u>Sample Size</u>	<u>Micrograms of Bi Voided</u>				<u>p-level</u>	<u>Cumulative Amount</u>	<u>Percent of total</u>
			<u>Min</u>	<u>Max</u>	<u>Median</u>	<u>Average</u>			
Total	Max. Str.	16	37	311	81	101			
(0-192 hrs)	Regular	16	30	188	70	75	0.30		
-12-0 hrs	Max. Str.	16	0	3	1	1			
(Pre)	Regular	16	0	4	1	1	0.92		
0-12 hrs	Max. Str.	16	1	69	10	15		15	15%
	Regular	16	3	41	16	17	0.63	17	23%
12-24 hrs	Max. Str.	16	1	58	9	14		29	29%
	Regular	16	3	27	9	10	0.35	28	37%
24-48 hrs	Max. Str.	16	5	59	13	18		47	47%
	Regular	16	3	23	11	11	0.19	39	52%
48-72 hrs	Max. Str.	16	3	38	10	12		59	59%
	Regular	16	3	25	8	9	0.34	48	64%
72-96 hrs	Max. Str.	16	1	30	10	11		70	69%
	Regular	16	0	25	5	7	0.19	55	74%
96-120 hrs	Max. Str.	16	3	37	7	9		79	79%
	Regular	16	0	21	6	6	0.25	61	82%
120-144 hrs	Max. Str.	16	2	27	8	9		88	87%
	Regular	16	0	12	5	5	0.09	67	89%
144-168 hrs	Max. Str.	16	1	25	4	7		95	94%
	Regular	16	0	13	4	4	0.17	71	94%
168-192 hrs	Max. Str.	16	1	20	4	6		101	100%
	Regular	16	0	11	4	4	0.25	75	100%

Note: p-level refers to the statistical comparison of the average amount (mcgs) Bi voided during the specified sample period.

Table 2b
Results of Supplemental Urine Bi Assays
Deleting Subjects 6, 1003 and 1004

<u>Sample Period</u>	<u>Treatment</u>	<u>Sample Size</u>	<u>Micrograms of Bi Voided</u>				<u>p-level</u>	<u>Cumulative Amount</u>	<u>Percent of total</u>
			<u>Min</u>	<u>Max</u>	<u>Median</u>	<u>Average</u>			
Total (0-192 hrs)	Max. Str.	13	37	119	79	73	0.66		
	Regular	13	30	141	69	69			
-12-0 hrs (Pre)	Max. Str.	13	0	3	1	1	0.60		
	Regular	13	0	4	1	1			
0-12 hrs	Max. Str.	13	1	18	8	9	0.07	9	12%
	Regular	13	3	41	13	15		15	22%
12-24 hrs	Max. Str.	13	1	19	9	9	0.99	18	25%
	Regular	13	3	19	8	9		24	35%
24-48 hrs	Max. Str.	13	5	20	13	12	0.40	30	42%
	Regular	13	3	22	10	11		35	51%
48-72 hrs	Max. Str.	13	3	15	8	9	0.80	39	54%
	Regular	13	3	17	9	9		44	64%
72-96 hrs	Max. Str.	13	1	19	9	9	0.04	48	66%
	Regular	13	2	10	5	6		50	73%
96-120 hrs	Max. Str.	13	3	12	6	6	0.45	54	74%
	Regular	13	0	9	6	5		55	80%
120-144 hrs	Max. Str.	13	2	16	8	8	<0.05	62	85%
	Regular	13	1	9	5	5		60	88%
144-168 hrs	Max. Str.	13	2	20	4	6	0.38	68	93%
	Regular	13	1	13	4	4		65	94%
168-192 hrs	Max. Str.	13	1	11	4	5	0.36	73	100%
	Regular	13	0	8	4	4		69	100%

Note: p-level refers to the statistical comparison of the average amount (mcgs) Bi voided during the specified sample period.

TABLE 3a

Results of Plasma SA Pharmacokinetic Parameter Analyses

<u>Parameter</u>	<u>Maximum Strength</u>	<u>Regular Strength</u>	<u>p-value</u>
Sample Size	16	16	
AUC 0-36 (mcg hr/ml)	1206.25	1284.45	0.08
Cmax (mcg)	106.58	110.47	0.21
Tmax (hrs)	4.19	4.22	0.89

TABLE 3b

Results of Plasma SA Sampling Time Analyses

<u>Sampling Time</u>	<u>SA Concentration (mcg/ml)</u>		<u>p-value</u>
	<u>Maximum Strength</u>	<u>Regular Strength</u>	
Sample Size	16	16	
0-hr	0.00	0.00	----
0.5-hr	12.04	8.96	0.40
1.0-hr	20.73	25.43	0.17
1.5-hr	43.33	47.32	0.55
2.0-hr	48.16	57.10	0.06
2.5-hr	67.33	74.11	0.15
3.0-hr	74.84	85.43	<0.01
3.5-hr	93.54	98.24	0.29
4.0-hr	98.54	108.71	0.02
5.0-hr	99.73	104.74	>0.05
6.0-hr	93.51	96.14	0.36
7.0-hr	86.57	88.45	0.35
8.0-hr	78.61	79.95	0.59
10-hr	65.07	69.42	>0.05
12-hr	52.69	55.02	0.24
16-hr	31.63	34.14	0.16
24-hr	7.70	8.67	0.48
36-hr	0.00	0.00	----

Table 4

Results of Urine SA Assays

<u>Sample Period</u>	<u>Treatment</u>	<u>Sample Size</u>	<u>Milligrams of SA Voided</u>	<u>p-level</u>
Total (0-192 hrs)	Max. Str.	16	340.67	0.02
	Regular	16	397.07	
-12-0 hrs (Pre)	Max. Str.	16	0.05	0.53
	Regular	16	0.02	
0-12 hrs	Max. Str.	16	209.35	0.03
	Regular	16	259.72	
12-24 hrs	Max. Str.	16	111.81	0.69
	Regular	16	116.94	
24-48 hrs	Max. Str.	16	18.85	0.90
	Regular	16	19.31	
48-72 hrs	Max. Str.	16	0.46	0.72
	Regular	16	0.57	
72-96 hrs	Max. Str.	16	0.11	0.67
	Regular	16	0.15	
96-120 hrs	Max. Str.	16	0.00	0.33
	Regular	16	0.05	
120-144 hrs	Max. Str.	16	0.00	0.26
	Regular	16	0.10	
144-168 hrs	Max. Str.	16	0.04	0.49
	Regular	16	0.16	
168-192 hrs	Max. Str.	16	0.00	0.33
	Regular	16	0.03	

Table 5
Results of Urine SU Assays

<u>Sample Period</u>	<u>Treatment</u>	<u>Sample Size</u>	<u>Milligrams of SU Voided</u>	<u>p-level</u>
Total (0-192 hrs)	Max. Str.	16	1127.14	0.11
	Regular	16	1239.45	
-12-0 hrs (Pre)	Max. Str.	16	0.18	0.33
	Regular	16	0.00	
0-12 hrs	Max. Str.	16	538.59	0.19
	Regular	16	613.21	
12-24 hrs	Max. Str.	16	476.88	0.27
	Regular	16	522.25	
24-48 hrs	Max. Str.	16	107.96	0.81
	Regular	16	101.83	
48-72 hrs	Max. Str.	16	3.14	0.49
	Regular	16	1.91	
72-96 hrs	Max. Str.	16	0.40	0.46
	Regular	16	0.13	
96-120 hrs	Max. Str.	16	0.00	----
	Regular	16	0.00	
120-144 hrs	Max. Str.	16	0.00	----
	Regular	16	0.00	
144-168 hrs	Max. Str.	16	0.00	----
	Regular	16	0.00	
168-192 hrs	Max. Str.	16	0.00	----
	Regular	16	0.00	

APPENDIX I

INVESTIGATOR'S FINAL REPORT / PROTOCOL

A Comparative, Randomized Crossover Bioavailability
Study of Multiple Oral Doses of Pepto Bismol Liquid

Protocol No. PB-118

QRC Study No. 996

Sponsored by:

The Procter & Gamble Company
11511 Reed Hartman Highway
Cincinnati, Ohio 45241


Philip D. Leese, M.D.
PRINCIPAL INVESTIGATOR
Quincy Research Center
5104 East 24th Street
Kansas City, Missouri 64127

1/28/86
Date of Report

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ADMINISTRATIVE SUMMARY

I. PROTOCOL INFORMATION

A. Title: A Comparative, Randomized, Crossover Bioavailability Study of Multiple Oral Doses of Pepto Bismol Liquid

B. Sponsor: The Procter & Gamble Company
11511 Reed Hartman Highway
Cincinnati, Ohio 45241

C. Sponsor Protocol ID: PB-118

D. Quincy Research Center ID Number: 996

E. Objective:

To compare the bioavailability of multiple doses of bismuth subsalicylate in two different formulations.

F. Experimental Design:

An open label, randomized, multiple dose, two-way crossover, bioavailability study

G. Study Participants: (Appendix D)

<u>Number Required by Protocol</u>	<u>Number Enrolled (Exposed to Test Material)</u>
16	18

H. Test Material: (Appendix F)

Bismuth Subsalsicylate Liquid (1.75% BSS) (Pepto Bismol)
Bismuth Subsalsicylate Liquid (3.5% BSS) Extra Strength

II. STUDY PERSONNEL (INVESTIGATOR AND FACILITIES):

- A. Principal Investigator: Philip T. Leese, M.D.
- B. Co-Investigators: John D. Arnold, M.D.
Walter N. Porter, M.D., Ph.D.
Gary A. Thompson, M.D.
- C. Clinical Facilities (Center): Quincy Research Center
5104 East 24th Street
Kansas City, Missouri 64127
(816) 483-1850
- D. Clinical Laboratory Facilities: Quincy Laboratory Services
5101 East 24th Street
Kansas City, Missouri 64127
(816) 483-1850
(DHS Registration No. 26-8118)
(CLIA No. 24-1110)
- E. Study Director: Judy Meinders, B.S.
Yuko Williams, M.S.
- F. Report Preparation: Julie Sewell

III. DRUG LEVEL ANALYTICAL FACILITIES: (Appendix J - Bioavailability)

Salicylate Samples: Kansas City Analytical Services
12302 Johnson Drive
Shawnee Mission, Kansas 66216

Bismuth Samples: Procter and Gamble
11511 Reed Hartman Highway
Cincinnati, Ohio 45241

IV. SPONSOR PERSONNEL:

<u>Name and Title</u>	<u>Site Visit Dates</u>
James B. Lucas, M.D. Medical Affairs Director	No visits reported
Douglas Ws. Bierer, Ph.D. Toxicologist	No visits reported
Frederick W. Mitchell, M.Sc. Monitor	No visits reported
Anthony Gonsalves Project Representative	No visits reported
Nancy Flennoy	9/23/85; 9/24/85

V. INSTITUTIONAL REVIEW BOARD (IRB): (Appendix C)

A. <u>IRB Committee:</u>	Quincy Research Center Institutional Review Committee
B. <u>Date of Charter:</u>	September 1, 1981
C. <u>IRB Chairman:</u>	H. Eugene Smith, M.D.
D. <u>Approval Dates:</u>	
1. Protocol	8/28/85; 10/16/85 (update information)
2. Consent Form	8/28/85

VI. ADMINISTRATIVE DATES:

- A. Protocol Start Date: 9/24/85
- B. Date Randomization Code Revealed: Open-label
- C. Protocol Completion:
1. Volunteers Screened for Enrollment 09/11/85-10/14/85
 2. Volunteers Admitted to Center: 09/23/85-10/15/85
 3. Volunteers Discharged from Center: 09/24/85-11/07/85
 4. Volunteers Discharged from Study: 09/25/85-11/18/85
 5. Issue of Case Report Forms: 11/21/85
 6. Return of Unused Test Material 01/07/86

VII. INVESTIGATIONAL DRUG ADMINISTRATION: (Appendix F, G, H)

- A. Formulation: Bismuth Subsalicylate Liquid
(1.75% BSS) (Pepto Bismol)
Bismuth Subsalicylate Liquid
(3.5% BSS) Extra Strength
- B. Mode of Administration: Oral
- C. Number of Treatment Periods: Two
- D. Schedule of Drug Administration:

Each medication bottle was vigorously mixed for 30 seconds and allowed to stand for two minutes immediately prior to pouring exactly 30 mls of the test material into the medicine cup from which it was administered according to the following schedule:

REGULAR STRENGTH: 30 mls at 30 minute intervals for a total of 8 doses (240 ml total)

DOUBLE STRENGTH: 30 mls at 1 hour intervals for a total of 4 doses (120 mls)

- E. Washout Interval: A minimum of six days between treatment periods

VIII. SCHEDULE OF PROCEDURES, TESTS, AND MEASUREMENTS: (Study Director's Schedule provided in Appendix I)

Flow Chart - Days

Procedure	Pre-Study	PERIOD: 1											PERIOD: 2												
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Informed Consent	X																								
Medical History	X																								
Chest X-ray*	X																								
Vital Signs	X																								
Physical Examination	X																								
Electrocardiogram	X																								
Clinical Laboratory	X																								X
Urine Drug Screen	X		X													X									
Blood Alcohol			X													X									
Check in to Center			X													X									
Serum Salicylate			X													X									
Special Diet			X	-----	X											X	-----	X							
Drug Administration			X													X									
Blood Collection																									
- Salicylate				X	X											X	X								
Blood Collection																									
- Bismuth				X	X											X	X								
Urine Collection																									
- Salicylate			X	-----	X											X	-----	X							
Urine Collection																									
- Bismuth			X	-----	X											X	-----	X							
Symptomatology			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge From Center											X														X
Washout Period										X	-----	X													
Discharge from Study																									X

* If none within twelve months prior to Day of Study 1, Period 1.

VIII. SCHEDULE OF PROCEDURES, TESTS, AND MEASUREMENTS: (cont.)

Flow Chart - Hours (cont.)

DAYS OF STUDY: 2,16

Procedure	Actual Time							
	0100	0500	0900	0930	1300	1730	2000	2100
	Experimental Time							
	16 hr	20 hr	24 hr	24.5 hr	28 hr	32.5 hr	35 hr	36 hr
Urine Collection	-----XX-----							
Vital Signs		X						
Blood Collection - Salicylate	X		X					X
Blood Collection - Bismuth								X
Breakfast				X				
Lunch					X			
Dinner						X		
Snack							X	

Flow Chart - Hours (cont.)

DAYS OF STUDY: 3,4,5,6,7,8 AND 17,18,19,20,21,22

Procedure	Actual Time					
	0500	0900	0930	1300	1730	2000
	Experimental Time					
	*					
Urine Collection	-----XX-----					
Vital Signs	X					
Breakfast			X			
Lunch				X		
Dinner					X	
Snack						X

* Experimental Time

<u>Days of Study</u>	<u>Experimental Time</u>
3,17	48 hour
4,18	72 hour
5,19	96 hour
6,20	120 hour
7,21	144 hour
8,22	168 hour

VIII. SCHEDULE OF PROCEDURES, TESTS, AND MEASUREMENTS: (cont.)

Flow Chart - Hours (cont.)

DAYS OF STUDY: 9,23

Procedure	Actual Time				
	0500	0800	0900	0930	1030
	Experimental Time				
	192 hr				
Vital Signs	X				
Clinical Laboratory*		X			
Urine Collection	-----X				
Breakfast				X	
Discharge From Center					X

* Day of Study 23 only.

IX. SUMMARY OF COMPLIANCE WITH PROCEDURES AND SCHEDULES:

The study was conducted according to protocol with the following exceptions:

Inclusion Deviation

Three subjects were entered into study participation weighing less than the minimum required weight of 65.0 kg.

<u>Subject Drug Number</u>	<u>Amount Underweight</u>
11	1.2 kg
12	1.9 kg
13	1.0 kg

Enrollment:

Sixteen Subjects were screened, qualified and admitted to the Center. On Day of Study 1, just prior to dosing, the gentleman who was to be dosed with medication assigned to Subject number six decided to remove himself from study participation. Between treatment periods, two Subjects (#01 and 15) removed themselves from participation. Three new Subjects were screened, qualified and enrolled in the study to complete the required number of subjects. These three Subjects were assigned drug numbers 06, 1003 and 1004.

Blood Collection

Three samples were collected five or more minutes later than scheduled. Otherwise, all blood samples were drawn either on time or within one to four minutes of the expected time.

X. CLINICAL OVERVIEW OF RESULTS OF THE STUDY

A. Symptomatology by Organ System

Table 1
Organ Systems

<u>Day of Study</u>	<u>Subject Drug Number</u>	<u>No Symptom</u>	<u>Digestive</u>	<u>Nervous</u>	<u>HEENT</u>	<u>Respiratory</u>	<u>Integument</u>
	01	X					
	02	X					
	03	X					
15	04		X				
	05	X					
	06	X					
	07	X					
17	08		X				
	09	X					
2	10			X			
4,5	11				X	X	
	12	X					
	13	X					
8	14						X*
	15	X					
5	16			X			
19	1003				X		
	1004	X					
	Totals:	11	2	2	2	1	1

<u>Organ system</u>	<u>Symptoms</u>
Digestive	Heartburn, nausea
Nervous	"Woozie", elevated temperature
HEENT	Sore throat, rhinorrhea, headache
Respiratory	Productive cough
Integument	Glass in left hand

* Reported Day of Study 8; accident occurred approximately one month ago.

B. CLINICAL LABORATORY: (Appendix K - Reference Ranges)

Table 2a
Hematology

Subject Drug Number	WBC (4.4-11.9 K/mm ³)			RBC (4.34-5.90 M/mm ³)		HGB (13.4-18.0 gm/dl)		HCT (39.0-51.4%)	
	Base	Final	F-UP	Base	Final	Base	Final	Base	Final
03	8.5	(12.9)	10.1						
04				4.54	(4.28)	15.1	(13.2)		
08				(4.25)	(4.17)				
09	(4.1)	(3.7)							
10				4.80	(4.27)	14.6	(13.3)		
11						14.9	(13.2)		
12						13.8	(13.3)	41.2	(38.9)
1004	(13.1)	(15.2)							

Subject Drug Number	MCV (78-97 u ³)		MCH (27.2-34.2 ug)		MCHC (33.4-36.3%)		SEG (36-75%)	
	Base	Final	Base	Final	Base	Final	Base	Final
04	(98)	(98)			34.1	(33.3)		
06					(33.1)	(33.1)	(78)	(79)
07					(32.8)	33.6		
08	(100)	(98)			(33.2)	(33.3)		
09					33.6	(33.3)		
10					(32.8)	33.7		
12					33.6	(33.2)		
13							67	(78)
14					(33.0)	33.4		
16					(32.6)	33.9		
1004	(101)	(101)	(35.4)	(35.4)				

Comments of the Investigator: Outlying baseline values were not felt to be clinically significant and therefore did not preclude enrollment in this clinical study. Outlying laboratory values presented here which were obtained subsequent to administration of test material were felt to be neither clinically significant in this test group nor related to study medication.

NOTE: Tables 2a, 2b, 2c display out of range clinical laboratory values for tests required according to protocol (enclosed in parentheses and highlighted). Previous and/or subsequent within range values for these tests are presented for comparison. Only those tests and Subjects having out of range values are included.

B. CLINICAL LABORATORY: (cont.)

Table 2a (cont.)
Hematology

Subject Drug Number	BAND (0-10)		LYMPH (22-58)		MONO (0-3)		EOSIN (0-6)		PLTCT (172-418 K/mm ³)	
	Base	Final	Base	Final	Base	Final	Base	Final	Base	Final
02							(8)	0		
05	0	(2)			0	(4)				
06	1	(2)	(21)	(19)						
08							(7)	(8)	177	(150)
09							3	(12)		
13			30	(19)						
1004	0	(3)								

Table 2b
Serum Chemistries

Subject Drug Number	SGOT (0-44 IU/L)			SGPT (0-50 IU/L)			BUN (0-17 mg/dl)		
	Base	Base2	Final	Base	Base2	Final	Base	Base2	Final
02				47		(67)			
09	(47)	44	(45)	40	45	(52)			
1003							(23)	15	(20)

Subject Drug Number	URIC (3.9-8.7 mg/dl)	
	Base	Final
04	4.5	(3.7)
10	4.0	(3.8)
14	(3.3)	(3.7)

Comments of the Investigator: Outlying baseline values were not felt to be clinically significant and therefore did not preclude enrollment in this clinical study. Outlying laboratory values presented here which were obtained subsequent to administration of test material were felt to be neither clinically significant in this test group nor related to study medication.

B. CLINICAL LABORATORY: (cont.)

Table 2c
Urinalysis

Subject Drug Number	WBC (0-15/HPF)		CAST (NEGATIVE)		CRYSTALS	
	Base	Final	Base	Final	Base	Final
03			0	(1 HY)		
07	5	(50)			0	(3+ AMORPH)
10	9	(40)			0	(1+ AMORPH)
11			(3 GRAN)	(1 HY)		
12	OCC	(100)				
14	FEW	(30)			(1+ CA OK)	0
16	FEW	(25)				
1004	FEW	(30)				

Comments of the Investigator: Outlying baseline values were not felt to be clinically significant and therefore did not preclude enrollment in this clinical study. Outlying laboratory values presented here which were obtained subsequent to administration of test material were felt to be neither clinically significant in this test group nor related to study medication.

C. INVESTIGATOR'S OVERALL CONCLUSIONS:

Eighteen Subjects were screened, qualified and enrolled in the PB-118 protocol. Two Subjects (#01,15) did not complete the study procedures. Sixteen Subjects completed their participation in the protocol as expected. All Subjects were normal, healthy, adult male volunteers between the ages of twenty and forty-five years (MEAN AGE: 28.94 YEARS) who weighed 63.1 to 81.0 kg (MEAN WEIGHT: 71.02 KG).

Six Subjects, as detailed below, had out of range clinical laboratory values (for which a repeat was ordered) at the time of discharge from the center. While these values may not have been felt to be clinically significant in this test population, it was requested as a follow-up measure that repeat tests be obtained. To date these gentlemen have not complied with the request to return to the Center and are considered to be lost to follow-up.

(Subject/Patient) Drug Number	Tests	Follow-up Status
09	EOSINOPHIL SGOT SGPT	Lost to follow-up Lost to follow-up Lost to follow-up
02	SGPT	Lost to follow-up
07	URINE WBC	Lost to follow-up
10	URINE WBC	Lost to follow-up
12	URINE WBC	Lost to follow-up
1004	WBC	Lost to follow-up

Adverse symptomatology observed and/or reported during the conduct of this study was generally mild in nature and, while some was felt to be possibly related to study medication, none of the symptoms were felt to be clinically significant and none warranted medical intervention or early termination from study participation.

Comments on the achievement of the pharmacokinetic objective of this protocol are pending review of analysis data produced elsewhere.

APPENDIX A
FINAL PROTOCOL

ATTACHMENT NO. 1

BLOOD COLLECTION SCHEDULE

Specimen [*] Designation [*]	Collection Time (hr)																		
	Pre-Drug																	Post-Drug	
	<u>0</u> ^{**}	<u>0.5</u>	<u>1</u>	<u>1.5</u>	<u>2</u>	<u>2.5</u>	<u>3</u>	<u>3.5</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>10</u>	<u>12</u>	<u>16</u>	<u>24</u>	<u>36</u>	
Bismuth	B								B				B		B				B
Total Salicylate	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S

Conditions: The specimens for determination of bismuth will be collected before the specimens for determination of total salicylate.

B - Blood specimen (10 ml) for determination of bismuth.

S - Blood specimen (7 ml) for determination of total salicylate.

* A total of 23 different specimens, representing a total quantity of 176 ml of blood, will be collected from each subject at each test period.

** Represents the time of administration of the first drug dose.

ATTACHMENT NO. 2

URINE COLLECTION SCHEDULE

Collection Interval (hr)

Specimen Designation	Pre-Drug		Post-Drug							
	-12.0	0-12,	12-24,	24-48,	48-72,	72-96,	96-120,	120-144,	144-168,	168-192
Bismuth	B	B	B	B	B	B	B	B	B	B
Total Salicylate	S	S	S	S	S	S	S	S	S	S

Conditions: The total urine volume will be recorded for each collection interval.

S - Urine Specimen (ml) for determination of salicylate.

B - Urine Specimen (ml) for determination of Bismuth.

Other Obligations of the Principal Investigator

Study Medication

The principal Investigator will be responsible for the dispensing, inventory and accountability of all clinical supplies exercising accepted medical and pharmaceutical practices. Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. An accurate record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection by the designated Sponsor representative(s) upon request. Upon completion or termination of the study, the investigator will return all unused clinical supplies to the Sponsor, along with a copy of the inventory record and a record of the clinical supplies returned.

Study Conduct

The study will be conducted in accordance with "Good Clinical Practices".

Case Report Form

All Case Report forms will be completed by either the investigator or a member of the investigator's staff. Case Report forms to be used in this study:

Study Roster	Adverse Experiences
Subject Acceptability	Blood Collection
Medical History	Urine Collection
Chest X-ray	Concomitant Medication
Physical Exam	Drug Administration
Laboratory	Discharge Summary
Symptom Observation	

The investigator will be responsible for the timeliness, completeness and accuracy of the information on the Case Report forms. All entries must be legibly recorded in black ink, with cross-outs initialed and dated. The investigator will make these forms available for thorough review and collection by the designated Sponsor representative(s).

Source Documents

The Investigator will maintain accurate office records on which the case report forms are based. The Investigator will allow the designated representative of the Sponsor to verify the information reported on the case report forms with these source documents. These reviews are for the purpose of corroborating adherence to the protocol and the completeness and exactness of the data being entered on the case report form.

Written Report

Within thirty (30) days of completion or termination of the study, the Investigator is required to submit a final report to the Sponsor. Suggested inclusions in the report are: study objectives, methods (including any deviation from the study protocol), findings by the Investigator as to the value of the experimental drug, and a discussion of all adverse experiences (if any) linked to the study drug. Subjects will be identified only by subject number in the final report.

Record Retention

The Investigator will retain all study records for a period of at least two (2) years after study completion, with the exception of the informed consent forms which must be retained for at least three (3) years. Included in these records are the protocol, case report forms, Review Board approval letters, drug accountability records, correspondence concerning the clinical trial, and the last known address of each subject. The investigator must contact the Sponsor prior to disposing of any records related to this study.

FDA Inspection

The Investigator will permit the FDA to inspect the facilities, protocol, and case report forms should the need ever arise. He/she may also be requested to present subject records pertaining to the clinical trial.

Publication Policy

The Sponsor reserves the right to first review and comment upon any manuscripts intended for publication or public presentation which encompass information obtained during the clinical study conducted by the Sponsor.

Principal Investigator's Agreement

I certify that I have reviewed and approved this protocol, appropriate informed consent forms and other associated documents and agree to abide by their terms.

Philip F. Leese, M.D. 8/28/85
Philip F. Leese, M.D. (Principal Investigator) Date

[Signature] 8/28/85
Chairman, Institutional Review Board Date

Fred W. Mitchell, M.Sc. 8-26-85
Fred W. Mitchell, M.Sc. (Clinical Monitor) Date

/pyt
PB1-PB-118
8/19/85

QRC-996

Study Medication:

The Bismuth Subsalicylate liquids (regular-strength and double-strength) for each subject will be dispensed from individual 16 oz. bottles, uniquely labeled with the subject's number. Just prior to each drug administration, the bottle contents will be mixed vigorously for 30 seconds and the contents allowed to stand for 2 minutes. Exactly 30mL of the medication will be placed on the medicine spoon for administration. The regular-strength medication will be administered to the subjects in multiple oral doses of 30 mL at half-hour intervals until a total of 8 doses has been given. The double-strength medication will be administered to the subject in multiple oral doses of 30 mL at 1-hour intervals until a total of 4 doses has been given. The exact time of each drug administration coincides with the blood or urine collection, the sequence of events will be as follows: blood collection, drug administration at exactly the stipulated time; and then urine collection. The subjects will not be allowed to lie down, but will be sitting or ambulatory, for at least 5 hours after the start of drug administration.

Collection and Handling of Specimens:

All specimens will be collected by personnel of the Quincy Research Center (QRC). Blood specimens (10 mL) will be collected by direct venipuncture for determination of bismuth using Vacutainers™ provided by the Sponsor. Blood specimens (7mL) will be collected by direct venipuncture for determination of total salicylate using Potassium Oxalate + NaF Vacutainers®. Blood will be collected, as just described, from each subject precisely at the times indicated in the Collection Schedule in Attachment No. 1. Each 10 mL blood specimen for determination of bismuth (1 pre-drug specimen and 4 post-drug specimens per subject) will be handled by QRC personnel according to instructions provided. Each 7 mL blood specimen for total salicylate (1 pre-drug and 17 post-drug specimens per subject) will be centrifuged, and the plasma transferred to appropriate containers according to instructions provided by KCAS. All specimens for salicylate analysis will then become the responsibility of KCAS.

Voided urine specimens (bladder completely emptied) will be obtained from each subject at the intervals indicated in Attachment No. 2. Each subject will be requested to empty the bladder at the conclusion of the collection interval. If necessary, urine specimens are to be refrigerated (not frozen) until the entire specimen for the interval is obtained. The exact time of the completion of each urine collection interval will be recorded. Following urine collection, the urine will be pooled, as necessary, for each collection interval. The total urine volume for the collection interval will be measured, and the volume recorded. The urine specimens for determination of total salicylate will be pipetted into aliquots according to the instructions provided by KCAS. The specimens for determination of bismuth will be handled according to instructions provided and transferred to containers provided by the Sponsor.

Each specimen container will be legibly labeled with the following information: study number, specimen, date, and collection time or interval. Each specimen for determination of total salicylate will be kept in a frozen state until analysis is performed. Each specimen for determination of bismuth collected prior to drug administration and for the period following drug administration will be shipped to the Sponsor as soon as possible after the final specimen is collected.

Drug Analysis:

Designated plasma and urine specimens will be analyzed for total salicylate by KCAS, 12302 Johnson Drive, Shawnee, Kansas, using a high performance liquid chromatography method on file with KCAS. The designated blood and urine specimens will be analyzed for bismuth by the Sponsor. The method is on file with the analytical laboratory, Procter and Gamble Company.

Study Management

A. Monitoring

The Sponsor's Clinical Monitor will be responsible for establishing the schedule and procedures to be followed for monitoring this study. Prior to the beginning of this study, the Investigator will be informed as to the anticipated frequency of the monitoring visits. In addition, the Investigator will receive reasonable notification prior to each monitoring visit. At each visit, the Investigator will be expected to cooperate with the Sponsor representative(s) for the review and verification of all case report forms, the drug supply and inventory records, and any additional records as may have been previously arranged between the investigator and the sponsor representative(s).

B. Protocol Revisions

With the exception of emergency situations, no changes or deviations in the procedures of this protocol will be permitted without the documented approval of the Sponsor's Clinical Monitor and the Institutional Review Committee which granted original approval for the study. This stipulation does not apply to those changes made to reduce discomfort or overt risk to subjects. In the event of an emergency, the Investigator shall institute any medical procedures which he deems appropriate. However, all such procedures must be promptly reported to the Sponsor.

C. Adverse Effects

Any adverse effects noted by the staff observers, the investigator or complaints from the subjects will be recorded stating the type, onset, duration, severity, and relationship to the study medication. Should such an event occur, the subject may be withdrawn from the study at the discretion of the Investigator. The subject will be followed until the problem has been resolved. Any side effects reported will be fully described and recorded on the Case Report Form, and immediately transmitted by telephone to the Sponsor.

PROTOCOL NUMBER PB-118

A comparative, randomized crossover bioavailability study of multiple oral doses of two bismuth subsalicylate (BSS) liquid formulations.

Background:

One of the formulations being tested is a liquid formulation of Bismuth Subsalicylate (BSS) that is marketed in the United States. BSS is a well-recognized treatment for Diarrhea, Upset Stomach, Heartburn, Indigestion and Nausea and is included in the FDA's proposed OTC monographs on Diarrhea and Overindulgence. The other formulation contains twice the concentration of BSS and will be dosed half as frequently. This study is designed to compare the bioavailability of these two formulations at their respective dosage regimens.

Purpose:

The purpose of this study is to compare the bioavailability of multiple doses of bismuth subsalicylate in two different formulations.

Investigator:

Philip T. Leese, M.D.

Location:

Quincy Research Center
5104 East 24th Street
Kansas City, Missouri

Sponsor:

The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, OH 45241

Sponsor's Monitor:

Fred. W. Mitchell, M. Sc.
The Procter & Gamble Distributing Co.
11511 Reed Hartman Highway
Cincinnati, OH 45241
Telephone: (513) 530-2312

Project Representative:

Anthony Gonsalves
The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, OH 45241
Telephone: (513) 530-2338

Should any unusual, unexpected or severe adverse reactions develop, contact one of the following people immediately:

Medical Affairs Director:

James B. Lucas M.D.
The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, OH 45241
Telephone: (513) 530-3350 - Work
(606) 781-3580 - Home

Toxicologist:

Douglas Ws. Bierer Ph.D.
The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, OH 45241
Telephone: (513) 530-2314 - Work
(513) 821-5330 - Home

Monitor:

Fred. W. Mitchell, M. Sc.
The Procter & Gamble Distributing Co.
11511 Reed Hartman Highway
Cincinnati, OH 45241
Telephone: (513) 530-2312 - Work

Clinical Test Facility:

The study will be performed at the Quincy Research Center, a self-contained unit with adequate dormitory space, examination rooms, and emergency care facilities.

Clinical laboratory tests required by this protocol will be performed by the Quincy Laboratory Services. This laboratory is government certified and participates in the U.S. Validate and the American College of Pathology (ACP), Coulter and Ames quality assurance programs on a monthly basis.

Salicylate analysis will be performed by the Kansas City Analytical Laboratories (KCAS). Properly prepared and frozen bismuth samples will be returned to the Sponsor for analysis.

Clinical Supplies:

The Sponsor will supply sufficient quantities of the study formulations to allow completion of the study. The lot numbers and expiration dates of the drugs supplied will be recorded in the final report.

At the conclusion of the study, Quincy will return any unused supplies to the Sponsor. If no supplies remain, this fact will be indicated in the final report.

Ethical Considerations:

This research will be carried out in accordance with the Basic Principles defined in the U.S. Federal Register, 46 (12), January 27, 1981, and the principles enunciated in the Declaration of Helsinki (Tokyo Accord).

Institutional Review Board:

This protocol will be reviewed by the Quincy Research Center Institutional Review Committee and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the U.S. Code of Federal Regulations (21 CFR Part 56, effective July 27, 1981).

Informed Consent:

The purpose of the study, the procedures to be carried out, and the potential hazards will be described to the patients in non-technical terms. Subjects will be required to read and sign a consent form summarizing the discussion prior to enrollment, and will be assured that consent may be withdrawn at any time without jeopardizing their medical care.

SUBJECT SELECTION

A. Enrollment

This study will involve 16 healthy males between 18 and 45 years of age, weighing 65.0 - 85.0 kg, and whose weights do not deviate by more than 10% from their ideal weights as described in the Table of "Desirable Weights of Adults" published by the Metropolitan Life Insurance Company (Appendix). Medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build and smoking habits will be recorded. "Healthy" is defined as having no overt symptoms or findings of disease (central nervous, cardiopulmonary, gas-trointestinal, hepatic, renal, or hemopoietic systems) or clinical laboratory values which might indicate potential interference with drug absorption, metabolism or excretion. Each subject is to receive a complete physical examination and the laboratory tests of hematopoietic, hepatic and renal functions listed below. These laboratory tests will be repeated at the end of the study before releasing the subjects.

1. Hematology

Hemoglobin, Hematocrit, Total and differential leukocyte count, Platelets.

2. Serum Chemistry

BUN, Uric Acid, Creatinine, Total Bilirubin, Alkaline phosphatase, SGOT, SGPT.

3. Urine Analysis

pH, Specific gravity, Protein, Sugar, Ketones, Microscopic examination.

A. Enrollment - continued

4. 2-hour creatinine clearance.
5. Urine and Blood drug and alcohol screen, prior to each medication period.

*and serum salicylate screen
DOM 8-22-85*

Exclusion Criteria

Subjects will be excluded from this clinical study if they have:

1. Cardiovascular, hepatic, renal, hematological or significant gastrointestinal disease, peptic ulcer, gastrointestinal bleeding, regional enteritis, or ulcerative colitis. Subjects with chronic gastrointestinal complaints or previous gastrointestinal surgery within the two months preceding the study.
2. Received either experimental within 30 days or prescription drugs or OTC within 14 days prior to drug administration.
3. Allergies to salicylates (aspirin) or bismuth.
4. Phenylketonuria

Clinical Procedures:

This is a randomized, 2-product crossover study. The liquid medications will be administered to 16 subjects. The test period will last for 22-days, consisting of 8 days of urine collection and blood sampling after drug treatment followed by 6 days of washout, again followed by an 8-day drug investigation phase. The subjects will be confined to the study site for each of the 8-day drug treatment periods. Subjects will receive standardized meals at controlled times throughout the entire confinement periods. A record will be kept of the menu and the time of each meal. The subjects will be instructed to fast after 9:00 P.M. on the day preceding drug administration. The first dose of drug will be administered about 1 hour after a light breakfast. The subjects will then receive lunch within 5 or 6 hours and dinner within 9 to 10 hours after the start of drug administration. During the 12 hours just prior to drug administration and for the 48 hours after drug administration, the subjects will be instructed to eat all of the food provided at each meal. No fluids other than those involved with drug administration and the designated meals will be allowed for 5 hours after the start of drug administration. Thereafter, water will be allowed ad libitum. The subjects will be instructed not to consume coffee, tea (except decaffeinated), carbonated beverages containing caffeine, alcoholic beverages, or chocolate during the 24 hours prior to drug administration and for the 36 hours after drug administration. In addition, the subjects will be monitored and instructed to avoid all products containing salicylates (e.g., aspirin, gum, candies, toothpastes, topical ointments, etc.) for the 24 hours prior to drug administration and for the 36 hours after drug administration. The subjects will also be instructed to avoid all products containing bismuth (e.g. topical ointments, suppositories, etc.) during the entire 22-day test period.

Subjects will indulge in normal levels of activity during the first 5 hours after drug administration, avoiding both vigorous exertion and complete rest.

REPLACEMENT

BIOAVAILABILITY PROTOCOL

PB-118

#996

1985 AUG 22 PM 2:44

**A COMPARATIVE, RANDOMIZED CROSSOVER BIOAVAILABILITY STUDY OF
MULTIPLE ORAL DOSES OF PEPTO-BISMOL LIQUID**

This document is a confidential communication of The Procter & Gamble Company. Acceptance of this document constitutes agreement by the recipient that the contents will not be disclosed to any third party without Procter's prior written approval.

/pyr
PB1/PB-118
8/15/85

PROTOCOL NUMBER PB-118

A comparative, randomized crossover bioavailability study of multiple oral doses of two bismuth subsalicylate (BSS) liquid formulations.

SUMMARY

9077 8-22-85

This protocol describes a randomized crossover bioavailability study. Following an overnight fast, 16 healthy, ~~non-smoking~~ male volunteers will receive either eight (8) (30mL) doses of the first bismuth subsalicylate formulation at half-hour intervals or four (4) (30mL) doses of the second bismuth subsalicylate formulation at 1-hour intervals. Blood samples will be collected over a 36-hour period and assayed for salicylate and bismuth concentrations. Pooled urine samples will be collected for 8 days and assayed for salicylate and bismuth concentrations. After a further 6-day washout period, the subjects will repeat the procedure with the complementary formulation.

Evaluation of bioavailability will be based upon a statistical comparison between the formulations of AUC values in the blood and total amounts excreted in the urine for both salicylate and bismuth.

Sponsor:

The Procter & Gamble Company
11511 Reed Hartman Highway
Cincinnati, OH 45241

Test Products:

Bismuth Subsalsicylate Liquid (1.75% BSS)
(Pepto-Bismol)

Bismuth Subsalsicylate Liquid (3.5% BSS)
Extra-Strength

Blood Sampling Schedule for Salicylate:

0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, and 36 hours after the first dose of test medication.

Blood Sampling Schedule for Bismuth:

0, 4, 8, 12 and 36 hours.

Urine Collection Schedule:

-12-0, 0-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192 hours, pooled specimens.

Analytical Methods:

Salicylates: HPLC method on file with Kansas City Analytical Services
Bismuth: HGAAS method on file with Procter & Gamble

1965 AUG 22 AM 9: 22

Art
Emily
Dan
Sharon
Sarah
Pat
Veronic
Judy
Juanita
Dr. Lee
Resistor
Dr. Inc
Julie
Comm (2
Comp F1

**A Comparative, Randomized Crossover Bioavailability Study of
Multiple Oral Doses of Pepto-Bismol Liquid**

The test materials to be employed in the proposed bioavailability study include two test products which contain bismuth subsalicylate as the active. These test products are similar in composition to Pepto-Bismol Liquid which has been marketed in the United States for over 80 years without serious adverse reactions. The active, bismuth subsalicylate, has been accepted for use as an OTC drug and as such is deemed to be safe and effective.

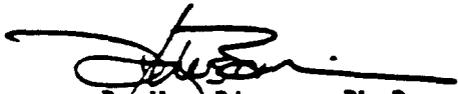
The two test products differ in that one of the test products contains twice the level of bismuth subsalicylate and a slightly different suspension system. Although the subjects will receive the test product in either four or eight divided doses over a four hour period, the total dose of bismuth subsalicylate for both products is the same (4.2 grams). Since bismuth subsalicylate contains salicylate, each subject will receive 1775 mg salicylate. This is approximately equivalent to the amount of salicylate in five, 325 mg aspirin tablets. The total amount of bismuth subsalicylate given over the four hour period is the same as current label indication for Pepto-Bismol Liquid.

The experimental products also contain excipients which are either "Generally Recognized As Safe" food ingredients, components in natural foods, or have been approved for use in pharmaceutical preparations.

In summary, the excipients should not pose any unreasonable safety hazard to the subjects in this study.

Since these products contain bismuth subsalicylate, they should not be taken by persons who are sensitive to aspirin. Bismuth subsalicylate in these preparations has been reported to cause ringing in the ears (tinnitus) and dizziness. These products have also been reported to cause temporary darkening of the stool. It is likely that some subjects in this study will experience one or more of these symptoms.

Despite the possible development of these reactions, neither the active ingredients nor the excipients pose an unreasonable risk to the subjects under the conditions of this study. This assessment is supported by previous experience in which these products or closely related products were have been administered acutely at exaggerated doses without significant effects to animals.


D. W. Bierer, Ph.D.
Section Head, Toxicology

/pyr
DWB01/D7

APPENDIX B
CONSENT FORM

FOR QRC USE ONLY

STUDY NAME: Pepto-Bismol
STUDY I.D.: 996
CLASS OF COMPOUND: Antidiarrheal
TYPE OF STUDY: Phase I Bio
DATE APPROVED BY IRC: 8/28/85
START DATE: 9/10/85
DATE REVISED: 8/28/85

VOLUNTEER AGREEMENT

DOCTORS IN CHARGE OF THIS STUDY: Philip T. Leese, M.D.
John D. Arnold, M.D.
Walter N. Porter, M.D., Ph.D.
Gary A. Thompson, M.D.

NAME OF MEDICINE:

The name of the medicine that you will take in this study is bismuth subsalicylate liquid (Pepto-Bismol).

USE:

Pepto-Bismol is a currently marketed over-the-counter medicine that is used to treat nausea, indigestion, and diarrhea. A new formulation has been developed which is 2 times as strong as the current Pepto-Bismol. This means that people would not need to take the medicine as often as with the currently marketed Pepto-Bismol.

PURPOSE:

This is a research study. The purpose is to measure how much medicine is in your blood and urine after you receive multiple oral doses of each formulation of Pepto-Bismol.

REQUIREMENTS:

YOU MUST:

1. Be a healthy male.

2. Take a physical exam and blood tests.
3. Follow the House Rules and study procedures or be dropped from the study.

YOU MUST NOT:

1. Have taken any investigational medicine for 30 days.
2. Have taken any prescription medicine for 14 days.
3. Have taken any over-the-counter medicines, especially aspirin or Pepto-Bismol, for 14 days before the study starts.
4. Have given blood for 30 days before the study starts, or give blood during the study, except for that which is required for the study.
5. Take any other medicine during the study, including the washout period, unless approved by the Quincy doctor.
6. Be allergic to aspirin or Pepto-Bismol.
7. Consume any coffee, tea, cola, chocolate, or alcohol for 24 hours before each dosing day.

PROCEDURES:

1. 16 subjects will participate in this study at QRC.
2. You will stay at Quincy Research Center for about 9 days during each treatment period. There are 2 treatment periods in the study separated by about a one-week interval.
3. The length of the study is approximately 23 days.
4. You will take the liquid medicine on Day 1 of each treatment period. During one treatment period, you will take the medicine every 30 minutes for a total of 8 doses. During the other treatment period, you will take the medicine every hour for a total of 4 doses.
5. You will be on a special diet.
6. During the study, we will take many samples of your blood by individual needle sticks. The amount of blood that will be taken is about 15 ounces (442 ml).
7. We will collect all of your urine during each treatment period.

8. You will not be allowed to engage in any strenuous activity.
9. For 5 hours after dosing you will not be allowed to lie down. You must be sitting, walking, or standing.

RISKS:

1. Possible side effects from bismuth subsalicylate are ringing in the ears, dizziness, and a temporary darkening in the color of the stool specimen.
2. Due to the amount of blood that we will take during the study, you should not give blood for 30 days after the study is over.
3. You must clearly understand that while you are on this study, the use of other drugs, including alcohol or marijuana, may cause you serious harm.
4. With all medicines or procedures, there may be risks that we do not know about.
5. Should additional information become available that might influence your willingness to continue in this study, you will be notified of these new findings.

BENEFITS

None.

COMPENSATION:

1. You will be paid \$500.00 if you are accepted for the study and finish all the tests. This fee will be paid at the end of the study.
2. If for any reason you cannot finish the study, or we decide to drop you, you will be paid for your time during the study, on a pro-rated basis. This fee will be paid at the end of the study.
3. You do not have to pay for any study-related medicines, procedures or treatment at Quincy Research Center.
4. If you are injured because of being on this study, treatment will be given to you at no cost. Compensation may be available under Missouri Worker's Compensation Law. This will be decided on a case-by-case basis.
5. Non-study related medical conditions may not be covered under Missouri Worker's Compensation Law.
6. There is no compensation available for injury resulting from horseplay.

RIGHT TO LEAVE THE STUDY:

1. As a volunteer, you will be starting the study of your own free will, without any kind of pressure, and you may quit the study any time you wish.
2. You may have to take more examinations, medicine, or tests if the doctor thinks they are necessary for your health.
3. If you have problems, you will get medical attention, and you might be dropped from the study. However, if the doctor thinks you can stay on the study, you can decide what you want to do.

CONFIDENTIALITY OF RECORDS:

1. Quincy Research Center will handle the medical information obtained in this study with the strictest confidence.
2. Employees of the Food and Drug Administration, the sponsoring drug company, and members of the Institutional Review Committee can look at, and copy, your medical record and the information collected during this study.

QUESTIONS:

This form has told you what the study is about. The volunteer recruiter will answer any questions you have now. If you have any questions about the study, or injuries as a result of this study, the study director, Judy Meinders, will assist you. The number to call is (816) 483-1850. If you have any questions regarding your rights as a research subject, you may call the secretary of the Institutional Review Committee at (816) 483-1850.

THE FOLLOWING QUESTIONS WERE ASKED

1. QUESTION: _____

ANSWER: _____

2. QUESTION: _____

ANSWER: _____

3. QUESTION: _____

ANSWER: _____

____ NO QUESTIONS ASKED

Date

Signature of Person Explaining
Consent Form

VOLUNTEER STATEMENT:

I am signing this form freely and am not being forced to do it.

The consent form has been read to me and I have received a copy of this form.

I agree to cooperate with all the medical personnel and to take the medicines and treatments, as directed.

By signing this consent form, I am authorizing release of my medical records to the Food and Drug Administration, the sponsoring drug company and the Institutional Review Committee.

Volunteer's Signature

Social Security Number

Birthdate

Age

Date

Witness

Date

APPENDIX C
INSTITUTIONAL REVIEW BOARD
APPROVAL DOCUMENTS

	<u>Protocol</u>	<u>Consent Form</u>
Formal review and approval	08/28/85	08/28/85
Expedited review and approval	10/16/85 (Update Information)	



Institutional Review Committee

Ellen Gilbreth, Executive Secretary

August 28, 1985

Philip T. Leese, M.D.
Quincy Research Center
5104 East 24th Street
Kansas City, Missouri 64127

Dear Doctor Leese:

The Institutional Review Committee of Quincy Research Center met on Wednesday, August 28, 1985, to review the following protocol:

#996 A Comparative, Randomized Crossover Bioavailability Study of Multiple Oral Doses of Pepto-Bismol Liquid (Pepto-Bismol - PB-118)

The Committee approved the protocol with the following modification:

Subjects must not have donated blood within 30 days prior to participation in the clinical trial.

The Committee reviewed and approved the consent form with the following modifications:

Under REQUIREMENTS, YOU MUST NOT, add as item 4: (YOU MUST NOT)

Have given blood for 30 days before the study starts, or give blood during the study, except for that which is required by the study.

Under RISKS, add as item 2:

Due to the amount of blood that we will take during the study, you should not give blood for 30 days after the study is over.

Philip T. Leese, M.D.

#996

August 28, 1985

Page 2

The Institutional Review Committee is to be notified immediately of the start date of the study.

In addition, you are required to notify the Committee of the following at any time during the conduct of the study:

1. Protocol changes
2. Deviations from the conduct of the study
3. Adverse events that occur to study patients
(Report adverse events to the Committee on either a monthly basis or at an interval decided upon by you.)

The Committee is also to be notified of the completion date of the study.

If this study is still in progress a year from this date, a report is required from you on its status. At the conclusion of the study, the Committee needs to receive a report.

The aforementioned approval is conditional upon the completion of any pre-investigational requirements by the FDA.

The Institutional Review Committee is in compliance with the requirements of Part 56, Sub-chapter D, Part 312 of the 21 Code of Federal Regulations published January 27, 1981, effective July 27, 1981.

Enclosed for your records are a listing of the committee members and the Bylaws and Operating Guidelines. Also enclosed is a copy of the appropriate consent form.

Do not hesitate to contact us if we can furnish additional assistance or information.

Sincerely yours,

INSTITUTIONAL REVIEW COMMITTEE



H. Eugene Smith, M.D.
Chairman

HES/nhl

Attachments: Committee Membership
Bylaws and Operating Guidelines
Consent Form



Quincy Research Center

John D. Arnold, M.D., Chairman

Federal Express

August 30, 1985

Fred W. Mitchell
Clinical And Biometrics HB-2J15C
Procter & Gamble Company
11511 Reed Hartman Highway
Cincinnati, OH 45241

RE: Pepto-Bismol (PB-118)
QRC #996

Dear Fred:

The Institutional Review Committee of Quincy Research Center met on Wednesday, August 28, 1985, and reviewed the above-referenced protocol. The protocol was approved with modification and the consent form was approved with modification.

To follow up on the approval, I have enclosed the following information:

1. A copy of the IRB approval letter
2. A copy of the approved consent form
3. The Bylaws and Operating Guidelines of our IRB
4. The IRB Membership list
5. The signed 1572 with appropriate CVs
6. The protocol signature page
7. The laboratory normal ranges for this study
8. The QRC Study Personnel Responsibility form

If you have any questions or require further information, please let me know.

Sincerely,

Sue Strickler
Director, Research Administrative
Services

Enclosures

/rb



Quincy Research Center

John D. Arnold, M.D., Chairman

October 16, 1985

Fred W. Mitchell
Clinical and Biometrics, HB-2J15C
Health & Personal Care Division
Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, OH 45241

RE: Pepto-Bismol (PB 118)
QRC #996

Dear Fred:

On October 16, 1985, the Chairman of the Institutional Review Committee of Quincy Research Center reviewed the update information on the above-referenced study. Enclosed please find a copy of the acknowledgement letter.

If you have any questions or require further information, please let me know.

Sincerely,

Sue Strickler
Director, Research Administration
Services

Enclosures

/rb



Institutional Review Committee

Ellen Gilbreth, Executive Secretary

October 16, 1985

Philip T. Leese, M.D.
Quincy Research Center
5104 East 24th Street
Kansas City, Missouri 64127

Dear Doctor Leese:

The Chairman of the Institutional Review Committee of Quincy Research Center conducted expedited review on Wednesday, October 16, 1985, to review the update information for the following protocol:

#996 A Comparative, Randomized Crossover Bioavailability Study of Multiple Oral Doses of Pepto-Bismol Liquid (Pepto-Bismol - PB-118)

The update information consisted of a protocol clarification consisting of Sampling Instructions for Blood Bismuth Analysis.

The Chairman acknowledged receipt of the update information.

Sincerely yours,

INSTITUTIONAL REVIEW COMMITTEE

H. Eugene Smith, M.D.
Chairman

HES/eng

APPENDIX D

VOLUNTEER DEMOGRAPHIC CHARACTERISTICS & STUDY PARTICIPATION RECORD

<u>Drug No.</u>	<u>Comp ID</u>	<u>Initials</u>	<u>Birthdate</u>	<u>Age</u>	<u>Race</u>	<u>Sex</u>	<u>Height (cm)</u>	<u>Weight (kg)</u>	<u>Frame Size</u>	<u>Smoker Yes/No</u>	<u>Date Screened For Study</u>	<u>Date Admitted To Center</u>	<u>I Disc Pr</u>
01	5586	WEA	06/04/54	31	C	M	183	72.4	S	YES	09/11/85	09/23/85	10/
02	12222	SRC	01/30/53	32	C	M	192	81.0	S	YES	09/11/85	09/23/85	10/
03	3960	JS	11/12/55	29	B	M	175	67.3	M	YES	09/11/85	09/23/85	10/
04	11339	SOW	08/09/63	22	B	M	176	72.2	S	YES	09/11/85	09/23/85	10/
05	1750	LDF	07/22/43	42	C	M	176	75.5	M	NO	09/13/85	09/23/85	10/
06	5037	ACW	05/27/63	22	B	M	177	66.7	M	YES	10/14/85	10/15/85	11/
07	11146	LT	07/27/56	29	B	M	170	76.7	L	YES	09/12/85	09/23/85	10/
08	4671	CFO	02/11/59	26	B	M	168	74.4	M	YES	09/11/85	09/23/85	10/
09	5796	BFM	01/03/44	41	B	M	188	78.2	M	NO	09/11/85	09/23/85	10/
10	12443	IB	06/17/50	35	B	M	180	72.3	S	YES	09/13/85	09/23/85	10/
11	3118	NWH	12/19/61	23	B	M	175	63.8	M	YES	09/13/85	09/23/85	10/
12	11465	RDR	08/01/61	24	B	M	170	63.1	M	YES	09/11/85	09/23/85	10/
13	11950	LHH	01/15/65	20	C	M	179	64.0	M	YES	09/19/85	09/23/85	10/
14	12469	JJJ	12/01/53	31	B	M	175	68.4	L	YES	09/19/85	09/23/85	10/
15	12468	IH	08/23/64	21	B	M	169	69.6	M	NO	09/18/85	09/23/85	09/
16	3888	IMM	12/21/64	20	B	M	164	65.8	M	YES	09/17/85	09/23/85	10/
1003	11559	GGL	08/25/57	28	C	M	176	75.5	L	YES	10/14/85	10/15/85	11/
1004	6054	JSB	08/04/40	45	C	M	185	71.5	M	YES	10/14/85	10/15/85	11/

Study Event Codes:

NC = Qualified, no show at check-in.

FA = Failed to qualify at check-in.

CS = Completed study.

DM = Discharge medical.

IP = Discharge protocol violation.

RS = Removal self.

IF = lost to followup.

APPENDIX E

VOLUNTEER SCREENING REPORT

<u>Subject Comp ID</u>	<u>Subject Initials</u>	<u>Screened For Study</u>	<u>Screening Code</u>
1750	LDF	09/13/85	OK
2420	CDR	09/11/85	RP
2664	DAH	10/14/85	DQ
3118	NAH	09/13/85	OK
3738	RLW	09/11/85	DQ
3764	LTD	09/12/85	MA
3888	LMM	09/17/85	OK
3960	JS	09/11/85	OK
4671	CRO	09/11/85	OK
4676	MJC	10/14/85	DQ
5037	ACW	10/14/85	OK
5337	DWS	09/11/85	DQ
5454	WET	09/11/85	MA
5586	WEA	09/11/85	OK
5796	ERM	09/11/85	OK
6054	JSB	10/14/85	OK
9529	HDS	09/11/85	OK
10755	GMC	09/11/85	RP
11113	DHG	09/17/85	OK
11146	LT	09/12/85	OK
11287	RVG	09/11/85	MA
11339	SCW	09/11/85	OK
11399	MSB	08/27/85	DQ
11465	RDR	09/11/85	OK
11559	GGL	10/14/85	OK
11950	LDH	09/19/85	OK
12005	TJL	10/14/85	DQ
12178	JES	09/13/85	DQ
12222	SRC	09/11/85	OK
12443	LB	09/13/85	OK
12468	DH	09/19/85	OK
12469	JJJ	09/19/85	OK

SCREENING CODES:

- DQ = Disqualified.
- MA = Marginal (sponsor clearance required).
- RP = Repeat test required.
- PD = Repeat results not available.
- OK = Qualified.
- NS = Contacted, scheduled, no show for screening.
- IN = Incomplete workup.
- NU = Qualified, not used for study.
- RC = Qualified, removed self prior to checkin.
- BU = Qualified, scheduled as backup.

APPENDIX E (cont.)

VOLUNTEER SCREENING REPORT

<u>Subject Comp ID</u>	<u>Subject Initials</u>	<u>Screened For Study</u>	<u>Screening Code</u>
12507	SLS	09/11/85	DQ
12519	LNB	10/11/85	PD
12521	NDH	09/11/85	DQ
12546	BGR	09/16/85	DQ
12547	JMC	09/16/85	PD
12633	GWR	10/14/85	DQ
12635	WHC	10/14/85	DQ
12636	DLB	10/14/85	DQ
12637	ART	10/14/85	DQ
12640	RHS	10/14/85	DQ

SCREENING CODES:

DQ = Disqualified.

MA = Marginal (sponsor clearance required).

RP = Repeat test required.

PD = Repeat results not available.

OK = Qualified.

NS = Contacted, scheduled, no show for screening.

IN = Incomplete workup.

NU = Qualified, not used for study.

RC = Qualified, removed self prior to checkin.

BU = Qualified, scheduled as backup.

APPENDIX F

ACCOUNTABILITY FOR INVESTIGATIONAL MATERIALS

Date Received	Description	Quantity				Date Prepared For Return
		Received	Protocol Required	Amount Used	Unused Amount	
09/20/85	Bismuth Subsalicylate liquid 1.75% BSS	9411.8 ml 20/16 oz Bottle	3840 ml	4320 ml	5091.8 ml	1/7/86
09/20/85	Bismuth Subsalicylate liquid 3.5% X-Strength	9411.8 ml 20/16 oz Bottle	1920 ml	2040 ml	7371.8 ml	

Lot number not specified.

Study Design: An open label, randomized, multiple dose, two-way crossover bioavailability study

Treatment Administration Plan:

<u>Treatment/Group*</u>	<u>Day(s) of Study</u>	<u>Treatment</u>	<u>Frequency</u>	<u>Total Daily Dose</u>
Regular Strength	Period 1, Day 1 Period 2, Day 15	30 ml	Eight doses at 30 minute intervals	240 ml
Extra Strength	Period 1, Day 1 Period 2, Day 15	30 ml	Four doses at 1 hour intervals	120 ml

* Two groups of eight subjects: each group received one of the two treatments on Day of Study 1 (Period 1); on Day of Study 15 (Period 2) the subjects were crossed over to receive the second of the two treatments.

Test material preparation procedure:

Drug was shaken in bulk bottles for 30 seconds. It was then poured into the dosing cups in the dorm immediately prior to administration.

APPENDIX G
RANDOMIZATION CODE

Randomization Code For Allocation Of Volunteers To Treatments

<u>Subject Drug No.</u>	<u>Treatment Period</u>	
	<u>1</u>	<u>2</u>
01	R	D
02	D	R
03	R	D
04	D	R
05	R	D
06	D	R
07	D	R
08	R	D
09	R	D
10	D	R
11	R	D
12	D	R
13	D	R
14	R	D
15	R	D
16	D	R
1003	R	D
1004	R	D

R = Regular Strength
D = Double Strength

APPENDIX H
DRUG ADMINISTRATION

Subject Drug No.	Date(s) of Dosing Treatment Period	
	1	2
01	09/24/85	*
02	09/24/85	10/08/85
03	09/24/85	10/08/85
04	09/24/85	10/08/85
05	09/24/85	10/08/85
06	10/16/85	10/30/85
07	09/24/85	10/08/85
08	09/24/85	10/08/85
09	09/24/85	10/08/85
10	09/24/85	10/08/85
11	09/24/85	10/08/85
12	09/24/85	10/08/85
13	09/24/85	10/16/85
14	09/24/85	10/16/85
15	09/24/85	*
16	09/24/85	10/16/85
1003	10/16/85	10/30/85
1004	10/16/85	10/30/85

* Subjects 01 and 15 removed themselves from study participation prior to treatment period 2.

APPENDIX I
STUDY DIRECTOR'S SCHEDULE

Study Schedule

DAY -1

1330 Check-in, breathalyzer, urine drug screen, serum salicylate
1730 Supper
2000 Snack
2050 Begin -12 to 0 hour urine
2100 NPO

DAY 1

0500 Vital signs, weight and temperature
0800 Breakfast
0845 0 hour bio (salicylate & bismuth)
0850 Complete -12 to 0 hour urine
0900 drug administration - 30 ml R or D, begin 0-12 hour urine collection
0930 30-minute bio (salicylate), dosing 30 ml R
1000 1 hour bio (salicylate), dosing 30 ml R or D
1030 1.5 hour bio (salicylate), dosing 30 ml R
1100 2 hour bio (salicylate), dosing 30 ml R or D
1130 2.5 hour bio (salicylate), dosing 30 ml R
1200 3 hour bio (salicylate), dosing 30 ml R or D
1230 3.5 hour bio (salicylate), dosing 30 ml R
1300 4 hour bio (salicylate & bismuth)
1400 5 hour bio (salicylate), lunch (after 5 hour bio)
1500 6 hour bio (salicylate)
1600 7 hour bio (salicylate)
1700 8 hour bio (salicylate & bismuth)
1800 Supper
1900 10 hour bio (salicylate)
2100 12 hour bio (salicylate & bismuth), end 0-12 hour urine, begin 12-24
hour urine

R = regular strength bismuth subsalicylate
D = double strength bismuth subsalicylate

APPENDIX I (cont.)
STUDY DIRECTOR'S SCHEDULE

Study Schedule (cont.)

DAY 2

0100 16 hour bio (salicylate)
0500 Vitals, weight and temperature
0900 24 hour bio (salicylate), end 12-24 hour urine collection, begin 24-48
hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack
2100 36 hour bio (salicylate & bismuth)

DAY 3

0500 Vitals, weight and temperature
0900 End 24-48 hour urine collection, begin 48-72 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 4

0500 Vitals, weight and temperature
0900 End 48-72 hour urine collection, begin 72-96 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 5

0500 Vitals, weight and temperature
0900 End 72-96 hour urine collection, begin 96-120 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

APPENDIX I (cont.)

STUDY DIRECTOR'S SCHEDULE

Study Schedule (cont.)

DAY 6

0500 Vitals, weight and temperature
0900 End 96-120 hour urine collection, begin 120-144 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 7

0500 Vitals, weight and temperature
0900 End 120-144 hour urine collection, begin 144-168 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 8

0500 Vitals, weight and temperature
0900 End 144-168 hour urine collection, begin 168-192 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 9

0500 Vitals, weight and temperature
0900 End 168-192 hour urine collection
0930 Breakfast
1030 Check-out

DAY 9-14

Washout period

APPENDIX I (cont.)

STUDY DIRECTOR'S SCHEDULE

Study Schedule (cont.)

DAY 14

1330 Check-in, breathalyzer, urine drug screen serum salicylate
1730 Supper
2000 Snack
2050 Begin -12 to 0 hour urine
2100 NPO

DAY 15

0500 Vital signs, weight and temperature
0800 Breakfast
0845 0 hour bio (salicylate & bismuth)
0850 Complete -12 to 0 hour urine
0900 Drug administration - 30 ml R or D, begin 0-12 hour urine collection
0930 30 minute bio (salicylate), dosing 30 ml R
1000 1 hour bio (salicylate), dosing 30 ml R or D
1030 1.5 hour bio (salicylate), dosing 30 ml R
1100 2 hour bio (salicylate), dosing 30 ml R or D
1130 2.5 hour bio (salicylate), dosing 30 ml R
1200 3 hour bio (salicylate), dosing 30 ml R or D
1230 3.5 hour bio (salicylate), dosing 30 ml R
1300 4 hour bio (salicylate & bismuth)
1400 5 hour bio (salicylate), lunch (after 5 hour bio)
1500 6 hour bio (salicylate)
1600 7 hour bio (salicylate)
1700 8 hour bio (salicylate & bismuth)
1800 Supper
1900 10 hour bio (salicylate)
2100 12 hour bio (salicylate & bismuth), end 0-12 hour urine collection,
begin 12-24 hour urine

DAY 16

0100 16 hour bio (salicylate)
0500 Vitals, weight and temperature
0900 24 hour bio (salicylate), end 12-24 hour urine collection, begin 24-48
hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack
2100 36 hour bio (salicylate & bismuth)

APPENDIX I (cont.)

STUDY DIRECTOR'S SCHEDULE

Study Schedule (cont.)

DAY 17

0500 Vitals, weight and temperature
0900 End 24-48 hour urine collection, begin 48-72 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 18

0500 Vitals, weight and temperature
0900 End 48-72 hour urine collection, begin 72-96 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 19

0500 Vitals, weight and temperature
0900 End 72-96 hour urine collection, begin 96-120 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 20

0500 Vitals, weight and temperature
0900 End 96-120 hour urine collection, begin 120-144 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 21

0500 Vitals, weight and temperature
0900 End 120-144 hour urine collection, begin 144-168 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

APPENDIX I (cont.)
STUDY DIRECTOR'S SCHEDULE

Study Schedule (cont.)

DAY 22

0500 Vitals, weight and temperature
0900 end 144-168 hour urine collection, begin 168-192 hour urine collection
0930 Breakfast
1300 Lunch
1730 Supper
2000 Snack

DAY 23

0500 Vitals, weight and temperature
0800 Lab
0900 End 168-192 hour urine collection
0930 Breakfast
1030 Check-out (final)

Please Note: When the exact time of dosing coincides with the blood or urine collection, the sequence of events will be 1) blood collection, 2) dosing, 3) urine collection.

APPENDIX I (cont.)

STUDY DIRECTOR'S SCHEDULE

Study Rules

1. You will be asked to eat all the food provided beginning 12 hours before and for 48 hours (0900 on Day 3) after dosing. During these periods, do not trade with other volunteers for foods you may prefer.
2. Please do not smoke for 15 minutes before vital signs are done. Nicotine raises your blood pressure.
3. We will be collecting all of your urine during both periods of this study. When you go to the bathroom for a bowel movement, please use a Texas catheter so that none of your urine is lost. Texas catheters are available in the dorm.
4. 23 tubes of blood will be collected on each of Days 1 and 15 after dosing.
5. All blood draws will be straight sticks. No catheters will be used.
6. Please keep ice in your chubby during each of the 9-day urine collection periods, which begin at 2100 (9:00 p.m.) on Day -1 and at 2100 on Day 14 and end on the morning of checkout.
7. Please be sitting on your bed for 5 minutes before your vital signs are done.
8. You are responsible to be on time for all procedures during the study. All procedures will be done on your bed for your safety. Please read the schedule to know when procedures are due.
9. You will be confined to the study site for each of the 9-day treatment periods.
10. Please do not eat or drink anything but water after 9:00 p.m. on Days -1 and 14.
11. Please do not drink anything other than what is given with meals and doses for 5 hours after the first dose on Days 1 and 15.
12. Please do not eat or drink anything containing caffeine, such as coffee, tea, Sanka, chocolate, cocoa and cola. Also, please do not drink alcoholic beverages.

APPENDIX I (cont.)
STUDY DIRECTOR'S SCHEDULE

Study Rules (cont.)

13. Please avoid using all products containing salicylates, such as aspirin, gum, candy, toothpaste, and ointments for the 24 hours just prior to dosing and for the duration of the study. Also avoid all products containing bismuth, such as ointments and suppositories, during the entire 22-day test period which includes the wash-out period.
14. Please carry out normal activity during the first 5 hours after dosing. Please do not participate in strenuous activities, yet avoid lying down. Please stay in the dormitory on Days 1 and 15 until we send you to lunch.

APPENDIX I (cont.)

STUDY DIRECTOR'S SCHEDULE

Study Procedures

1. General: This is a randomized, multiple dose, 2-product crossover study. The liquid medications will be administered to 16 subjects. The 22-day test period consists of 36 hours of blood sampling and 8 days of urine collection for the first treatment period, 6 days of wash-out, and a repeat of 36 hours of blood sampling and 8 days of urine collection for the second treatment period after dosing with the complementary medication. Dosing with the regular-strength medication will take place at 30-minute intervals over a period of 3.5 hours. Dosing with a double-strength medication will take place at one-hour intervals over a period of 3 hours. Blood collections for salicylate and bismuth will be at various intervals for 36 hours post dose.
2. Check-in: Subjects will check in on Monday, September 23 (Day -1) and again on Monday, October 7 (Day 14) at 1330. At each check-in, subjects will be screened for urine drug screen (50 ml), alcohol (breathalyzer), and serum salicylate (7 ml gray top).
3. Diet: All subjects will be on a standard house diet, with the exception of breakfast on Day 1 and Day 15. Records of menu and meal times will be kept.

Meals will be served at the following times:

DAY -1	Supper	1730
	Snack	2000
	NPO	2100
DAY 1	Breakfast	0800
	Lunch	1400
	Supper	1800
	NPO	2300
DAYS 2-8	Breakfast	0930
	Lunch	1300
	Supper	1730
	Snack	2000
	NPO	2300
DAY 9	Breakfast	0930
DAY 14	Supper	1730
	Snack	2000
	NPO	2100

APPENDIX I (cont.)
STUDY DIRECTOR'S SCHEDULE

Study Procedures (cont.)

DAY 15	Breakfast	0800
	Lunch	1400
	Supper	1800
	NPO	2300

DAY 16-22	Breakfast	0930
	Lunch	1300
	Supper	1730
	Snack	2000
	NPO	2300

DAY 23	Breakfast	0930
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4. Fluids: With the exception of 5 hours post dose, water may be taken ad-lib. Subjects will not be allowed food or beverages containing xanthines or caffeine.
5. Medication: The study medication will be mixed vigorously for 30 seconds and allowed to stand for 2 minutes before being administered in multiple doses of 30 ml each on Days 1 and 15 beginning 0900. A two-minute stagger will be used.
6. Discharge Lab: Please obtain the following specimens at 0800 on Day 23.
 - 1 - 12 ml urine for UA
 - 1 - 10 ml red top
 - 1 - 7 ml lavender

APPENDIX I (cont.)

STUDY DIRECTOR'S SCHEDULE

Study Procedures (cont.)

7. Bio: Please obtain the following specimens at the times listed.

	Hour	Time	Tube
DAY 1, 15:	0	0845	*1 - 10 ml royal blue 2 - 7 ml gray
	0.5	0930	1 - 7 ml gray
	1	1000	1 - 7 ml gray
	1.5	1030	1 - 7 ml gray
	2	1100	1 - 7 ml gray
	2.5	1130	1 - 7 ml gray
	3	1200	1 - 7 ml gray
	3.5	1230	1 - 7 ml gray
	4	1300	*1 - 10 ml royal blue 1 - 7 ml gray
	5	1400	1 - 7 ml gray
	6	1500	1 - 7 ml gray
	7	1600	1 - 7 ml gray
	8	1700	*1 - 10 ml royal blue 1 - 7 ml gray
	10	1900	1 - 7 ml gray
	12	2100	*1 - 10 ml royal blue 1 - 7 ml gray
DAY 2, 16:	16	0100	1 - 7 ml gray
	24	0900	1 - 7 ml gray
	36	2100	*1 - 10 ml royal blue 1 - 7 ml gray

*Collect first

8. Vital Signs: 5-minute sitting blood pressure, pulse and respiration, temperature, and weight each morning at 0500.
9. Urine Collection: A -12 to 0 hour collection will begin at 2050. All subjects will empty their bladders 10 minutes before the collection begins. All subjects will be sent to the bathroom to empty their bladders after the 0-hour bios have been completed on Day 1. At those times at which blood draws and urine collections coincide, the subjects will be sent to the bathroom to empty their bladders immediately after completion of the blood draws. At all other times, subjects will be instructed to empty their bladders beginning at exactly the stipulated

APPENDIX I (cont.)

STUDY DIRECTOR'S SCHEDULE

Study Procedures (cont.)

time, using a two-minute stagger. Urine collection for each period will continue for 8 days with 0-12 hour, 12-24 hour, then at 24-hour intervals of 24-48 hour, 48-72 hour, 72-96 hour, 96-120 hour, 120-144 hour, 144-168 hour and 168-192 hour.

10. Discharge: On Day 9, subjects will leave the center for a six-day wash-out period. Final discharge is on Day 23, after the second treatment period.
11. NPO: All subjects will be NPO except for water from 2100 on Day -1 until breakfast on Day 1, and from 2100 on Day 14 until breakfast on Day 15. On all other days, subjects will be NPO at 2300.
12. Activity: Normal levels of activity should be carried out during the first 5 hours post the initial dose. No strenuous activity is permitted, but subjects must be sitting or ambulatory during this time.

APPENDIX I (cont.)
STUDY DIRECTOR'S SCHEDULE

Diet

DAY -1

Supper - 1730

House Diet

Snack - 2000

House Diet; however, must eat all food provided.

DAY 1

Breakfast - 0800

Orange juice	1/2 c
Cold cereal	3/4 c
Sugar	1 tsp
Toast	2 slices
Butter	2 tsp
Milk	8 oz

Must eat all food provided

Lunch - 1400

House Diet; however, must eat all food provided.

Supper - 1800

House Diet; however, must eat all food provided.

DAYS 2-8

All meals are house diet, but subjects are asked to eat all food provided on Day 2.

Breakfast - 0930

Lunch - 1300

Dinner - 1730

Snack - 2000

APPENDIX I (cont.)
STUDY DIRECTOR'S SCHEDULE

Diet (cont.)

DAY 9

Breakfast - 0930

DAY 14

Supper - 1730

House Diet

Snack - 2000

House Diet - Subjects are asked to eat all food provided.

DAY 15

Breakfast - 0800

Orange Juice	1/2 c
Cold cereal	3/4 c
Sugar	1 tsp
Toast	2 slices
Butter	2 tsp
Milk	8 oz

Must eat all food provided.

Lunch - 1400

House Diet, but subjects are asked to eat all food provided.

Supper - 1800

House Diet, but subjects are asked to eat all food provided.

APPENDIX I (cont.)
STUDY DIRECTOR'S SCHEDULE

Diet (cont.)

DAYS 16-22

All meals are house diet, but subjects are asked to eat all food provided on Day 16.

Breakfast - 0930
Lunch - 1300
Dinner - 1730
Snack - 2000

DAY 23

Breakfast - 0930

The diet must exclude all xanthine-containing food and beverages such as coffee, tea, cola, Sanka, chocolate, or cocoa.

APPENDIX J

BIOAVAILABILITY SAMPLE HANDLING PROCEDURES

I. SAMPLE LABEL AND SPECIMEN LOG IDENTIFICATION INFORMATION

The first three numbers correspond to the Study ID number which is permanently assigned to each protocol. The next four or five numbers are the Subject's Computer ID number. The Computer ID number belongs permanently and exclusively to one particular Subject. The remaining digits correspond to the number of samples collected for a single Subject during the study and the sample type. For example: If 15 samples are to be collected, the numbers would run from 1 to 15. The sample type code follows the sequential sample number and is a code representing the type of sample contained in the storage tube or bottle. Sample type codes: P=Plasma, S=Serum, C=Cells, WB=Whole Blood, U=Urine, FE=Feces, SAL=Saliva, SP=Sputum, E=Emesis, GP=Gauze Pad.

The top line of the sample label corresponds with the data entered in the Sample Identification column on the Specimen Log.

Sample types required on this study: Plasma, Whole Blood, Urine.

II. SPECIMEN COLLECTION PROCEDURE

A. Blood (Sample required: Plasma-Salicylate)

1. Tube size: 7 ml
2. Stopper color: Gray
3. Anti-coagulant: Potassium oxalate and sodium fluoride
4. Tube ID#: T-2045PS
5. Tube Lot#: 8507193A1

B. Whole blood - Bismuth

1. Tube size: 10 ml
2. Stopper color: Navy (trace metals tube)
3. Anti-coagulant: 143 USP units of Sodium Heparin
4. Tube ID#: T-6527
5. Tube Lot#: 4J049

C. Urine

1. Collection container: Polyethylene bottle with paper lined metal cap
2. Urine collection container is chilled on wet ice in a styrofoam cooler during the collection interval

APPENDIX J (cont.)

BIOAVAILABILITY SAMPLE HANDLING PROCEDURES

III. SAMPLE PROCESSING

A. Plasma for Salicylate analysis

1. Centrifugation
 - a. Maximum time after draw: within 30 minutes
 - b. Speed: 2500 RPM
 - c. Temperature: 4°C
 - d. Length of spin: 15 minutes
2. Storage container: Sarstedt #546
3. Decanted with: Glass pipet
4. Freezing/refrigeration: Frozen in dry ice; stored in a -10 to -20°C freezer in an upright position

B. Whole blood for Bismuth analysis

1. Storage container: Sarstedt #541 (13 ml capacity)
2. Freezing: Frozen in a -10°C to -20°C freezer
3. Amount required: Minimum of 6 ml

C. Urine

1. Total volume calculated by specific gravity

FORMULA: Total volume weight minus the tare weight equals the corrected weight which is divided by the specific gravity resulting in the total volume of urine.

2. pH required: Yes
3. Aliquot size: Salicylate : 30 ml plus 7 ml aliquot
Bismuth: 30 ml plus 7 ml aliquot
4. Storage container: 60 ml Nalgene and 100 ml Nalgene bottles; Sarstedt #541 tube (13 ml)
5. Freezing/refrigeration: Freeze in a -10°C to -20°C freezer in an upright position
6. Special handling of sample: Four aliquots were saved from each collection interval; two for salicylate analysis; two for bismuth analysis

IV. SAMPLE PACKING AND SHIPPING

- A. Samples photographed (Kodak 100ASA print film; 36 exposure roll; film developed to negatives; stored in study files)
- B. Samples packaging
 1. Packed in freezer-safe zip lock plastic bags by experimental time period.
 2. Special packaging: None
- C. Shipping container: Styrofoam cooler

APPENDIX J (cont.)

BIOAVAILABILITY SAMPLE HANDLING PROCEDURES

- D. Samples packed in dry ice sufficient to maintain them in a frozen state for a maximum of 72 hours.
- E. Samples shipped by priority overnight courier service unless instructed otherwise by sponsor.
- F. Courier Service: Salicylate samples: QRC Courier
Bismuth samples: Federal Express
- G. Notification call made to designated recipient.
- H. Confirmation call placed after expected arrival time the following day.

V. SAMPLE RECEIPT INSTRUCTIONS

- A. Log in samples checking against submission record accompanying shipment.
- B. Call immediately if discrepancy is found (816) 483-1850 Bio Department.
- C. Return signed copy of submission record to QRC in self-addressed stamped envelope.

VI. SAMPLES SHIPPED TO:

A. Salicylate samples:

Teresa Reimer
Kansas City Analytical Service
12302 Johnson Drive
Shawnee Mission, Kansas 66216

Sample types shipped to this address: Plasma and urine

Sample shipment date: 11/07/85

B. Bismuth samples:

Fred Mitchell
Procter & Gamble
11511 Reed Hartman Highway
Cincinnati, Ohio 45241

Sample types shipped to this address: Whole blood and urine

		<u>Airbill number(s)</u>
Sample shipment dates:	10/02/85	831-940-255
	10/16/85	831-940-196
	11/07/85	831-944-212

APPENDIX K

PHASE I

LABORATORY REFERENCE RANGES
HEALTHY MALES (18-50 YEARS OF AGE)

Test (Code)	Method	Reference Range	Units
<u>HEMATOLOGY</u>			
Hemoglobin (HGB)	Coulter 'S' spectro- photometer	13.4-18.0	gm/dl
Hematocrit (HCT)	Coulter 'S' electronic computation	39.0-51.4	%
Red Blood Count (RBC)	Coulter 'S' non- optical counting	4.34-5.90	M/mm ³
White Blood Count (WBC)	Coulter 'S' non- optical counting	4.4-11.9	K/mm ³
Mean Corpuscular Volume (MCV)	Coulter 'S' averaging RBC pulse heights	78-97	μ ³
Mean Corpuscular Hemoglobin (MCH)	Coulter 'S' electronic calculation	27.2-34.2	μg
Mean Corpuscular Hemoglobin Concentration (MCHC)	Coulter 'S' electronic calculation	33.4-36.3	%
Differential:	Stained-smear microscopy		
Neutrophils, segmented (SEG)		36-76	%
Neutrophils, bands (BAND)		0-1	%
Lymphocytes (LYMPH)		22-58	%
Atypical lymphocytes (ATLIM)		0	%
Monocytes (MON)		0-3	%
Eosinophils (EOSIN)		0-6	%
Basophils (BASO)		0-1	%
Metamyelocytes (METPM)		0	%
Myelocytes (MELO)		0	%
Platelet Estimate (PLEST)		Adequate	NA
RBC Morphology (RMORP)		Interpretation	NA

APPENDIX K (cont.)

PHASE I

LABORATORY REFERENCE RANGES
HEALTHY MALES (18-50 YEARS OF AGE)

Test (Code)	Method	Reference Range	Units
Platelet Count (PLTCT)	Thrombo Counter C counting	172-418	K/mm ³
<u>SERUM CHEMISTRIES</u>			
Uric acid (URIC)	Colorimetric Azino Method by Klose Hitachi Analyzer	3.9-8.7	mg/dl
BUN (BUN)	Talke & Schubert Enzymatic Method Using Coupled Urease GLH Enzyme System	0-17	mg/dl
Creatinine (CREAT)	Modified Jaffe' Reaction - Hitachi Analyzer	0.7-1.4	mg/dl
Total Bilirubin (TBIL)	Modified Malloy - Evelyn method - Hitachi Analyzer	0.0-1.0	mg/dl
Alkaline Phosphatase (ALKP)	Housamen method using Amp buffer, p-nitrophenol phosphate - Hitachi Analyzer	54-132	IU/L
SGOT (ASTOT)	Bergmeyer & Burt method using optimal Substrate Concentration - Hitachi Analyzer	0-44	IU/L

APPENDIX K (cont.)

PHASE I

LABORATORY REFERENCE RANGES
HEALTHY MALES (18-50 YEARS OF AGE)

Test (Code)	Method	Reference Range	Units
SGPT (ALTPT)	Bergmeyer & Burt method using optimal Substrate Concentration - Hitachi Analyzer	0-50	IU/L
Serum Salicylate, Quantitative (SALQN)	Modified Trinders	BL*	mg/dl

URINALYSIS

pH (URH)	Electrometric	5.2-7.0	NA
Specific Gravity (SPGR)	Ames N Multistix SG	1.005-1.030	NA
Urine Glucose (UGLU)	Ames N Multistix SG	Negative	NA
Urine Ketones (KEIT)	Ames N Multistix SG	Negative	NA
Urine Protein (UPRO)	Ames N Multistix SG	Negative	NA
Microscopic WBC (UWBC)	Microscopic examination	0-15	/HPF
Microscopic RBC (URBC)	Microscopic examination	0-6	/HPF
Microscopic Bacteria (BACT)	Microscopic examination	Negative	NA
Microscopic Casts (CAST)	Microscopic examination	Negative	/LPF

* Below detectable limits.

APPENDIX K (cont.)

PHASE I

LABORATORY REFERENCE RANGES
HEALTHY MALES (18-50 YEARS OF AGE)

Test (Code)	Method	Reference Range	Units
<u>OTHER</u>			
Urine Drug Screen (UES)	Toxi-Lab ^R thin layer chromatography	All Negative	NA
Ethyl Alcohol (ALCO)	Calbiochem Stat-Pack Ethyl Alcohol Test	BUL*	mg/dl
Creatinine Clearance (CLR)	Calculation from Jaffe' Reaction	Greater than 75	ml/min

* Below detectable limits.