CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020049

Trade Name: PENTASA CAPSULES 250 MG

Generic Name: MESALAMINE

Sponsor: MARION MERRELL DOW

Approval Date: 05/10/93

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APPLICATION: 020049

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter				
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling				
Medical Review(s)				
Chemistry Review(s)				
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)	**X**			
Bioequivalence Review(s)				
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020049

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 21 1992

NDA: 20-049

MESALAMINE
Pentasa™
Capsules 250 mg
Marion Merrell Dow

SUBMISSION DATES:
November 29, 1990.
October 23, 1991.
December 3, 1991.

REVIEWER: Lydia C. Kaus Boggs, MS, PhD

TYPE OF SUBMISSION: NDA - Controlled Release Formulation

SYNOPSIS:
The firm has studied the pharmacokinetics of mesalamine (5-ASA, 5-amino salicylic acid) in a delayed release capsule formulation. Mesalamine is to be used in the adult population; there are no statements in the labeling for pediatric use. Dose proportionality of Pentasa™ was studied in the dosing range covered in the labeling. No studies were performed in special populations such as those that are renally or hepatically impaired or in the elderly. No drug interaction studies were carried out. Two food effect studies were submitted. An acceptable interim dissolution method was provided. No pharmacodynamic/pharmacokinetic studies were provided, however since this drug's action is more local this information would be difficult to provide. A bioequivalency study was provided but it did not include the final 'to be marketed' formulation of the drug. The firm believes that the formulation studied in the bioequivalency study is sufficiently similar to the 'to be marketed' formulation. The firm studied both single dose and steady-state kinetics of mesalamine in this delayed release formulation.

Proposed Dose: Initially 0.5G four times daily, may be increased to 1G four times daily.

RECOMMENDATION:
The firm's NDA 20-049 does meet the requirements for the Division of Biopharmaceutics. Athough there has been no study to show the bioequivalence of mesalamine in its final market form to those used in the pivotal clinical trials, the 'to be marketed formulation' has been used on a compassionate trial basis.

. Also, the in vitro - in vivo correlation that falls into the Type 2 USP classification further supports the final 'to be marketed' formulation (statistically significant correlations were shown for Cmax and AUC at 1 and 2 hour dissolution sampling times). This is acceptable provided the firm changes their dissolution specification as descibed in this review and has tight controls on the ingredients of their final 'to be marketed' formulation.

TABLE OF CONTENTS: Page No.

Note: Appendix II contains more detailed data/information such as dosage formulation, assay validation information, individual subject data and statistical analyses. This information is being retained in the Division of Biopharmaceutics, and can be obtained upon request.

BACKGROUND:

Mesalamine as a delayed release formulation is intended to be used as a single oral agent for the induction of clinical remission and for the relief of symptoms in patients with ulcerative colitis. The firm has submitted five biopharmaceutic studies in support of their submission.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS:

I. BIOAVAILABILITY/BIOEQUIVALENCE:

A. Relative Bioavailability:

Pentasa™ was compared to an enema and a suspension of sulfasalazine in this submission. The extent of absorption of mesalamine is dependent on the region of the gastrointestinal tract to which it is exposed and is therefore dependent on an oral formulation's release characteristics. One gram of 5-ASA in the form of a suspension was rapidly absorbed. Mean C_{max}'s following administration of this suspension were 14.72 μg/mL %CV 26%) and 11.4 μg/mL (%CV 20%) for 5-ASA and acetyl

5-ASA respectively. The mean $T_{max's}$ for 5-ASA and acetyl 5-ASA from the suspension were 0.98 h (%CV 54) and 1.44 h (%CV 41%) respectively. About 21% of 5-ASA was excreted unchanged in the urine and 57% was excreted as the metabolite acetyl 5-ASA: 13% was eliminated in the feces chiefly as acetyl 5-ASA When given as Pentasa™ capsules (four 250 mg capsules), the mean $C_{max's}$ were 0.98 μg/mL (%CV 53%) and 1.83 μg/mL (%CV 46%) for 5-ASA and acetyl 5-ASA respectively and mean $T_{max's}$ were 3.8 h (%CV 52%) and 3.7 h (%CV 46%) for 5-ASA and acetyl 5-ASA respectively. The variability in the $C_{max's}$ were higher for Pentasa™ ; Urinary recovery accounted for 29% of the dose as acetyl 5-ASA and less than 0.2% was recovered as 5-ASA. 40% of the dose was eliminated in the feces. Again %CV's were high. Therefore not all the drug was accounted for after administration of Pentasa™ (**Study PAST0348, Vol. 1.37, pp.6-6080**).

B. Bioequivalence:

The firm failed to show bioequivalence between the pilot production formulation used in a safety and efficacy trial and a full production lot formulation used in ulcerative colitis efficacy trial The not been tested in any safety and efficacy trials, but has been used in

C. Food effect:

A high-fat meal decreased to a large extent the rate and extent of absorption of 5-ASA from Pentasa™. The mean AUC was reduced from 4537.68 ng h/mL (%CV 37%) to 1318.38 ng h/mL (%CV 63%) after food and C_{max} was reduced from 977.32 ng/mL (%CV 51%) to 286.37 ng/mL (%CV 87%) after food. Again there was high variability among subjects and this increased after a high-fat meal. Fecal sampling was not taken for the food vs. fasting treatments for this study. Urinary excretion of acetyl 5-ASA fell from 26.8% to 17.7% of the dose given after food. The time to peak was prolonged from a mean of 3.5 h to 4.0 h after food in 46% of the subjects studied (**Study PAST0310**). The firm further investigated this food effect to determine whether the effect was due to the formulation. Again a high-fat meal decreased the rate and extent of absorption of Pentasa™ and a suspension formulation of the drug 5-ASA. The decrease was similar for both formulations and the firm therefore concluded that Pentasa™'s formulation was not contributing to the decrease in bioavailability. Mean AUC's decreased by 62% and 50% for the capsule and suspension formulations respectively, after food and mean $C_{max's}$ for 5-ASA decreased by 62% and 64% for the capsule and suspension formulations respectively, after food. Fecal excretion of total salicylates increased from a mean of 40% to 46% of the dose after food for the capsule and increased from a mean of 13% to 27.7% for the suspension after food. Total salicylates represent both released and unreleased salicylate. However the total dose recovered was less for the suspension after food (89.8% for fasting and 71.9% after food) (**Study PAST0348**). The free salicylates in feces decreased from a mean of 232.2 mg to a mean of 194.4 mg after food with Pentas™, whilst these increased from a mean of 80.1 mg to a mean of 147.7 mg with the 5-ASA suspension.

II. PHARMACOKINETICS:

Single dose studies:

After a single dose of 500mg mesalamine using mean C_{max} was 423.4 ng/mL (%CV 32%), mean AUC_{0-96} was 1213 ng h/mL (%CV 46%). and mean T_{max} was 3.1 h (%CV 45%). A single dose of one gram (four mesalamine capsules - gave a mean C_{max} of 966 ng/mL (%CV 62%), a mean AUC_{0-48h} of 3572 ng h/mL (%CV 49%) and mean T_{max} of 2.74 h (%CV 44%). The rate and extent of bioavailability was greater than for azulfidine equivalent to 960 mg of mesalamine (AUC_{0-48h} of 1560 ng/mL (%CV 51%), mean C_{max} of 169 ng/mL (%CV 55%)). It must be remembered that azulfidine is cleaved by gut bacteria to yield 5-ASA, which then becomes available for absorption in the lower gastrointestinal tract as reflected by the mean T_{max} of 10.9 h (%CV 39%) (**Study # 10-67B-001**).

Multiple dose study:

Mesalamine was studied at doses 250 mg, 500 mg and one gram every six hours for 25 doses, giving mean AUC_{ss} for 5-ASA of 815 ng h/mL, 2495 ng h/mL and 7285 ng h/mL for 250 mg, 500mg and 1000 mg qid respectively (**Study # 10-67C-101**). The results of the statistical analyses showed that trough levels of 5-ASA were not significantly different between Day 6 and Day 7 implying that steady-state had been reached. Normalized Cmax and AUC were significantly different between treatments and therefore 5-ASA was not dose proportional between 250 mg to 1 g QID at steady-state. Urinary excretion was significantly different between treatments for normalized 5-ASA, but not for the normalized acetylated metabolite. Only Cmax was dose proportional for the metabolite acetyl 5-ASA in plasma between treatments. The fluctuation in plasma levels was also significantly different between treatments. The normalized amounts of 5-ASA in the feces were not significantly different between treatments, however they were outside the 90% confidence interval for the two one-sided t-test. The normalized amounts of acetyl 5-ASA in the feces were significantly different between treatments.

III. METABOLISM:

The metabolism of mesalamine was not studied for this particular submission, however published data is available on this for other dosage forms and in general for mesalamine. The primary metabolite is N-acetyl 5-amino salicylic acid

Other metabolism that occurs is conjugation to glucuronic and sulfuric acid and these are relatively minor pathways.

IV. DOSE AND DOSAGE FORM PROPORTIONALITY:

Mesalamine was not dose proportional between 250 mg to 1000mg qid dosage regimen which may be due to saturation of metabolism (**Study # 10-67C-101**). A full scale production lot was used but not the formulation. The metabolite acetyl 5-ASA showed dose proportionality for AUC_{ss} between 250 mg to 1000 mg qid dosage regimen of the parent compound.

V. SPECIAL POPULATIONS:

No special populations were studied by the firm, but several published papers were submitted. No labeling claims were made with regard to special populations.

VI. DRUG INTERACTIONS:

A published paper on famotidine was submitted. However the firm did not put this in the la eling.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

No PK/PD relationships were described in the submission. This would be difficult to achieve as most of mesalamine's action is thought to be local to the intestinal mucosa.

VIII. FORMULATION:

Market Formulation:

COMPOSITION	
COMPONENT	**CONTENT (MG/CAPSULE)**
Mesalamine (5-ASA)	250.0
Sugar	
Talc,	
Ethylcellulose	
Hydroxypropyl Methylcellulose	
White Wax	
Castor Oil	
Colloidal Silicon Dioxide	
Stearic Acid	
Acetylated monoglyceride	
TOTAL	
Gelatin Capsule	

The to be marketed formulation has not been tested in major safety and efficacy trial, but was used in compassionate trials (PAPR0003 and PAPR0005).

IX. DISSOLUTION:

Firm's Dissolution specs:

X. ASSAY:

Mesalamine and its major metabolite were analyzed in plasma, urine and fecal samples. An method was used across studies

Overall the assay validation was satisfactory. In all of the biopharmaceutics studies except the first described in this review, samples were stored

COMMENTS TO BE SENT TO THE FIRM:

Labeling Comments:

Under **DESCRIPTION** and *"Aspects of Drug Delivery"*:

1. The firm describes the dosage form as a unique ethylcellulose-coated, controlled-release formulation. There is no evidence to suggest that the dosage form is particularly unique and the use of controlled-release is debatable. The phrase should read *"is an ethylcellulose-coated, delayed-release formulation"*. Also the description *"prepared by micro-encapsulation of mesalamine-containing beads"* should be replaced by *"prepared by coating of mesalamine-containing beads with ethylcellulose"*.

2. The firm uses the phrase *"predictable uniform and continuous release "* to describe Pentasa™ as a dosage form. This is based on dissolution data and not any in vivo data. Plasma levels have not been described in the target population, which has different transit times and enteral pH conditions. Also the pharmacokinetic data presented does not strongly support a controlled release formulation. The phrase should read *"predictable uniform and continuous release based on in vitro dissolution data".*

3. The firm also states *"release is continuous from the duodenum to the rectum, and drug delivery is not significantly affected by the .....or increased bowel activity."* This statement is based on studies using dosage forms other than the firm's proposed dosage form.

The phrase should be replaced by *"release is continuous from the stomach and duodenum to the rectum. No studies have been undertaken with this particular formulation to show that drug delivery is*

not significantly affected by the .....or increased bowel activity."

4. The firm states under **Absorption** *"Based on urinary excretion data, 20 to 30% of the mesalamine in PENTASA is absorbed. In contrast .....aqueous suspension, mesalamine is approximately 80% absorbed."* This should be restated as *"Based on urinary excretion data, at least 20 to 30% of the mesalamine in PENTASA is absorbed. In contrast .....aqueous suspension, mesalamine is at least 80% absorbed."*

5. The firm states under **Human kinetics and Metabolism** *"Oral mesalamine pharmacokinetics were nonlinear when Pentasa capsules were dosed from 250 mg to 1 g four times daily, suggesting saturable first-pass metabolism."*
This should be restated as *"Oral mesalamine pharmacokinetics were nonlinear when Pentasa capsules were dosed from 250 mg to 1 g four times daily and may be due to saturable metabolism."*

General labeling comments:
6. The firm should state that Pentasa™ has not been studied in renal failure nor in patients with hepatic failure nor in the elderly.

7. The effect of food is complex and has been omitted from the labeling. The effect of food on the efficacy of this dosage form would be difficult to study. The clinical trials it seems were undertaken without control to food intake.

8. The Reviewing Medical Officer may want to consider the dosing recommendation in the labeling to suggest a more gradual dose increase if required from 0.5 G qid to 0.75 G qid due to the nonlinearity shown by this drug in the AUC's between doses 0.5 G to 1 G qid.

9. Also the labeling should be made absolutely clear regarding the term dose, ie. whether this reflects daily doses or otherwise.

APPEARS THIS WAY
ON ORIGINAL

5/15/92,
5/18/92

Lydia C. Kaus Boggs, MS, PhD.
Reviewer, Division of Biopharmaceutics.

Biopharm Day 4/28/92 (Ameeta Parekh, Lydia Kaus Boggs, Tom Ludden, Nicholas Fleischer, Henry Malinowski)
FT Initialed by Nicholas Fleischer,Ph.D. 5/18/92
Acting Branch Chief, Pharmacokinetic Evaluation.

cc: NDA 20-049, HFD-180, HFD-426 (Reviewer), (Fleischer), Chron, Division, Drug, Review, FOI (HFD-19).PC:N20-049. 11/23/91.

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APPENDIX I

SINGLE DOSE BIOAVAILABILITY STUDY

TITLE: A SINGLE DOSE BIOAVAILABILITY STUDY OF 5-AMINOSALICYLIC ACID FROM ORAL DOSAGE FORMS IN NORMAL SUBJECTS (**STUDY #** 10-67B-001) VOL.1.21,pp. 6-72

OBJECTIVES:

1. To determine the relative biovailability of four experimental formulations of Marion's 250 mg 5- aminosalicylate acid (5-ASA, mesalamine) controlled-release capsules These formulations were compared to Pentasa tablets (Treatment T, The capsule formulation that best approximated Pentasa tablet was then used in Phase II and Phase III clinical safety and efficacy trials.

2. To develop an in vivo/in vitro correlation for the four capsule formulations and two lots of Pentasa tablets.

3. To determine the adequacy of the newly developed 5-ASA assay methodology.

Objective #1 was not relevant to this NDA in that the tablet has not been used for any of the pivotal US clinical trials nor biopharmaceutic studies.

INVESTIGATOR:
J. Kisicki and C. Ryan

DATE OF CLINICAL STUDY: 6/21/86 - 8/13/86
DATE OF ANALYTICAL STUDY: 7/8/86 - 9/3/86

SUBJECTS:
Twenty-two healthy, male subjects completed the study. The average age was 25.4 $\pm$ 4.6 years old and the average weight was 168.5 $\pm$ lb.

DRUG SUPPLIES:
Treatment T: Two Pentasa 250 mg slow-release tablets
Manufactured 2/86

Treatment A: Two 5-ASA 250 mg slow-release capsules
manufactured 4/86

Treatment B: Two Pentasa 250 mg slow-release tablets
Manufactured 2/86

Treatment C: Two 5-ASA 250 mg slow-release capsules
manufactured 4/86

Treatment D: Two 5-ASA 250 mg slow-release capsules manufactured 4/86

Treatment E: Two 5-ASA 250 mg slow-release capsules manufactured 4/86

STUDY DESIGN AND DOSAGE ADMINISTRATION:

The study was described as a balanced incomplete block design. Each subject received 500 mg oral doses over four study periods. The randomization scheme is shown in the appendix. Treatment T was always given as the first treatment. The firm identified several outliers and the statistical analyses were performed with and without these outliers. Note that these outliers were not directly pertinent to the in vitro - in vivo correlation since they were outliers for the following:

Subject 6:
a) Treatments T, A, B, D fecal elimination data of the salicylates
b) Treatment B renal excretion data of acetyl 5-ASA.
c) Treatment B plasma data of both 5-ASA and acetyl 5-ASA.

Subject 18:
a) Treatment D fecal elimination data of the salicylates
b) Treatment T plasma data of 5-ASA.

Treatments T and B were the tablets.

Collection of biological samples:

Blood samples were collected at 0, 0.5, 1, 2, 3, 4, 5, 8, 12, 18, 27, 36, 48, 60, 78 and 96 hours after dose administration. Pooled urine samples were collected pre-dose and at the intervals: 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours, 48-72 hours and 72-96 hours. Fecal samples were collected also up to 96 hours.

ANALYTICAL METHODOLOGIES:

Plasma Assay:

Within Day Accuracy, Precision and Sensitivity:

Date 5/19/86

Conc. (ng/mL)	5-ASA	Acetyl 5-ASA
10	10.60 (8.7)	11.30 (4.7)
80	76.05 (4.4)	77.07 (7.5)
160	165.13 (6.5)	154.37 (3.2)
300	--	297.68 (9.73)
900	--	976.87 (4.89)
1200	--	1324.87 (9.83)

(%CV), N=6

Inter-day accuracy and precision:

Conc. (ng/mL)	5-ASA	Acetyl 5-ASA
10	10.03 (11.0)	10.70 (9.7)
80	81.88 (7.6)	78.56 (4.9)
160	165.76 (5.9)	156.36 (3.5)
300	--	301.15 (6.75)
900	--	911.53 (7.1)
1200	--	1250.13 (7.9)

(%CV), N=18

Urine Assay:

Within Day Accuracy, Precision and Sensitivity:

Date 4/11/86

Conc (μg/mL)	5-ASA	Acetyl 5-ASA
1	1.18 (8.5)	--

2	1.95 (8.2)	--
5	4.62 (3.9)	--
10	10.10 (3.0)	--
20	21.17 (4.9)	22.51 (5.3)
50	50.81 (8.7)	51.09 (10.2)
100	99.91 (8.2)	100.83 (13.1)

(%CV), N=3

Inter-Day Accuracy and Precision:

Conc (μg/mL)	5-ASA	Acetyl 5-ASA
1	1.17 (7.8)	--
2	1.93 (6.2)	--
5	4.78 (8.2)	--
10	10.02 (6.5)	10.27 (8.2)
20	19.87 (7.6)	20.32 (13.6)
50	47.86 (12.0)	47.85 (13.7)
100	101.21 (9.3)	102.07 (13.3)

(%CV)

Feces Assay:

Within Day Accuracy and Precision:
Tables were not provided.

Inter-day reproducibility:

Standards:	5-ASA	Acetyl 5-ASA
0.8 ng	0.84 (11)	0.81 (11)

1.57 ng	1.69 (3.6)	1.66 (4.2)
3.30 ng	3.43 (4.4)	3.45 (3.8)
6.6 ng	6.89 (1.9)	6.85 (1.0)
16.5 ng	15.84 (1.8)	15.85 (1.8)
33.0 ng	33.13 (1.1)	33.13 (1.3)

(%CV)

PHARMACOKINETIC RESULTS:

The pharmacokinetic parameters are reported for Treatment D and pharmacokinetic studies.

Plasma

Parameter	5-ASA	Acetyl 5-ASA
C_{max} ng/mL	423.4 (32.1)	902.0 (27.0)
T_{max} h	3.1 (44.7)	3.6 (38.5)
AUC_{0-n}	1213.0 (45.6)	9274.9 (42.8)

(%CV)

Fecal

Free 5-ASA (mg)	57.1 (79)
Free Salicylates (mg)	158.6 (38)
Total Salicylates (mg)	289.3 (34) =57.9% of dose

(%CV)

Urine

Acetyl 5-ASA (mg)	131.4 (26)
5-ASA (mg)	0.5 (184)
Total Salicylates (mg)	103.1 (25)

(%CV)

The rest of the pharmacokinetic parameters and the correlation relationship are in the attachments.

Comments:

1. The assay methods for plasma, urine and feces samples were adequate.

2. The statistical data was not critiqued as comparisons were being made to a European marketed form of the drug which the firm was trying to match in a capsule form. The formulation described as Treatment D was chosen in subsequent clinical and pharmacokinetic studies. The pharmacokinetic information on this particular treatment is described in the review.

3. The *in vitro-in vivo* correlation was suggested by the firm from a significant linear correlation between the mean pharmacokinetic parameters for 5-ASA of C_{max} and AUC_{o-n} and the dissolution times of one hour and two hours No support was given for a significant correlation with the remaining dissolution times.

4. It must be noted

Subsequently formula was used in clinical and pharmacokinetic studies but on a pilot scale. No reference was made both in terms on performance. Also the ranges covered by the final formulation composition for the to be marketed capsule formulation encompass the values for most of the lab scale formula studied. Therefore a strict range of these individual ingredients needs to be adhered to so that the in vitro - in vivo correlation holds.

5. The AUC's determined for this correlation were based for the most part on four to five data points per subject and in the case of the slowest dissolving formulation as little as one plasma level. This was mainly due to the plasma levels quickly falling below the LOQ for the assay. Also the plasma levels of 5-ASA fell below the LOQ well before the elimination phase of the plasma level - time curve. However the data

The plasma levels fell below the LOQ at about 6 hours post administration and had the effect of determining truncated AUC's which makes the correlation far less robust.

6. The incomplete block design was poor since the first period was always Treatment T, also the rest of the Treatments were not balanced.

7. The correlation described by the firm is classified as Type 2 under the USP criteria. Examining plasma levels in general for Formulations/Treatments A, C, and D

The accepability of this Type 2 correlation would depend on tighter controls being set for the ranges

of the individual ingedients of specification.

and the tightening of the dissolution

Conclusion

There is a correlation between the

performance of the different formulations

Although, there have been no biopharmaceutic nor pharmacokinetic studies undertaken with the final 'to be marketed' product, the in vitro-in vivo relationship is acceptable provided the firm sets the dissolution specification as descibed in the summary page 6 and also the firm must control tightly the ranges for individual ingredients composing the formulation.

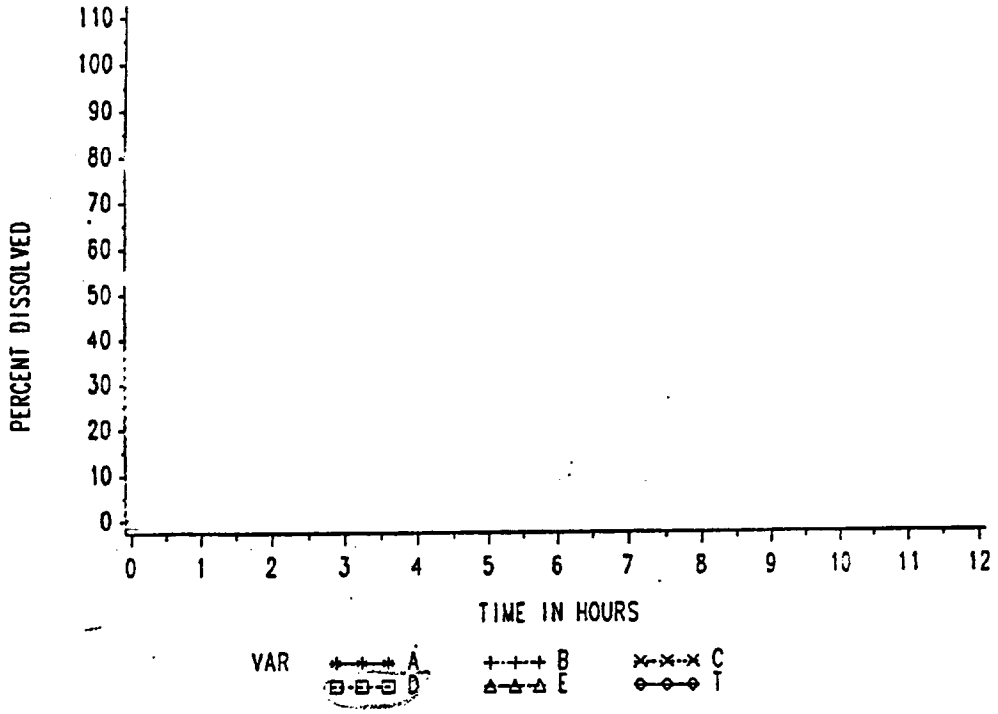

Figure 2-2. Cumulative 5-ASA Dissolved vs Time

Reference to Supporting Data:	**Vol**	**Page**
Full Report H10-67B-001, Dissolution Rate Tables	**1.21**	**6-114**
	through	
	1.21	**6-124**

Note: Trt A: (Two 5-ASA 250 mg capsules, PD048677,
Trt C: (Two 5-ASA 250 mg capsules, PD048676,
Trt D: (Two 5-ASA 250 mg capsules, PD048679
Trt T: (Two Pentasa 250 mg tablets, PD048613,
Trt B: (Two Pentasa 250 mg tablets, PD048610,
Trt E: (Two 5-ASA 250 mg capsules, PD048680,)

- Serial blood, urine, and fecal samples were collected up to 96 hours following dosing. 5-ASA and its major metabolite, acetyl 5-ASA, were measured from all three biological fluids to determine relative bioavailability of salicylates among the various treatments.

F. Human Pharmacokinetics and Bioavailability Summary
3. Biopharmaceutics Studies of Pentasa Capsules (Marion Laboratories, Inc.)

- IN VIVO/IN VITRO CORRELATION

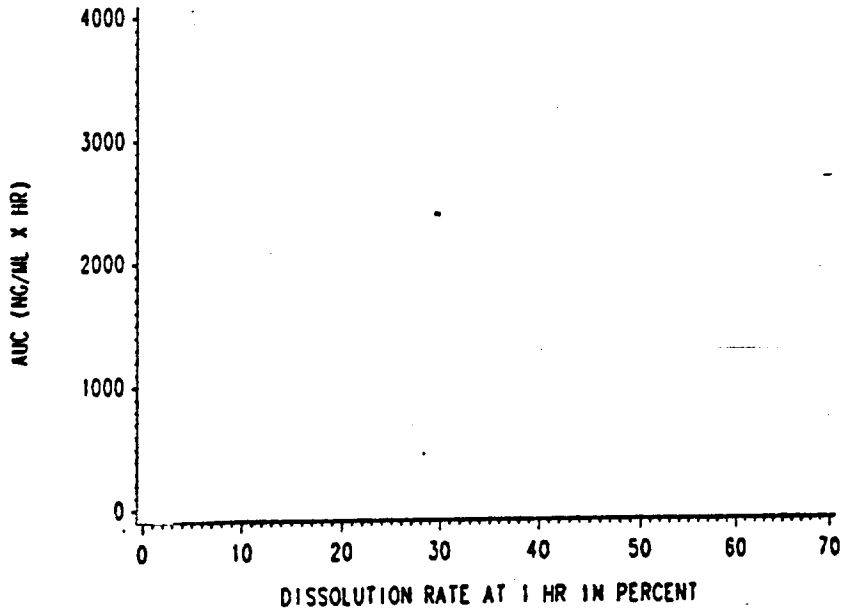

Figure 2-7. In Vivo/In Vitro Correlation of 5-ASA Parameter with 95% Confidence Interval. No. 10-67B-001

References to Supporting Data:	**Vol**	**Page**
Full Report H10-67B-001, Table 61	1.21	6-188

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Table 61

SUMMARY OF IN VIVO/IN VITRO CORRELATION OF 5-ASA PLASMA KINETIC PARAMETERS

Study No. 10-67B-001

Dissolution (% Dose)	AUC(0-n) (ng/ml x hr)		
	Equation	R^2	p-value
1 hr 2 hr			0.0034 0.0180
Dissolution (% Dose)	**Cmax (ng/ml)**		
	Equation	**R^2**	**p-value**
1 hr 2 hr			0.0071 0.0164
Dissolution (% Dose)	**tmax (hr)**		
	Equation	**R^2**	**p-value**
4 hr 6 hr 8 hr 12 hr			0.0006 0.0089 0.0050 0.0087

R^2	*Linear Regression Equation*	*p-values of slope*
	AUC	0.0034
	Cmax	0.0071

it.

$p < 0.05$ Statistical significance.

- 5-ASA PLASMA RESULTS

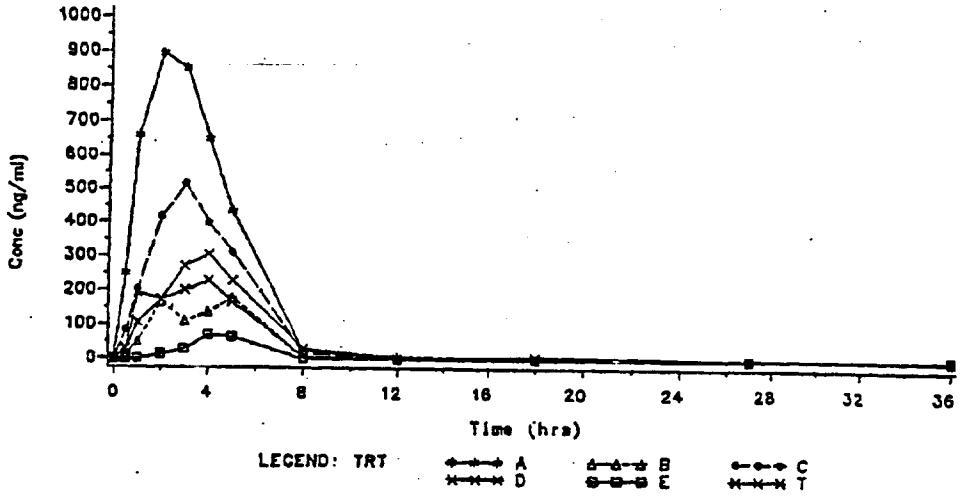

Figure 2-3. Mean 5-ASA Plasma Profiles (Without Outliers). Study No 10-67B-001

References to Supporting Data:	**Vol**	**Page**
Full Report 10-67B-001, Tables 1 to 6	**1.21**	**6-126**

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ON ORIGINAL

Table 61

SUMMARY OF IN VIVO/IN VITRO CORRELATION OF 5-ASA PLASMA KINETIC PARAMETERS

Study No. 10-67B-001

Dissolution (% Dose)	AUC(0-n) (ng/ml x hr)		
	Equation	R^2	p-value
1 hr 2 hr			0.0034 0.0180
Dissolution (% Dose)	**Cmax (ng/ml)**		
	Equation	R^2	p-value
1 hr 2 hr			0.0071 0.0164
Dissolution (% Dose)	**tmax (hr)**		
	Equation	R^2	p-value
4 hr 6 hr 8 hr 12 hr			0.0006 0.0089 0.0050 0.0087

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f. Investigational Formulations

The following table summarizes the formulation usage by lot number in all relevant studies included in this submission:

Table 2-4. Investigational Formulations

Protocol	*Study Type*	*Location*	*Lot Number† (Packaging Number)*	*Batch Scale*	*Formula*
10-67B-001	Pharmacokinetic	Vol 1.21 Page 6.72	PD048613 PD048610 PD048676 PD048677 PD048680 PD048679		
0-67Z-001	Pharmacokinetic	Vol 1.25 Page 6-1284	PD068635		
67C-001 (500-67C-886-4)	Phase I	Vol 1.42 Page 8-180	PD068635 (PD078608) (PD078609) (PD078610)		
67C-039 (500-67C-886-3)	Phase I	Vol 1.43 Page 8-480	PD068635 (PD078608)		
10-67C-101	Phase I	Vol 1.29 Page 6-2795	N7036		
PAPR0001	Clinical Efficacy	Vol 1.60 Page 8-5403	N7034 N7035 (PD028716) (PD028717)		
PAPR0003	Compassionate	Vol 1.73 Page 8-9474	C7227 C7238 H7197 H7198 H7200 RD7913 RD9228		
PAPR0005	Compassionate	Vol 1.80 Page 8-11512	C7238 C7227 H7197 H7199 RD7913 RD9228		
500-67C-386-1	Clinical Efficacy	Vol 1.46 Page 8-1195	PD068635		
PAPR0013 (PAST0310)	Pharmacokinetic	Vol 1.33 Page 6-4675	PD068635 N7035		
PAPR0015 (PAST0348)	Pharmacokinetic	Vol 1.37 Page 6-6080	N7036		

† Some early studies list product by packaging lot number rather than capsule lot number. The packaging lot numbers are included in parentheses following the capsule lot number contained in that package.

in vitro - in vivo correlation study

Form.	IR ETC	CR ETC	CR HPMC	ETCir:cr	RATIOS CR ETC:HPMC	
				1:1.48	1:1	C
				1:0.74	1:3	A
				1:1.75	1:0.7	E
				1:1.60	1:0.85	D
				1:2.75	1:0.85	
				1:0.81	1:0.85	
				1:1.9	1:0.85	

proposed ratios in manuf. process

IRETC 2.003to12.02
8.45to14.79 CR ETC
7.15to12.52 CR HPMC

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7. Microbiology: N/A

(b) Drug Product:

1. Components:

2. Composition:

Letter Page 4 DRAFT PAGE 24

H.E. 2. **Since there will be different amounts used, you should provide a list of particular values for each ingredient within a target range in the statement of composition.**

The applicant has provided a table with the expected ranges of the components.

Table 1. Final Formulation Composition

Ingredient	Proposed Market Formulation mg/capsule	Expected Ranges mg/capsule
Mesalamine	250.0	
Sugar		
Talc		
Colloidal Silicon Dioxide		
Talc		
White Wax		
Ethylcellulose		
Castor Oil.		
Stearic Acid,		
Ethylcellulose		
Hydroxypropyl Methylcellulose		
Acetylated Monoglyceride		
Total Capsule Fill Weight		

Table 2 describes the proposed market formulation with its expected ranges of ingredients.

Table 2. Final Formulation Composition		
Ingredient	Proposed Market Formulation mg/capsule	Expected Ranges mg/capsule
Mesalamine		
Sugar		
Talc		
Colloidal Silicon Dioxide		
Talc		
White Wax		
Ethylcellulose		
Castor Oil		
Stearic Acid		
Ethylcellulose		
Hydroxypropyl Methylcellulose		
Acetylated Monoglyceride		
Total CR Solids		
Total Capsule Fill Weight		

†Percentages calculated w/w based on the

Formulation Development: Four capsule formulations with varying dissolution rates were developed initially. These capsule formulations, were screened for general pharmacokinetics and bioavailability as reported under protocol 10-67B-001 (Vol. 1.21 page 6-72). Composition of each capsule and the tablet are listed in tables 4 and 5.

Table 4. Investigational Formulations Composition

Ingredient	Formula Content mg/capsule	Content mg/capsule	Content mg/capsule	Content mg/capsule
Mesalamine				
Sugar				
Talc				
Colloidal Silicon Dioxide,				
Ethylcellulose				
Hydroxypropylmethylcellulose				
Acetylated Monoglyceride				
White Wax,				
Ethylcellulose				
Castor Oil,				
Stearic Acid,				

Table 5.

Ingredient	Formula

SINGLE DOSE BIOAVAILABILITY STUDY

TITLE: A SINGLE DOSE BIOAVAILABILITY STUDY OF 5-AMINOSALICYLIC ACID FROM VARIOUS ORAL DOSAGE FORMS IN NORMAL SUBJECTS (STUDY # 10-67Z-001) VOL.1.25, pp. 6-1284.

OBJECTIVES:
1. To determine the relative bioavailability of Pentasa 250 mg slow release capsules (Marion) and 1% enema compared to Azulfidine tablets .

INVESTIGATOR:
J. C. Kisicki and C. F. Ryan

DATES OF CLINICAL STUDY: 11/14/86 - 12/27/86
DATES OF ANALYTICAL STUDY: 11/20/87-4/14/87

SUBJECTS:
Thirty-six healthy subjects took part in the study (25.7 ± 4.6 years old; 169.2 ± 21.1 lb weight). Dropouts were replaced to complete the three treatments. The subjects were non-smokers and within 10% of their ideal body-weight. The inclusion and exclusion criteria were adequately described. Subject #27 dropped out after Period I for personal reasons and was not replaced.

DRUG SUPPLIES:
Treatment A: One gram (four capsules) of 5-ASA as Pentasa 250 mg slow-release capsules Pilot scale-up. Manufactured 6/86 pilot scale-up lot of

Treatment B: One gram (100 mL) of 5-ASA as Pentasa enema 1% Manufactured 3/25/86.

Treatment C: About 960 mg of 5-ASA as five Azulfidine™ 500 mg tablets

STUDY DESIGN AND DOSAGE ADMINISTRATION:
This was three-way , randomized crossover study. The drug was administered in a clinical facility after an overnight fast. Three hours after drug administration the subjects were given a standard breakfast which contained average fat content and a serving of 100% bran cereal. A standardized lunch and dinner were served six hours and 11 hours after drug administration.

Collection of biological samples:
Blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, 72, 84 and 96 hours post dose. Urine samples were collected pre-dose and at the following

intervals: 0-4 hours, 4-8 hours, 16-24 hours, 24-48 hours, 48-72 hours and 72-96 hours. Fecal samples were also collected.

Plasma samples were assayed for 5-ASA and acetyl 5-ASA. Fecal samples were assayed and characterized for Free and Total 5-ASA, Free and Total acetyl 5-ASA, total released dose (ie total free salicylates), total recovered dose (Free and unreleased salicylates) and % available free 5-ASA (% of administered dose recoverable as free 5-ASA).

ANALYTICAL METHODOLOGIES:

Plasma Assay:

Within Day Accuracy, Precision and Sensitivity:
Batch #760

Conc. (ng/mL)	5-ASA	Acetyl 5-ASA
10	10.28 (9.2)	11.55 (12.7)
160	159.92 (3.9)	169.57 (12.8)
1200	1194.56 (3.7)	1215.17 (8.0)

(%CV), N=6

Inter-day accuracy and precision:

Conc. (ng/mL)	5-ASA	Acetyl 5-ASA
10	10.54 (8.6)	10.54 (13.6)
160	163.61 (5.7)	163.75 (6.7)
1200	1197.71 (6.6)	1212.66 (5.3)

Within Day Accuracy, Precision and Sensitivity:
Batch #990

Conc. (ng/mL)	5-ASA	Acetyl 5-ASA
10	11.62 (11.5)	10.50 (9.5)
160	159.80 (3.8)	167.23 (4.9)
1200	1165.45 (1.0)	1203.25 (.9)

(%CV), N=6

Inter-day accuracy and precision:

Conc. (ng/mL)	5-ASA	Acetyl 5-ASA
10	11.06 (16.4)	10.10 (16.9)
160	168.11 (5.8)	164.76 (8.0)
1200	1211.59 (8.8)	1195.63 (9.8)

(%CV), N=26-30

Urine Assay:

Conc (μg/mL)	5-ASA	Acetyl 5-ASA
1	1.18 (8.5)	--
2	1.95 (8.2)	--
5	4.62 (3.9)	--
10	10.10 (3.0)	--
20	21.17 (4.9)	22.51 (5.3)
50	50.81 (8.7)	51.09 (10.2)
100	99.91 (8.2)	100.83 (13.1)

(%CV), N=3

Inter-Day Accuracy and Precision:

Conc (μg/mL)	5-ASA	Acetyl 5-ASA
1	1.17 (7.8)	--
2	1.93 (6.2)	--
5	4.78 (8.2)	--
10	10.02 (6.5)	10.27 (8.2)
20	19.87 (7.6)	20.32 (13.6)
50	47.86 (12.0)	47.85 (13.7)
100	101.21 (9.3)	102.07 (13.3)

(%CV)
This was the same validation method and data as described for study 10-67B-001.

Feces Assay:

Standards:	5-ASA	Acetyl 5-ASA
0.98 ng	0.97 (6.2)	0.96 (5.2)
1.96 ng	1.90 (3.7)	1.92 (5.7)
3.92 ng	3.99 (4.5)	3.99 (4.3)
7.84 ng	7.81 (1.9)	7.80 (1.3)
11.76 ng	11.67 (2.7)	11.74 (3.1)
15.69 g	15.73 (1.9)	15.68 (1.3)

caused the release of 5-ASA from the formulation

PHARMACOKINETIC RESULTS:

Table 1: Mean Pharmacokinetic Parameters.

TREATMENT	C_{max} ng/mL (%CV)	T_{max} h (%CV)	AUC_{0-n} ng.h/mL (%CV)	RELATIVE F to azulfidine (%CV)
PLASMA 5-ASA				
PENTASA CAPSULE	965.7 (61.5)	2.74 (44.4)	3572.3 (48.8)	2.87 (86.2)
ENEMA	558.4 (48.0)	1.66 (86.6)	2538.6 (77.1)	2.28 (108)
AZULFIDINE TABLETS	169.4 (55.2)	10.9 (38.8)	1560.5 (50.9)	N/A
PLASMA ACETYL 5-ASA				
PENTASA	1758.0 (35.8)	3.18 (44.2)	18785.7 (35.2)	1.57 (37.2)
ENEMA	1059.0 (51.2)	2.79 (50.3)	7342.8 (81.2)	0.64 (81.9)
AZULFIDINE TABLETS	718.9 (31.7)	12.1 (38.8)	12003.4 (27.5)	

Table 2: Mean Fecal Content Analyses

			TOTAL SALICYLATES	
TREATMENT	**FREE 5-ASA (%CV)**	**FREE SALICYLATES (%CV)**	**MG (%CV)**	**% DOSE (%CV)**
PENTASA	133.6 (82%)	270 (63)	465.7 (60)	46.6 (60)
ENEMA	246.5 (63)	255.2 (61)	362.5 (59)	36.3 (59)
AZULFIDINE	137.3 (75)	243.0 (54)	315.3 (61)	32.8 (61)

Table 3: Mean Data for amount excreted in the urine

TREATMENT	**ACETYL 5-ASA %DOSE (%CV)**	**5-ASA % DOSE (%CV)**
URINARY ACETYL 5-ASA		
PENTASA	18.8 (42)	0.6 (109.5)
ENEMA	8.8 (72)	0.24 (99.2)
AZULFIDINE TABLET	12.9 (38)	0.16 (126)

STATISTICAL ANALYSIS:

Variables were checked for violations of the assumptions of homogeneity of variance and normality of the residuals. Where appropriate log transformations were undertaken.

Outliers:

Subject #	Treatment
30	A
32	B
9	C

The above subjects were considered outliers on the basis of being outside the mean ± 3SD. Subject #30 had no detectable plasma concentration of 5-ASA. Statistical results with and without outliers gave the same conclusions. Cmax, AUC_{0-n} and T_{max} were significantly different for all treatments which is to be expected from the differences in the route of administration and the region in the gastrointestinal tract exposed to 5-ASA, which is dependent on the dosage form.

COMMENTS:

1. The relative bioavailability of Pentasa™ and enema to azulfidine tablets from the 5-ASA plasma data was 2.87 and 2.28 respectively. The relative bioavailability of Pentasa™ and enema to azulfidine tablets from acetyl 5-ASA plasma data was 1.57 and 0.64 respectively. The relative bioavailability of Pentasa™ and enema to azulfidine tablets from the acetyl 5-ASA urinary excretion data was 1.46 and 0.68 respectively.

2. Mean C_{max} in plasma for 5-ASA in Pentasa™ was 965.7 ng/mL and for the enema was 558.4 ng/mL: both higher compared to the mean C_{max} for azulfidine of 169.4 ng/mL. The higher C_{max} for Pentasa is reflective of release of 5-ASA occurring earlier in the gastrointestinal tract.

3. Fecal elimination of free salicylates was similar for the dosage forms investigated (271 mg, 255 mg and 243 mg for Pentasa™, mesalamine enema and azulfidine tablets respectively). However, the mean fecal and free 5-ASA alone was different being lower for Pentasa™ and Azulfidine (133.6 mg and 137.3 mg respectively) than the enema (246.5 mg).

F. Human Pharmacokinetics and Bioavailability Summary
3. Biopharmaceutics Studies of Pentasa Capsules (Marion Laboratories, Inc.)

- 5-ASA PLASMA RESULTS

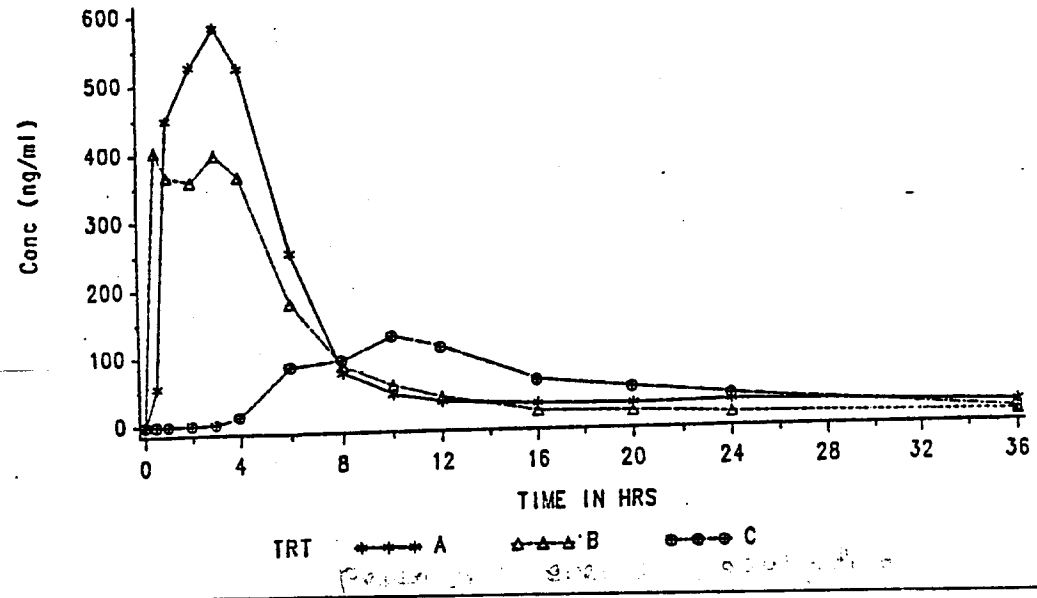

Figure 2-8. Mean 5-ASA Plasma Profiles (Without Outliers). Study No 10-67Z-001

References to Supporting Data:	**Vol**	**Page**
Full Report, Tables 1 to 3	**1.25**	**6-1331**

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F. Human Pharmacokinetics and Bioavailability Summary
3. Biopharmaceutics Studies of Pentasa Capsules (Marion Laboratories, Inc.)

- ACETYL 5-ASA PLASMA RESULTS

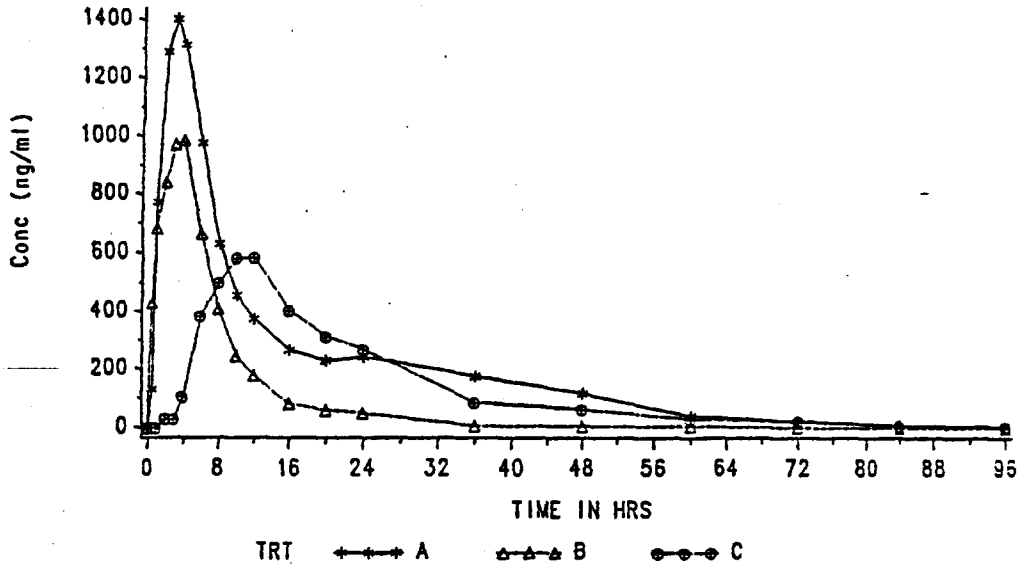

Figure 2-9. Mean Acetyl 5-ASA Plasma Profiles (Without Outliers). Study No. 10-67Z-001

References to Supporting Data:	Vol	Page
Full Report, Tables 11 to 13	1.25	6-1344

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- TOTAL SALICYLATE URINARY ELIMINATION RESULTS

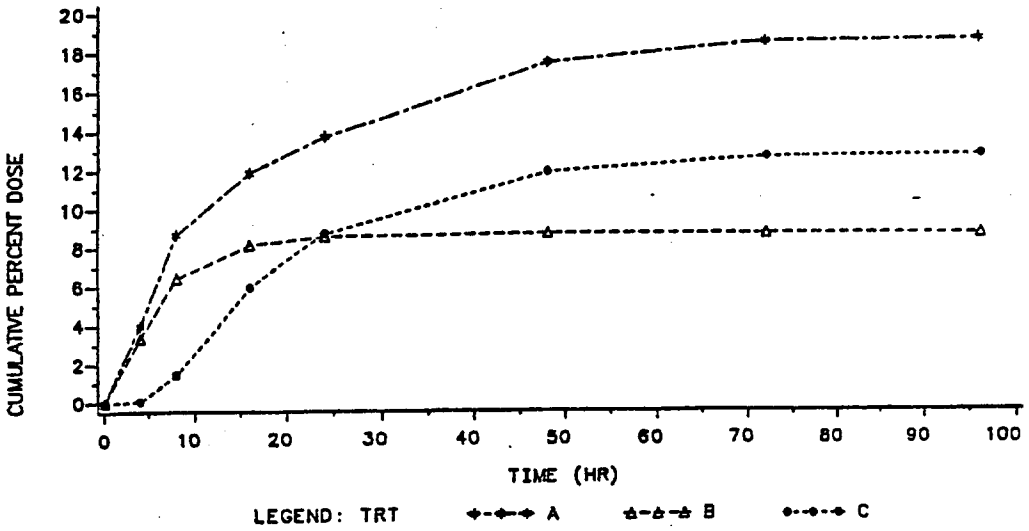

Figure 2-11. Mean Acetyl 5-ASA Cumulative Urinary Excretion Results. Study No. 10-67Z-001

References to Supporting Data:	Vol	Page
Full Report, Tables 24 to 26	1.25	6-1360

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TITLE: MULTIPLE-DOSE BIOAVAILABILITY AND DOSE-PROPORTIONALITY STUDY OF PENTASA CAPSULES IN HEALTHY VOLUNTEERS **(STUDY # 10-67C-101)** VOL.1.29, pp. 6-2795.

OBJECTIVES:

1. To determine the dose-proportionality of Pentasa™ capsule when administered four times daily.

2. To determine the bioavailability of Pentasa™ compared to Azulfidine suspension as the reference when administered 250 mg four times daily.

SUBJECTS:

Twenty-eight healthy volunteers 27.3 ± 4.6 years old and 172.3 ± 16.8 lb weight took part in the study. The treatments were administered in the clinical facility after an overnight fast. Six subjects were dropouts; two were noncompliant, two dropped out for personal reasons, one subject had epididymitis and another had injured fingers.

DRUG SUPPLIES:

Treatment A: One 250 mg Pentasa™ capsule every six hours for 25 doses, 1G per day .

Treatment B: Two 250 mg Pentasa™ capsules every six hours for 25 doses, 2G per day.

Treatment C: Four 250 mg Pentasa™ capsules every six hours for 25 doses, 4G per day.

All from full-scale Production Lot N7036 Tested in a safety and efficacy trial (PAPR0002).

Treatment D: Thirteen mL of Azulfidine suspension (250 mg/5 mL salicylsulfapyridine, SASP, every six hours for 25 doses, 2.6 G/day ≡ 250 mg 5-ASA four times daily or 1 G per day.

DATES OF CLINICAL STUDY: 1/24/88-5/18/88
DATES OF ANALYTICAL STUDY: 2/9/88-6/23/88

STUDY DESIGN AND DOSAGE ADMINISTRATION:

This was four-way , randomized crossover study. The drug was administered in a clinical facility after an overnight fast. On Day 1, a pre-dose blood sample was taken. On Days 5 and 6, trough levels were collected. Serial blood samples were taken at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 48, 72, and 96 hours following the final dose (#25)
Urine samples were collected pre-dose and then at five intervals: 0-6 h, 6-18 h, 18-30 h and 30-66 h. On Day 5 all fecal samples were collected until the 7 am dose (#25) on Day 7.There was a ten day washout period between study periods.

ANALYTICAL METHODOLOGIES:

Plasma Assay:

Specificity: Example showed the of interest being
The firm stated that the method was specific with no however a
was not shown.

Linearity: for both 5-ASA and acetyl 5-ASA over the
concentration and from

Two extraction methods were used:

Inter-Day Accuracy, Precision and Sensitivity:

Plasma Assay Inter-day Performance			
Standard Conc. ng/mL	10 ng/mL	160 ng/ml	1200 ng/ml
5-ASA	10.54 (8.6) n=40	163.61 (5.7) n=40	1197.71 (6.6) n=30
Acetyl 5-ASA	10.54 (13.6) n=40	163.75 (6.7) n=39	1212.66 (5.3) n=30

() ≡ %CV

Inter-Day Accuracy, Precision and Sensitivity:

Plasma Assay Inter-Day Performance			
Standard Conc. ng/ml	10 ng/ml	160 ng/ml	1200 ng/ml
5-ASA	11.06 (16.4) n=26	168.11 (5.8) n=28	1211.59 (8.8) n=27
Acetyl 5-ASA	10.10 (16.9) n=26	164.76 (8.0) n=30	1195.63 (9.8) n=27

Urine:
Sensitivity:
Linearity:
Precision and accuracy: For 0.3 μg/mL 5-ASA standard %CV 9% (n=57) mean=0.32 μg/mL
For 0.3 μg/mL Acetyl 5-ASA standard %CV 9.7% (n=50), mean=0.31 μg/mL
Within Batch Accuracy and Precision:

	5-ASA CONCENTRATION OF QUALITY CONTROLS (μG/ML)					
BATCH #	0.3	3.0	10.0	10	75	200
814 %CV						
815 %CV						
816 %CV						
817 %CV						

	Acetyl 5-ASA CONCENTRATION OF QUALITY CONTROLS (μG/ML)					
BATCH #	0.3	3.0	10.0	10	75	200
814 %CV						
815 %CV						
816 %CV						
817 %CV						

Batch to Batch Accuracy and Precision:

5-ASA CONCENTRATIONS μG/ML					
N=4			N=4		
0.3	3.0	10	10.0	75.0	200.0
0.33 (12.1)	2.99 (3.3)	9.93 (3.6)	9.97 (3.3)	74.13 (1.1)	198.98 (3.2)
ACETYL 5-ASA CONCENTRATIONS μG/ML					
0.3	3.0	10.0	10.0	75.0	200.0
0.31 (16.1)	3.04 (6.6)	9.96 (7.3)	10.16 (6.3)	74.90 (2.6)	200.75 (2.7)

() ≡ %CV

PHARMACOKINETIC RESULTS:
The firm identified several outliers defined as being outside mean ±SD range:
Plasma Data:
Treatment A:5-ASA Subjects 10A, 16 Acetyl 5-ASA Subjects 10A, 16
Treatment B:5-ASA Subjects 10A Acetyl 5-ASA Subjects 10A, 16
Treatment D:5-ASA Subjects 1, 3A Acetyl 5-ASA Subjects 3A, 16

RELATIVE BIOAVAILABILITY:
Plasma Data:
5-ASA relative bioavailability to Azulfidine was found to be compared to a single-dose study where probably due to its non-linear 'kinetics.

Acetyl 5-ASA had a relative bioavailability to Azulfidine of which was comparable to the single dose study of

Urine Data:
Acetyl 5-ASA to Azulfidine gave a relative bioavailability of

Fecal Data:
Treatment B Subject 16 and Treatment D subject 20 both had a single fecal sample in 48 hour. These were said to be slow transit subjects and had no detectable salicylates. Several subjects did not produce any fecal samples during the study period:

SUMMARY OF SLOW GI TRANSIT SUBJECTS		
SUBJECT #	TREATMENT	PERIOD
12A	A	I
22	A	II
3A	A	IV
16A	A	IV
13	B	II
12A	B	III
16	B	III
8	B	IV
10A	B	IV
14	C	II
19	C	III
4	C	IV
11	C	IV
12A	C	I
10A	D	II
13	D	III
14	D	IV

Subject 13 (Treatment C) and Subject 22 (Treatment B) dropped out in the final study period. Slow transit subjects did not necessarily show a trend in their AUC's nor Cmax's compared to the other subjects.

SUMMARY OF PHARMACOKINETIC RESULTS:

Table VII Summary of Pharmacokinetic Parameters from Plasma Data

Pharmacokinetic parameter	250 mg QID	Treatment: Mesalamine CR 500 mg QID	1G QID
5-ASA in Plasma			
$C^{ss}max$ ng/mL (%CV)	233.04 (55.2)	672.52 (38.5)	1772.47 (39.8)
T_{max} h (%CV)	2.77 (52.1)	2.96 (50.5)	2.78 (64.0)
AUC^{ss} ng/mL.h (%CV)	815.97 (64.7)	2495.19 (42.8)	7285.72 (47.6)
C^{ss} ng/mL (%CV)	135.99 (64.7)	415.86 (42.8)	1214.29 (47.6)
Acetyl 5-ASA in Plasma			
$C^{ss}max$ ng/mL (%CV)	1005.57 (40.6)	1940.96 (31.6)	3445.20 (35.0)
T_{max} h (%CV)	3.29 (49.5)	2.57 (54.9)	2.87 (62.4)
AUC^{ss} ng/mL.h (%CV)	4691.86 (43.9)	8886.32 (33.2)	15775.54 (35.7)
C^{ss} ng/mL (%CV)	781.98 (43.9)	1481.05 (33.2)	2629.26 (35.7)

Table VIII Summary of Pharmacokinetic Parameters from Urine Data

5-ASA in Urine

		Treatment: Mesalamine CR	
Parameter	250 mg QID	500 mg QID	1G QID
mg (%CV)	2.29 (146.2)	4.57 (22.6)	38.89 (74.0)
% Dose	0.92	0.91	3.89

Acetyl 5-ASA in Urine

mg (%CV)	56.04 (50.2)	136.15 (76.5)	230.88 (40.0)
% Dose	17.5	21.2	18.0

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Table IX Amount of Salicylates in Feces

Parameter	Treatment mesalamine CR		
	250 mg QID	500 mg QID	1 G QID
Free 5-ASA mg (%CV)	182.5 (80.5)	410.0 (62.3)	880.6 (61.9)
Total 5-ASA mg (%CV)	446.8 (48.6)	1240.0 (59.7)	2576.2 (58.7)
Total acetyl 5-ASA (%CV) mg	549.6 (64.5)	954.9 (50.5)	1339.5 (56.0)
Total salicylates (%CV) mg	875.42 (52.8)	1984.8 (50.7)	3621.0 (55.3)

STATISTICAL ANALYSES:

Dose-proportionality of 5-ASA and acetyl 5-ASA was determined on the dose-normalized AUC_{ss} and $Cmax_{ss}$ and the cumulative amounts of 5-ASA and acetyl 5-ASA excreted in the urine and feces.

The results of the statistical analyses showed that trough levels of 5-ASA were not significantly different between Day 6 and Day 7 implying that steady-state had been reached.

Normalized Cmax and AUC were significantly different between treatments and therefore 5-ASA was not dose proportional between 250 mg to 1 g QID at steady-state. Mean AUC at steady-state increased about nine-fold from 815.97 ng/mL.h (%CV 52%) to 7285.6 ng/mL.h (%CV 48%) with a fourfold increase in dose. Urinary excretion was significantly different between treatments for 5-ASA, but not for the acetylated metabolite. Only Cmax was dose proportional for the metabolite acetyl 5-ASA in plasma between treatments. The fluctuation in plasma levels was also significantly different between treatments. The normalized amounts of 5-ASA in the feces were not significantly different between treatments, however they were outside the 90% confidence interval for the two one-sided t-test.

TABLE X

PHARMACOKINETIC PARAMETER	P-VALUES	
	5-ASA	ACETYL 5-ASA
NORMALIZED AUC_{SS}	<0.0001	0.0033
NORMALIZED C_{MAXSS}	<0.0001	0.08
T_{MAX}	0.83	0.35
RATIO	0.012	0.26
FLUCTUATION	0.002	0.51
NORMALIZED URINE EXCRETION	<0.0001	0.72
NORMALIZED FREE FECAL	0.39	.008
NORMALIZED TOTAL FECAL	0.16	0.005

TABLE XI
90% CI FOR FECAL 5-ASA AND ACETYL 5-ASA

PARAMETER (NORMALIZED)	TREATMENT	RATIO %	90% CI
5-ASA	C/A B/A C/B	142 125 113	165,179 90,161 83,143
Total Salicylates	C/A B/A C/B	97 102 96	69,126 75,129 67,124
Total ACETYL 5-ASA	C/A B/A C/B	50 77 65	27,74 55,100 34,96

TABLE XII
90% CI FOR PLASMA 5-ASA AND ACETYL 5-ASA

PARAMETER (NORMALIZED)	TREATMENT	RATIO %	90% CI
5-ASA AUC_{SS}	C/A B/A C/B	229 167 137	195,269 142,197 116,161
5-ASA C_{MAXSS}	C/A B/A C/B	187 144 130	165,209 122,167 114,145
ACETYL 5-ASA AUC_{SS}	C/A B/A C/B	84 95 88	77,91 88,104 80,96
ACETYL 5-ASA C_{MAXSS}	C/A B/A C/B	85 97 89	76,96 86,108 79,100

CONCLUSIONS:

1. Mesalamine showed non-linear kinetics when dosed from 250 mg to 1 G four times a day, may be due to saturable first-pass metabolism. Mean AUC at steady-state increased about nine-fold from 815.97 ng/mL.h (%CV 65%) to 7285.6 ng/mL.h (%CV 48%) with a fourfold increase in dose. Mean C_{max} at steady-state increased about eight-fold from 233 ng/mL (%CV 55%) to 1772 ng/mL (%CV 40%) with a fourfold increase in dose. This saturable first-pass effect is also indicated by the ratio of the metabolite to the parent decreasing with increasing dose eg AUC metabolite:parent decreases from 5.75 to 3.56 to 2.16 as the dosing is increased form 250 mg to 500 mg to 1 G QID respectively.

2. Steady-state had been reached by Day 6 of treatment.

Pentasa® Capsules
(mesalamine)

F. Human Pharmacokinetics and Bioavailability Summary
3. Biopharmaceutics Studies of Pentasa Capsules (Marion Laboratories, Inc.)

- 5-ASA PLASMA RESULTS (All Subjects):

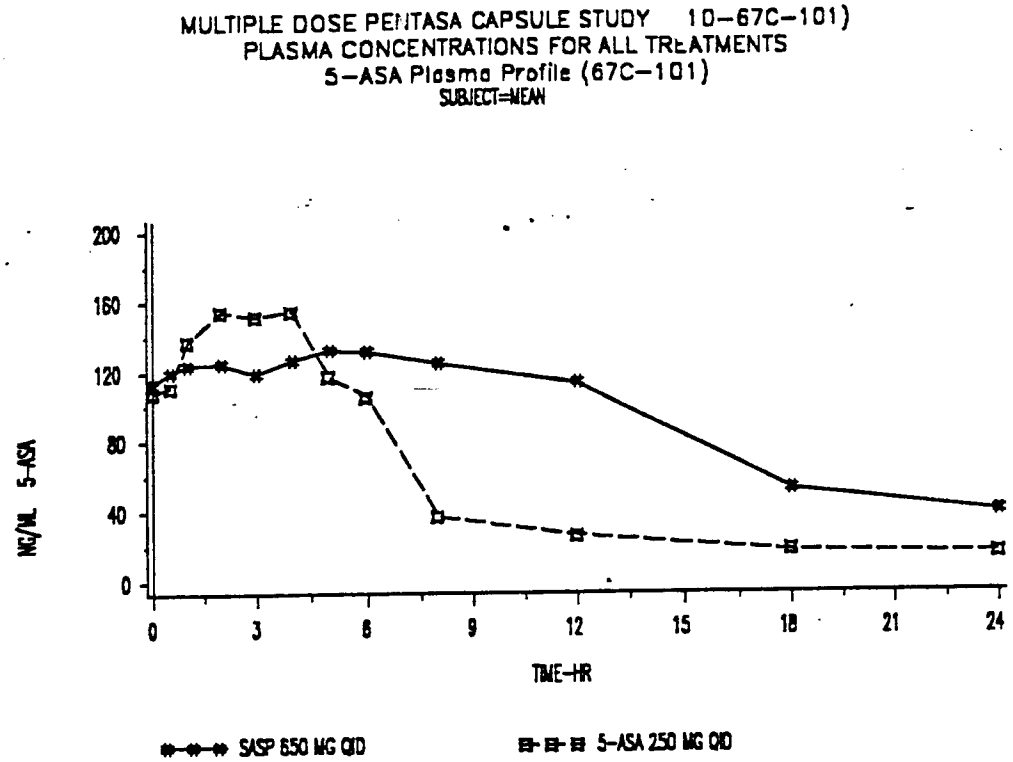

Figure 2-12. Mean 5-ASA Plasma Concentration Profile, No. 10-67C-101. (Treatments A and D only)

References to Supporting Data:	**Vol**	**Page**
Full Report, Tables 1 to 4	**1.29**	**6-2844**

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Pentasa® Capsules
(mesalamine)

F. Human Pharmacokinetics and Bioavailability Summary
3. Biopharmaceutics Studies of Pentasa Capsules (Marion Laboratories, Inc.)

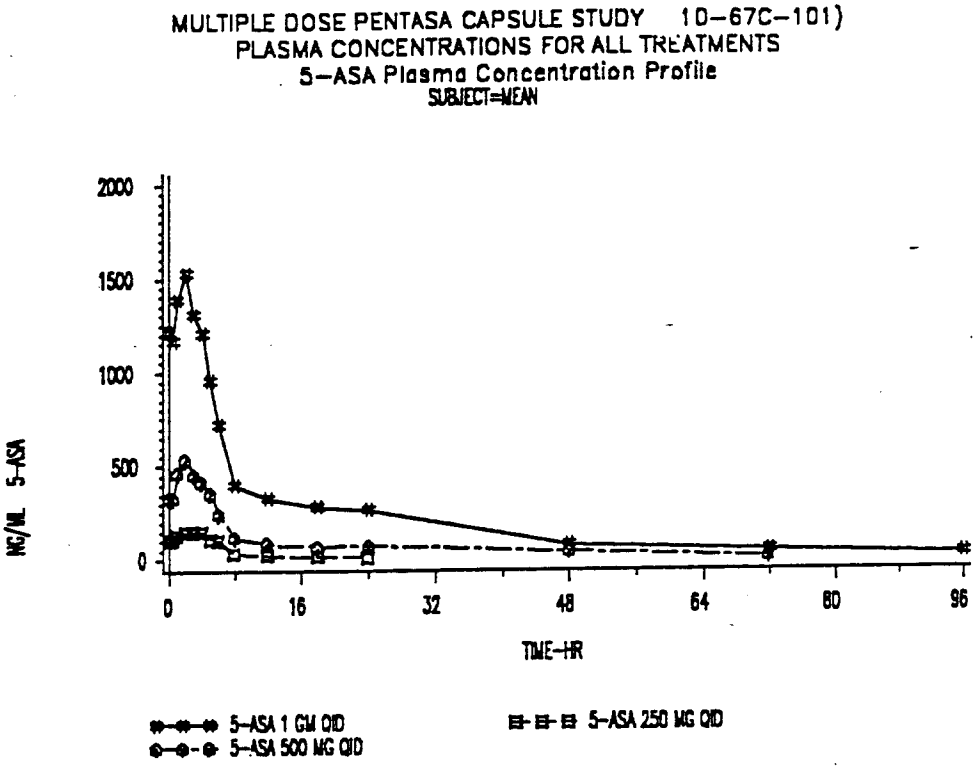

Figure 2-13. Mean 5-ASA Plasma Concentration Profile, No. 10-67C-101. (Treatments A, B and C)

References to Supporting Data:	Vol	Page
Full Report, Tables 1 to 3	1.29	6-2844

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- ACETYL 5-ASA PLASMA RESULTS (All Subjects)

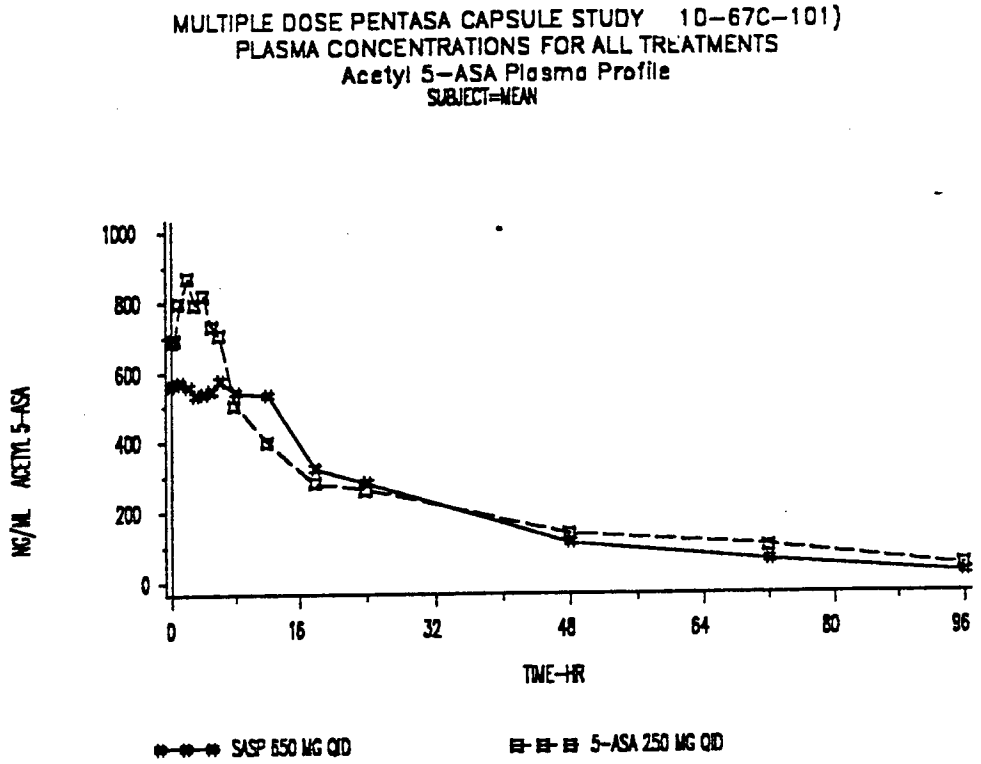

Figure 2-14. Mean Acetyl 5-ASA Plasma Concentration Profile, 10-67C-101. (Treatments A and D)

References to Supporting Data:	Vol	Page
Full Report, Tables 10 and 13	1.29	6-2861

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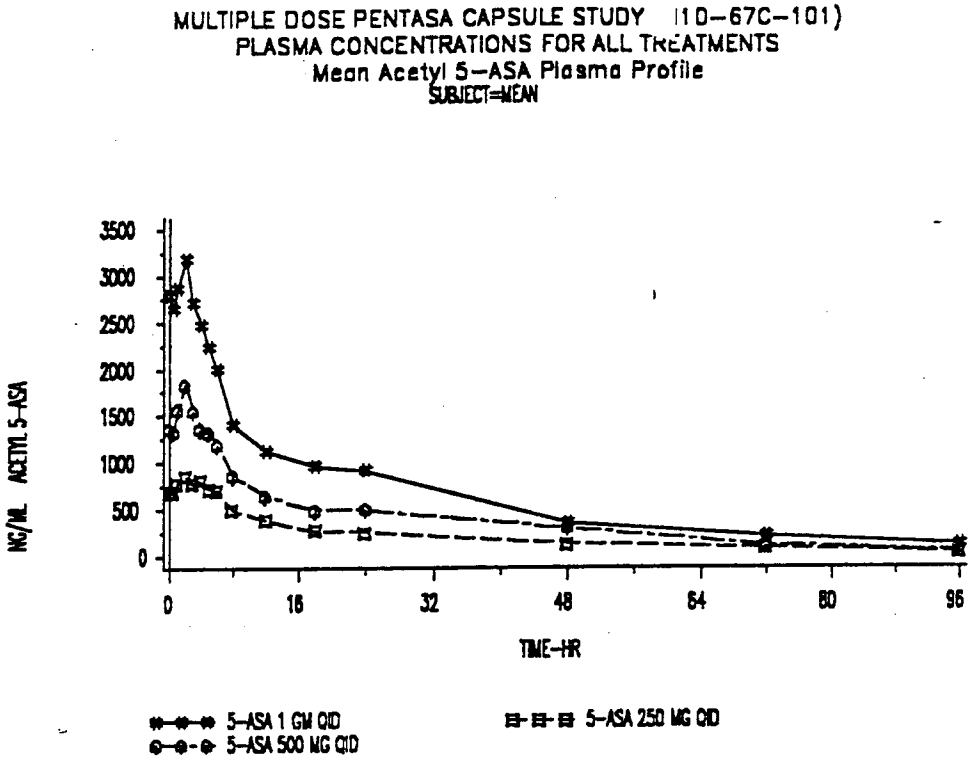


Figure 2-15. Mean Acetyl 5-ASA Plasma Concentration Profile, 10-67C-101. (Treatments A, B, and C)

References to Supporting Data:	Vol	Page
Full Report, Tables 10 to 12	1.29	6-2861

- STEADY-STATE TOTAL SALICYLATE URINARY ELIMINATION RESULTS

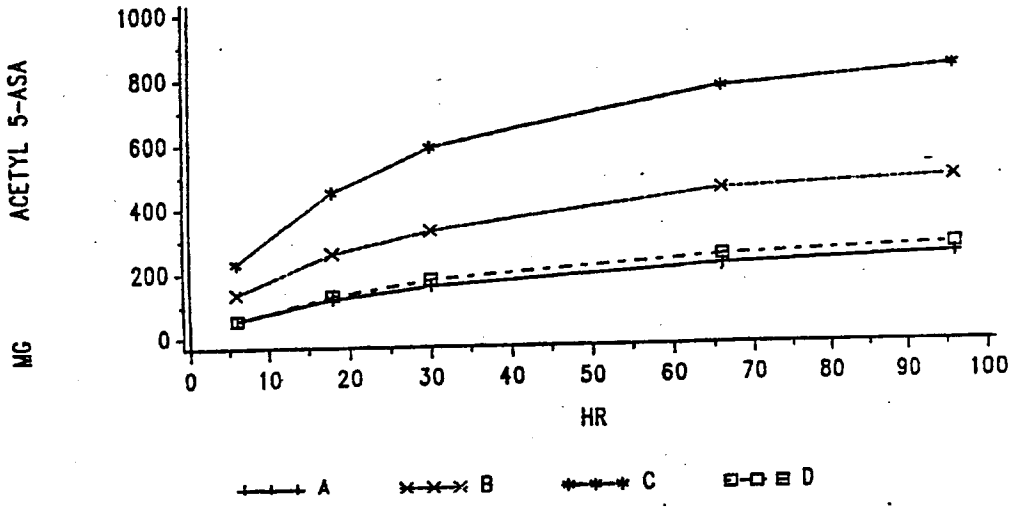
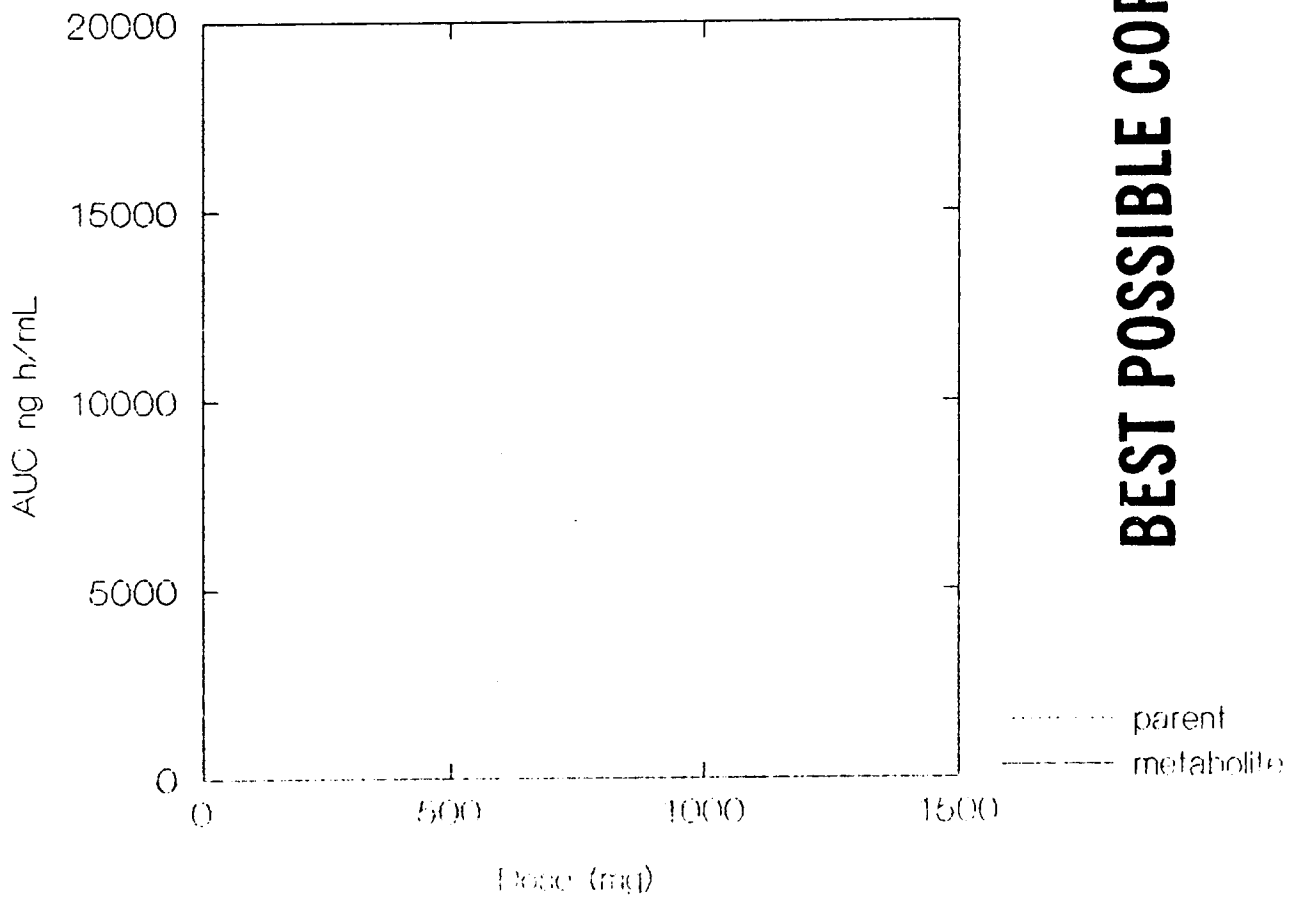


Figure 2-17. Mean Acetyl 5-ASA Cumulative Urinary Excretion Results.. Study No. 10-67C-101

References to Supporting Data:	**Vol**	**Page**
Full Report, Tables 27 to 30	**1.29**	**6-2887**

Pentasa(TM) Dose Proportionality Study



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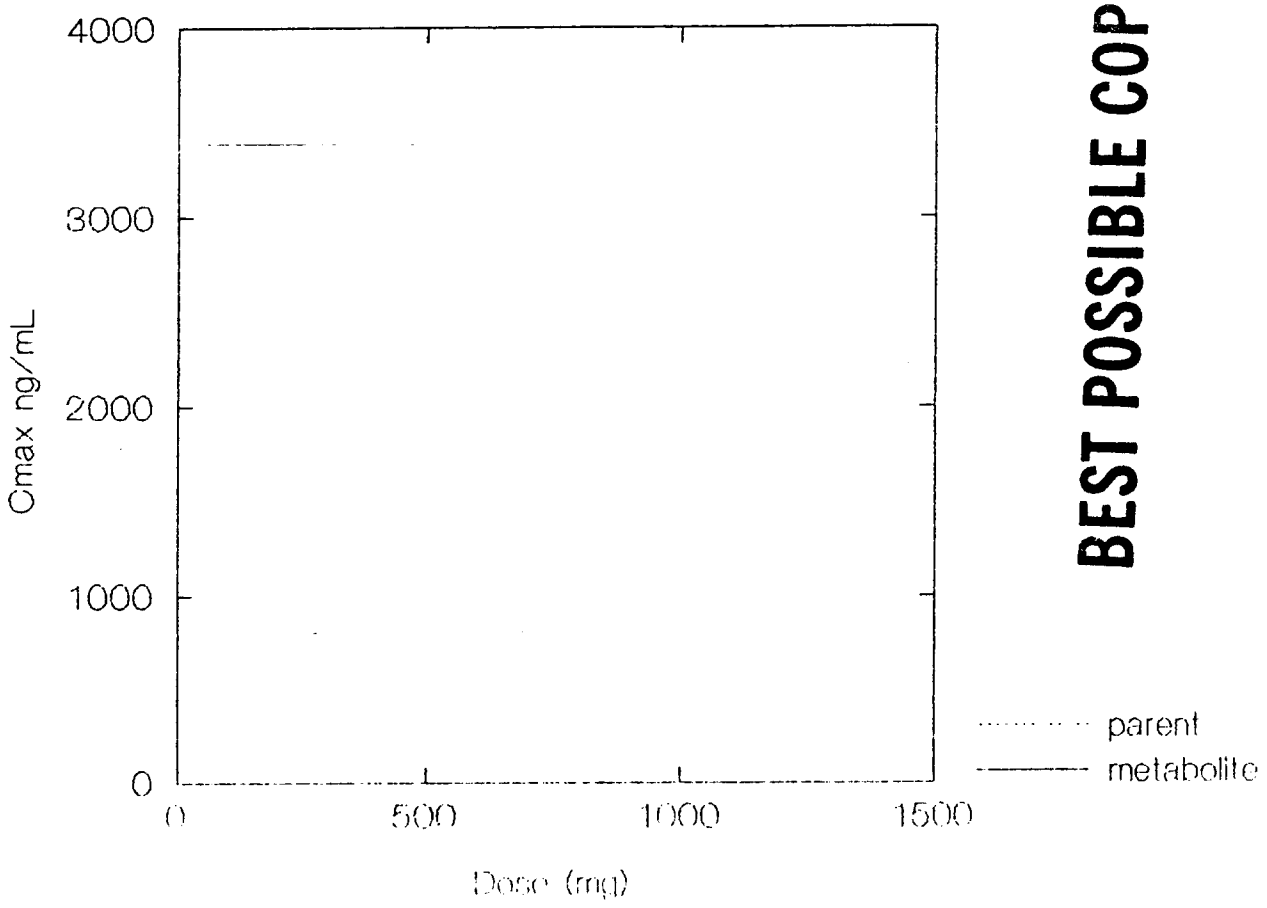
Pentasa(TM) Dose Proportionality Study



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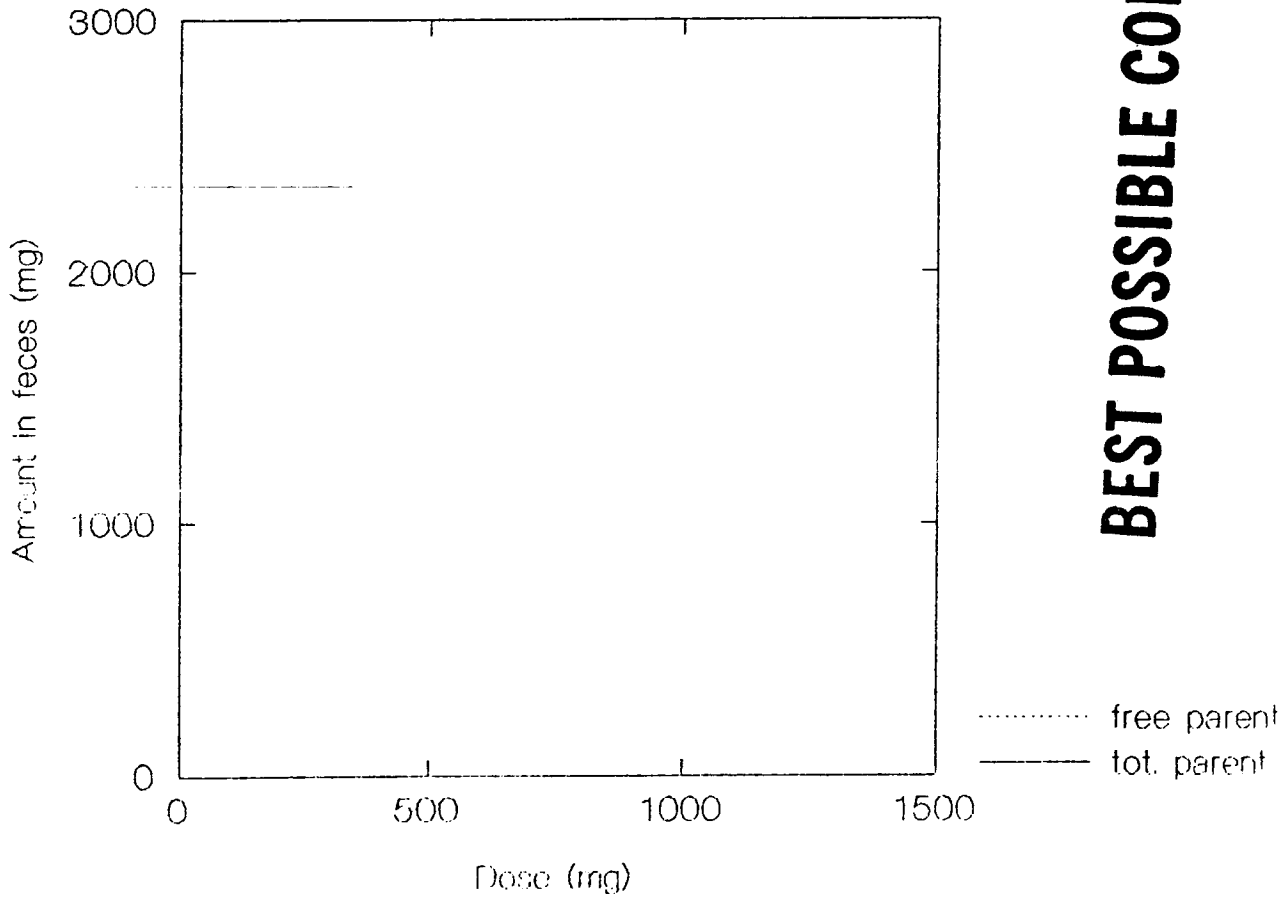

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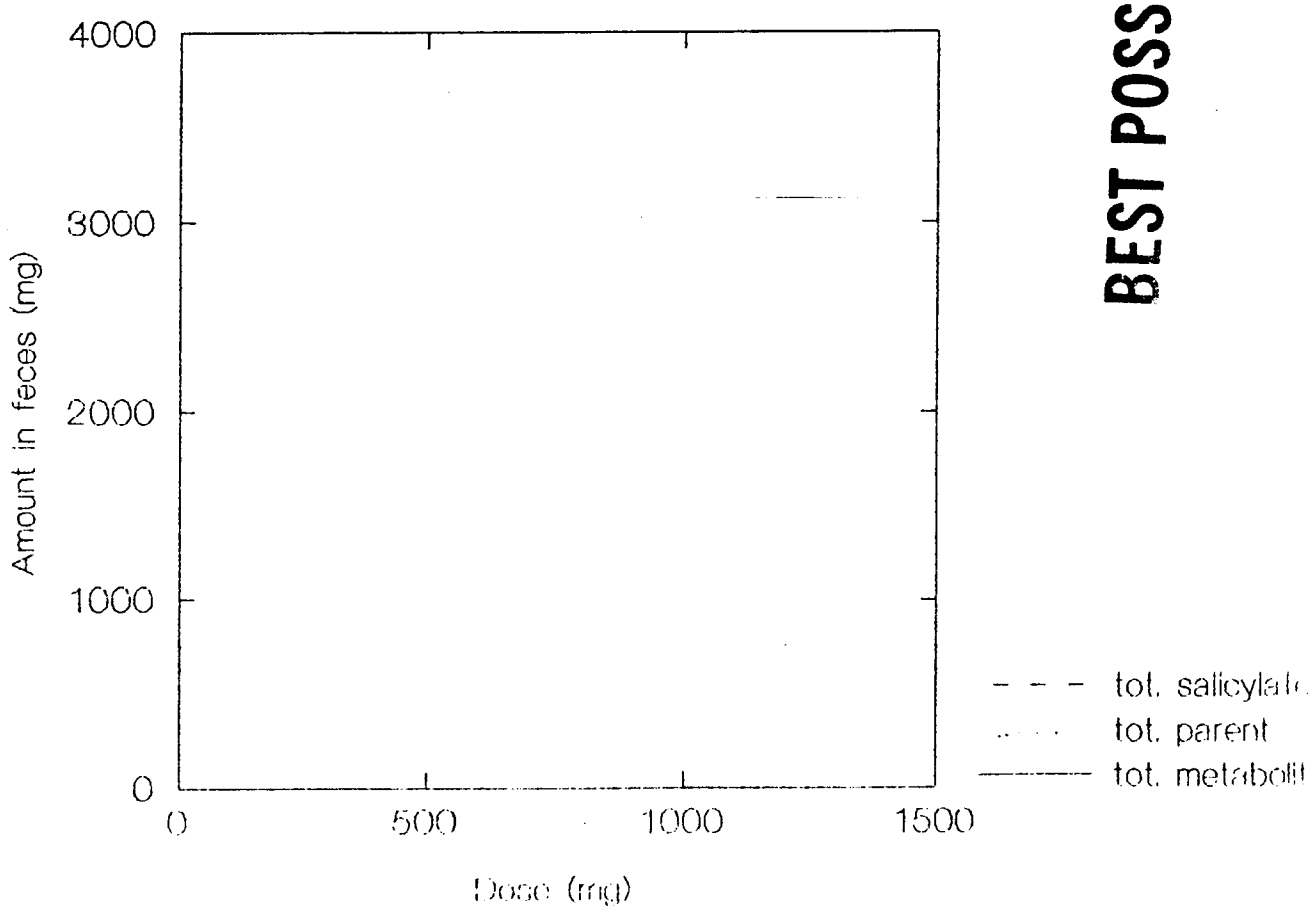
Pentasa(TM) Dose Proportionality Study



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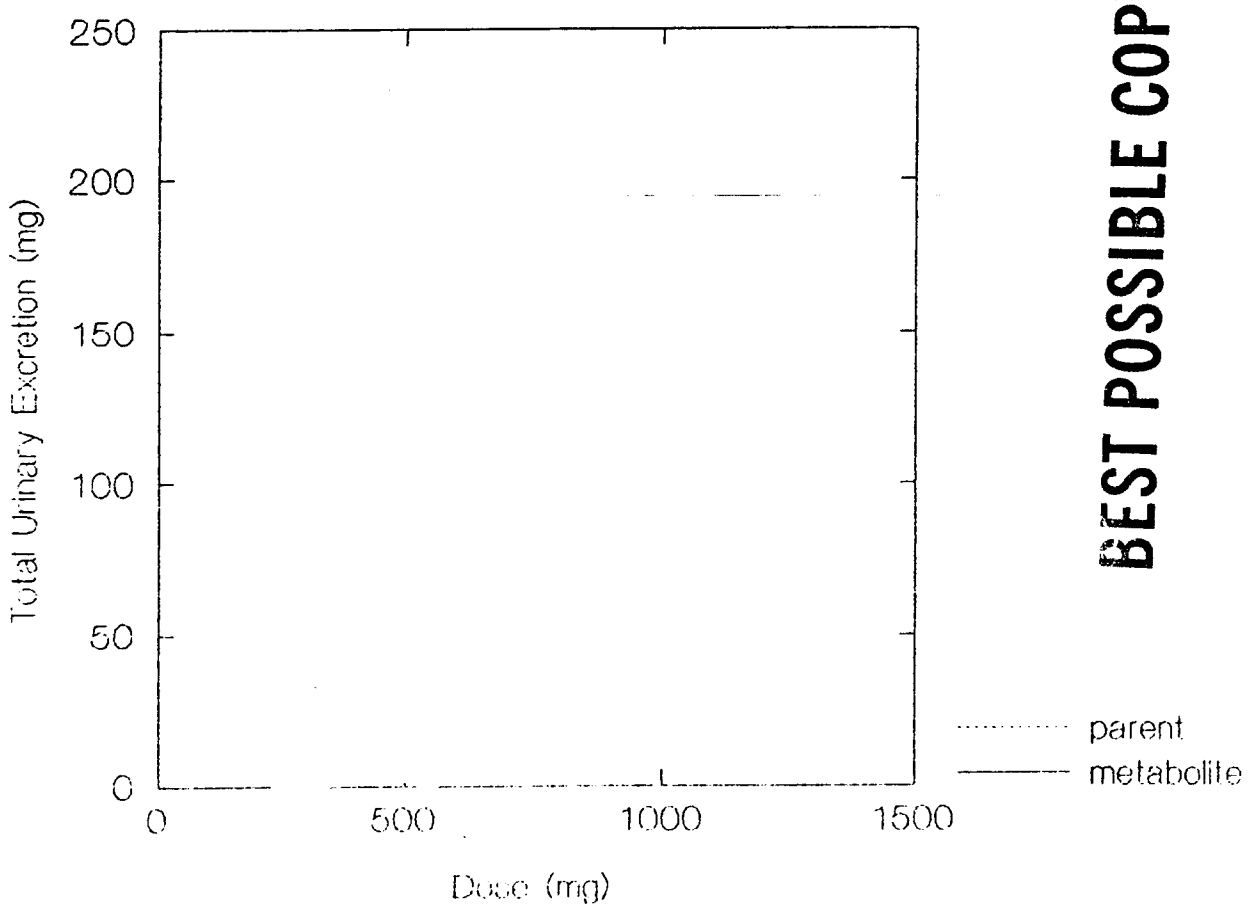
Pentasa(TM) Dose Proportionality Study



FOOD EFFECT STUDY AND BIOEQUIVALENCE STUDY:

TITLE: The Effect of Food on Pentasa Capsule Bioavailability (**STUDY #** PAST0310) VOL.1.33, pp. 6-4675.

INVESTIGATOR:
James Kisicki,

OBJECTIVES:
1. To determine the effect on bioavailability of a high-fat meal coadministered with Pentasa™ capsule (Marion).

2. To determine the bioequivalence between a pilot scale-up and full-scale production Pentasa™ capsule lot.

SUBJECTS:
Twenty-eight healthy volunteers took part in this four-way crossover study. The mean age was 29.2±7 years and the mean weight was 170.1± 20.5 lb weight.

Subject # 22 dropped out after Day 2 of Period I due to personal reasons and was replaced by Subjects 22A.

No outliers were identified by the firm.

DRUG SUPPLIES:
Treatment A: Four 250 mg Pentasa™ capsules (1 GM production Lot N7035 Fasting healthy volunteers.

Treatment B: Four 250 mg Pentasa™ capsules (1 GM pilot Lot PD068635 Fasting healthy volunteers.

Treatment C: Four 250 mg Pentasa™ capsules (1 GM production Lot N7035 with high-fat meal to healthy volunteers.

Treatment D: Four 250 mg Pentasa™ capsules (1 GM production Lot N7035; Marion healthy volunteers. *Replicate of Treatment A.*

Capsule Lot PD068635 (Treatment B) was used in safety and efficacy trial Protocol # PAPR0009. Capsule Lot N7035 (Treatments A,C and D) was used in an ulcerative colitis efficacy trial, PAPR0001.

CLINICAL STUDY DATES: 4/29/88-6/28/88
ANALYTICAL STUDY DATES: 5/12/88-8/10/88

STUDY DESIGN AND DOSAGE ADMINISTRATION:

This was four-way , randomized crossover study. One arm of the study was a replicate of the first treatment (Treatment A). The drug was administered in a clinical facility after an overnight fast. Each subject received a single dose of four Pentasa capsules in four study periods described above. There was an eleven day washout period between Study Periods I and IV. The study was originally designed to have a fifth arm in which patients with mild ulcerative colitis were studied.

Collection of Biological Samples:

Blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, and 72 hours after dose administration. Pooled urine samples were collected pre-dose and at the intervals: 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours, 48-72 hours. Fecal samples were collected also after Treatments A and B only.

The high-fat breakfast consisted of two scrambled eggs, three slices of bacon, two slices of toast with butter and jelly and 8 oz of whole milk. This is slightly different qualitatively from the standard high-fat breakfast. No breakdown of the relative calorific content of fat, carbohydrate etc. was given.

ANALYTICAL METHODOLOGIES:

Specificity:

Linearity:

Two extraction methods were used: liquid-liquid extraction and ion-exchange extraction.

Plasma Assay:

Within Day Accuracy, Precision and Sensitivity:

Standard	10 ng/mL	80 ng/mL
Mean (N=12)	9.84	82.14
%CV	7.4	6.6
%Recovery	98.4	102.7

	320 ng/mL	1280 ng/mL
Mean(N=12)	310.84	1315.19
%CV	5.5	4.6

%Recovery	97.1	102.7

Between Day Precision

	10 ng/mL	80 ng/mL
Mean (N=2)	9.75	81.14
%CV	8.4	5.8

	320 ng/mL	1280 ng/mL
Mean (N=2)	318.58	1326.31
%CV	5.5	8.1

Acetyl 5-ASA:

Within Day Accuracy, Precision and Sensitivity:

Standard	10 ng/mL	80 ng/mL
Mean (N=12)	9.80	80.35
%CV	7.0	5.0
%Recovery	92.6	100.4

	320 ng/mL	1280 ng/mL
Mean(N=12)	324.99	1312.15
%CV	4.8	11.0
%Recovery	101.6	105.7

Between Day Precision

	10 ng/mL	80 ng/mL
Mean (N=2)	9.54	81.46
%CV	7.5	5.0

	320 ng/mL	1280 ng/mL
Mean (N=2)	319.32	1312.15
%CV	5.7	9.0

The method was cross-validated

Urine samples 5-ASA:

Within Day Accuracy, Precision and Sensitivity:

Standard	Mean (N=3)	%CV	%Recovery
1 ng/mL	1.16	9.5	116
2 ng/mL	1.95	8.1	98.5
5 ng/mL	5.03	11.4	100.4
10 ng/mL	9.46	8.6	94.6
20 ng/mL	19.46	9.9	97.3
50 ng/mL	50.11	2.5	100.2
100ng/mL	105.48	13.2	105.5

Between Day Accuracy, Precision and Sensitivity:

Standard	Mean (N=3)	%CV	%Recovery
1 ng/mL	1.17	7.8	117
2 ng/mL	1.93	6.2	96.5
5 ng/mL	4.78	8.2	95.6
10 ng/mL	10.02	6.5	100.2
20 ng/mL	19.87	7.6	99.4
50 ng/mL	47.86	12.0	95.7
100ng/mL	101.21	9.40	101.2

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PHARMACOKINETIC RESULTS:

Table 1. Summary of Results for 5-ASA

Pharmacokinetic parameter 5-ASA:		TREATMENT			
		B	A	D	C
$AUC_{[0-72h]}$ ng.h/mL	Mean	4931.93	4148.78	4537.68	1318.38
	SD	1817.61	1615.37	1670.23	833.36
	%CV	36.85	38.94	36.81	63.21
C_{max} ng/mL	Mean	1010.58	867.56	977.32	286.37 -
	SD	867.56	492.02	495.07	250.00
	%CV	85.85	56.71	50.66	87.30
Tmax h	Mean	3.11	3.36	3.46	4.04
	SD	1.57	1.73	1.71	1.71
	%CV	50.58	51.41	49.37	42.38

Table 2. Summary of Results for Acetyl 5-ASA.

Pharmacokinetic parameter Acetyl 5-ASA:		TREATMENT			
		B	A	D	C
$AUC_{[0-72h]}$ ng.h/mL	Mean	26027.63	22413.99	24086.24	17160.46
	SD	7083.88	6245.72	6917.66	6069.36
	%CV	27.22	27.87	28.72	35.37
C_{max} ng/mL	Mean	1926.1	1682.56	1853.82	1216.6
	SD	1024.76	519.17	638.51	422.29
	%CV	27.22	27.87	28.72	35.37
Tmax h	Mean	3.50	3.96	3.86	4.18
	SD	1.53	1.71	1.43	1.44
	%CV	43.64	43.14	37.15	34.58

STATISTICAL ANALYSIS:
Summary of statistical analysis of 5-ASA in plasma:

Table III 5-ASA in Plasma

Pharmacokinetic Parameter	Treatment Comparison	90% CI% 2 one-sided t test	Conclusion
**$AUC_{(0-n)}$	B/A	-3.7 , 29.0	Not BE
	C/A	-76.2, -68.2	Not BE
**C_{max}	B/A	-20.4, 26.6	Not BE
	C/A	-78.1, 65.2	Not BE
T_{max}	B/A	-31.6, 7.9	Not BE
	C/A	-1.7, 37.9	Not BE

** Log Transformed

Table IV Acetyl 5-ASA in plasma

Pharmacokinetic Parameter	Treatment Comparison	90% CI 2 one-sided t-test	Conclusion
**$AUC_{(0-n)}$	B/A	-6.0, 19.5	BE
	C/A	-31.9, 23.3	Not BE
C_{max}	B/A	-10.0, 19.1	BE
	C/A	-38.6, 18.7	Not BE
T_{max}	B/A	-23.0, 7.5	Not BE
	C/A	-8.8, 21.7	Not BE

** Log Transformed

Table V 5-ASA and Acetyl 5-ASA in Urine

Pharmacokinetic Parameter	Treatment Comparison	90% CI 2 one-sided t test	Conclusion
5-ASA:			
Total Urinary Excretion	B/A	-3.9 , 57.3	Not BE
	C/A	-95.2, 34.0	Not BE
Acetyl 5-ASA			
Total Urinary Excretion	B/A	-4.7, 16.9	BE
	C/A	-38.0, 25.9	Not BE

Statistical summary for 5-ASA and Acetyl 5-ASA in feces:

Table VI 5-ASA, Acetyl 5-ASA and Total in Feces

Pharmacokinetic Parameter	Treatment Comparison	90% CI 2 one-sided t test	Conclusion
5-ASA:			
Free	B/A	-42.9, 59.7	Not BE
Total	B/A	-5.8, 62.1	Not BE
Acetyl 5-ASA			
Free	B/A	-54.6, 35.0	Not BE
Total	B/A	-36.6, 45.2	Not BE

Individual Ratio Analyses:

C_{max}
Bioequivalence:
Under fasting conditions:

	Test/Ref			
Ratio	Trt B/Trt A	Trt B/Trt D	Trt A/Trt D	Trt D/Trt A
% Passed	32%	32%	32%	25%
% Below	11%	43%	25%	43%
% Above	32%	25%	43%	32%

It should be noted that the %CV's were high

The Effect of Food:
Fasting vs. Food (Trt C)

Ratio	Trt C/Trt A	Trt C/Trt D
% Passed	7%	7%
%Below	93%	93%
% Above	0%	0%

It should be noted that the effect of food was quite dramatic and was the same for both production lots: food decreased substantially the peak plasma concentrations for the majority of subjects.

$AUC^{(0\text{-}72h)}$
Bioequivalence:
Under fasting conditions:

	Test/Ref			
Ratio	Trt B/Trt A	Trt B/Trt D	Trt A/Trt D	Trt D/Trt A
% Passed	57%	54%	54%	57%
% Below	11%	14%	14%	29%
% Above	32%	32%	32%	14%

It should be noted that the %CV's were

The Effect of Food:
Fasting vs. Food (Trt C)

Ratio	Trt C/Trt A	Trt C/Trt D
% Passed	0%	0%
%Below	100%	100%
% Above	0%	0%

It should be noted that the effect of food was quite dramatic and was the same for both production lots: food decreased substantially the AUC for all subjects.

T^{max}
Bioequivalence:
Under fasting conditions:

	Test/Ref			
Ratio	Trt B/Trt A	Trt B/Trt D	Trt A/Trt D	Trt D/Trt A
% Passed	25%	25%	36%	50%
% Below	39%	39%	25%	25%
% Above	36%	36%	39%	25%

It should be noted that the %CV's were high

The Effect of Food:
Fasting vs. Food (Trt C)

Ratio	Trt C/Trt A	Trt C/Trt D
% Passed	36%	29%
% Below	18%	25%
% Above	46%	46%

It should be noted that the effect of food was not as dramatic as shown for the other parameters but was similar for both production lots: food prolonged the time to peak plasma concentration in 46% of the subjects.

Conclusions:

1. 5-ASA as formulated in the pilot lot formulation is bioinequivalent to the production lot both in its rate and extent of absorption as shown by 90% CI and the two one-sided t-test.

2. Acetyl 5-ASA, the metabolite was found to be bioequivalent in its rate and extent to the production lot.

3. The presence of food was shown to reduce the rate and extent of absorption and to prolong the time to peak in 46% of the subjects.

4. After food, the extent of bioavailability of mesalamine was reduced by about 70% and the rate as measured by C_{max} was reduced by around 69%.

The reviewer requested further statistical analyses to be undertaken, in which the food arm of the study was eliminated and also the replicate arms were compared to each other to give some idea of the variability within a Lot when tested *in vivo*.

Results of further analyses:

Re-analysis #1 Comparison of the two different formulations excluding the food arm in the statistical analysis and comparing the replicates individually.

Re-analysis #2 Comparison of the two different formulations excluding the food arm in the statistical analysis and combining the replicates.

Pharmacokinetic Parameter	Pair Comparison	Original Results	Re-analysis #1	Re-analysis #2
5-ASA		% Diff (90% CI)	%Diff (90% CI)	% Diff (90% CI)
AUC	B-(A=D)	11.5 (-4, 29)	N/A	13.6 (-22,-1.7)
	B-A	N/A	18.9 (5, 33)	N/A
	B-D	N/A	8.7 (-4, 22)	N/A
C_{max}	B-(A=D)	0.4 (-20, 27)	N/A	-1.1 (-20, 21)
	B-A	N/A	5.6 (-17, 34)	N/A
	B-D	N/A	-7.5 (-27, 17)	N/A
Acetyl 5-ASA				
AUC	B-(A=D)	12.5 (6, 20)	N/A	11.9 (7, 17)
	B-A	N/A	16.1 (10, 22)	N/A
	B-D	N/A	8.1 (3, 14)	N/A
C_{max}	B-(A=D)	3.5 (-10, 19)	N/A	3.2 (-9, 17)
	B-A	N/A	7.3 (-7, 24)	N/A
	B-D	N/A	-0.8 (-14, 15)	N/A

Comparison of the replicates to themselves was made and gave the following results:

Pharmacokinetic Parameter	Pair Comparison	% Diff (90% CI)
5-ASA		
AUC	D-A	9.4 (-5, 23)
C_{max}	D-A	14.2 (-10, 45)
Acetyl 5-ASA		
AUC	D-A	7.5 (2, 13)
	D-A	8.3 (-6, 25)

The within-subject variability:

Parameter	Within-subject CV (%)
5-ASA	
AUC	29%
C_{max}	65%
Acetyl 5-ASA	
AUC	12%
C_{max}	35%

Conclusions:

1. The comparison of the replicates to themselves show how variable the product behaves *in vivo* in that bioequivalence from the plasma data could not be shown. The firm was not asked to re-analyze the urine nor fecal data. Only AUC for the metabolite, acetyl 5-ASA showed bioequivalence within the same lot. The inherent variability in the plasma level data for this drug makes it difficult to show bioequivalence between treatments using the same production lot. This makes the in vitro-in vivo correlation important and the ranges set for individual ingredients in the manufacturing process to be strictly controlled as well as the dissolution specification.

2. The AUC and C_{max} was within the 90% CI for the metabolite when Treatment B was compared to Trt D and the combined Trt A=D, but not for comparison to the replicate Trt A. AUC and C_{max} for the parent 5-ASA showed bioinequivalence for all comparisons.

3. The firm also showed that the within-subject CV was much greater for 5-ASA plasma parameters than for acetyl 5-ASA parameters. A within-subject variability of 30% would require more than 80 subjects to pass the 2 one-sided t-test.

- ACETYL 5-ASA PLASMA RESULTS

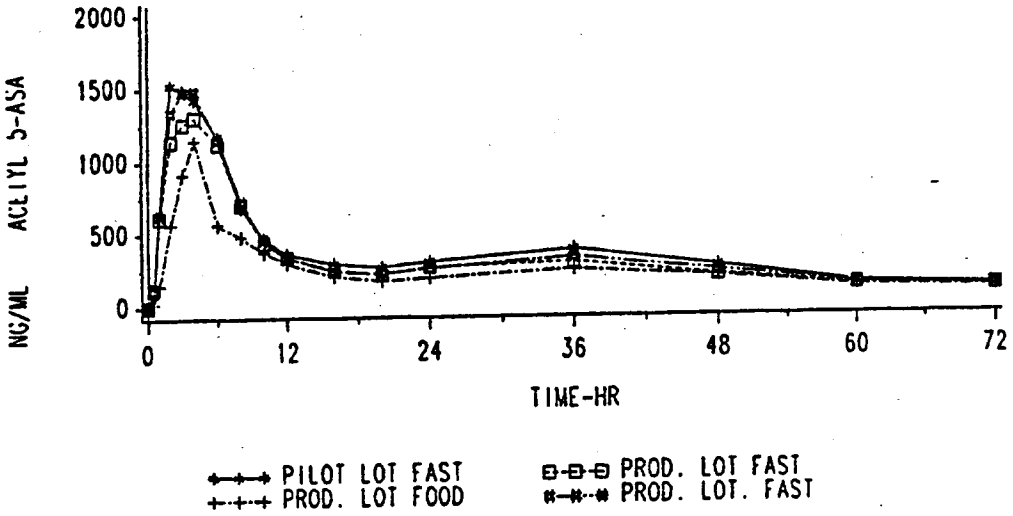

Figure 2-19. Mean Acetyl 5-ASA Plasma Concentration Profile.. Study No. PAST0310

References to Supporting Data:	Vol	Page
Full Report, Tables 10 to 13	1.33	6-4736

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Pentasa® Capsules
(mesalamine)

F. Human Pharmacokinetics and Bioavailability Summary
3. Biopharmaceutics Studies of Pentasa Capsules (Marion Laboratories, Inc.)

- TOTAL SALICYLATE URINARY ELIMINATION RESULTS

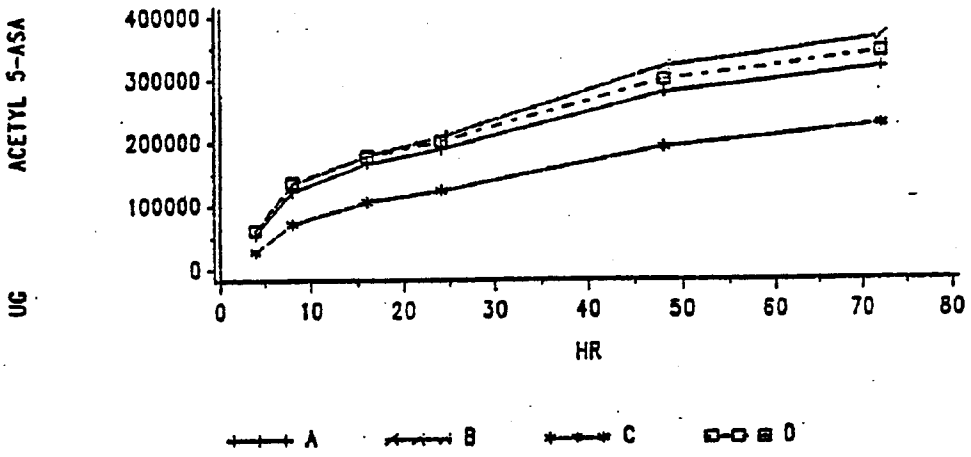

Figure 2-21. Mean Cumulative Acetyl 5-ASA Urinary Excretion Results. Study No. PAST0310

Note: Treatment A = Production fasting
Treatment B = Pilot fasting
Treatment C = Production with food
Treatment D = Production fasting

References to Supporting Data:	**Vol**	**Page**
Full Report, Tables 25 to 28	**1.33**	**6-4760**

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- TOTAL SALICYLATES FECAL ELIMINATION RESULTS

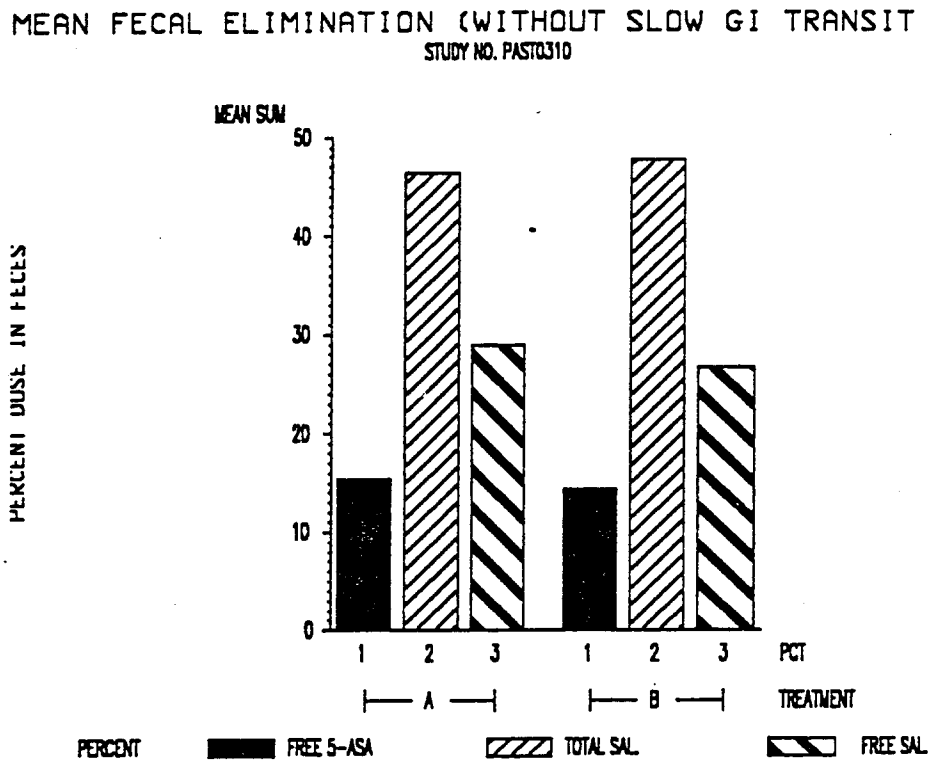

Figure 2-20. Mean Salicylates Fecal Elimination (Study No. PAST0310)

Free 5-ASA = Formulation released 5-ASA
Total Sal. = Formulation bound and released 5-ASA and acetyl 5-ASA
Free Sal. = Formulation released 5-ASA and acetyl 5-ASA
Treatment A = Production fasting
Treatment B = Pilot fasting

References to Supporting Data:		**Vol**	**Page**
Full Report, Tables 19 and 20	APPEARS THIS WAY ON ORIGINAL	**1.33**	**6-4754**

FOOD EFFECT STUDY ON BIOAVAILABILITY

TITLE: Mechanism of Interaction Between Pentasa™ Capsules and High Fat Content Breakfast during Coadministration. (**STUDY #** PAST0348) VOL.1.37, pp. 6-6080.

OBJECTIVES:
1. To compare Pentasa™ pharmacokinetics between healthy subjects and ulcerative colitis patients.

2. To determine the effect of high fat content meal coadministration on Pentasa™ capsule bioavailability.

INVESTIGATOR: Dr. James Kisicki,

DATE OF CLINICAL STUDY: 5/7/89-6/23/89
DATE OF ANALYTICAL STUDY: 5/17/89-7/26/89

SUBJECTS:
Twenty-four subjects took part in the study. Subjects 15 and 21 dropped out of the study due to noncompliance and were not replaced. however since the pharmacokinetic results were within ±2SD ranges, their data was included. Subjects 9, 2 and 18 were outside ±2SD ranges and were considered outliers, but were included in the analyses.

DRUG SUPPLIES:
Treatment A: Four Pentasa ™ 250 mg controlled release capsules given to fasting healthy volunteers. Full-scale production lot # N7036 This is not the final to be marketed formulation.

Treatment B: Four Pentasa ™ 250 mg controlled release capsules given to healthy volunteers after high-fat breakfast. Full-scale production lot # N7036

Treatment C: Single mesalamine suspension (5-ASA) 1 gm suspension given to fasting healthy volunteers (lot # PD048931).

Treatment D: Single 1 gm mesalamine suspension given to healthy volunteers after high-fat breakfast.

STUDY DESIGN AND DOSAGE ADMINISTRATION:
This was four-way , randomized crossover study. The drug was administered in a clinical facility to 24 volunteers. The high-fat-content meal comprised of two scrambled eggs, three slices of bacon, two slices of toast with butter and jelly and 8 oz of whole milk.

Collection of biological samples:
Serial blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, and 48 hr postdose. Also samples were collected at 60, 72 and 96 hours postdose for Treatments A and B.

Urine was collected over seven consecutive intervals; 0-4 hours, 4-8 hours, 8-16 hours, 16-24 hours, 24-48 hours (Treatments C and D), 48 to 72 hours and 72 to 96 hours. Fecal samples were collected during each study period. A ten day washout period was included between study periods.

ANALYTICAL METHODOLOGIES:

Plasma Assay:

Within Day Accuracy, Precision and Sensitivity:

Standard	10 ng/mL	160 ng/mL	1200 ng/mL
Mean (N=40)	10.54	163.61	1197.71
%CV	8.6	5.7	6.6
%Recovery	105.4	102.3	99.8

Between Day Precision

	10 ng/mL	160 ng/mL	1200 ng/mL
Mean (N=40)	10.54	163.75	1212.66
%CV	13.6	6.7	5.3
%Recovery	105.4	102.3	101.1

Acetyl 5-ASA:
Similar results were obtained for accuracy, precision and recovery both within and day-to-day for acetyl 5-ASA.

The method was cross-validated

Urine samples 5-ASA:
Within Day Accuracy, Precision and Sensitivity:

Standard	Mean	%CV	%Recovery

	(N=3)		
1 ng/mL	1.18	8.5	116
2 ng/mL	1.95	8.2	97.5
5 ng/mL	4.62	3.90	92.40
10 ng/mL	10.10	3.00	101.00
20 ng/mL	21.17	4.90	105.80
50 ng/mL	50.81	8.7	101.6
100ng/mL	99.91	8.2	99.90

Between Day Accuracy, Precision and Sensitivity:

Standard	Mean (N=3)	%CV	%Recovery
1 ng/mL	1.17	7.8	117
2 ng/mL	1.93	6.2	96.5
5 ng/mL	4.78	8.2	95.6
10 ng/mL	10.02	6.5	100.2
20 ng/mL	19.87	7.6	99.4
50 ng/mL	47.86	12.0	95.7
100ng/mL	101.21	9.40	101.2

Fecal assay:
The method showed acceptable accuracy, precision, reproducibility and linearity.

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PHARMACOKINETIC RESULTS:

Table 1. Summary of Results for 5-ASA in plasma

Pharmacokinetic parameter 5-ASA:		TREATMENT			
		A	B	C	D
$AUC_{[0-n]}$ ng.h/mL	Mean	4370.13	1643.28	29056.1	14649.4
	SD	1813.17	890.79	5710.33	5406.80
	%CV	41.49	54.21	19.65	36.91
C_{max} ng/mL	Mean	986.44	373.24	14720.8	5231.29
	SD	523.18	293.13	3864.56	2060.37
	%CV	53.04	78.54	26.25	39.39
Tmax h	Mean	3.48	5.17	0.98	1.94
	SD	1.83	2.39	0.533	1.42
	%CV	52.64	46.25	54.44	73.51

Treatment A: Four Pentasa ™ 250 mg controlled release capsules given to fasting healthy volunteers. Full-scale production lot # N7036

Treatment B: Four Pentasa ™ 250 mg controlled release capsules given to healthy volunteers after high-fat breakfast. Full-scale production lot # N7036

Treatment C: Single mesalamine suspension (5-ASA) 1 gm suspension given to fasting healthy volunteers (lot # PD048931).

Treatment D: Single 1 gm mesalamine suspension given to healthy volunteers after high-fat breakfast.

Table 2. Summary of Results for Acetyl 5-ASA in plasma.

Pharmacokinetic parameter Acetyl 5-ASA:		TREATMENT			
		A	B	C	D
$AUC_{[0-n]}$ ng.h/mL	Mean	24228.4	17996.5	40140.7	31281.8
	SD	6363.15	5604.21	8249.42	6176.29
	%CV	26.26	31.14	20.55	19.74
C_{max} ng/mL	Mean	1832.24	1246.76	11401.3	5755.93
	SD	796.656	497.56	2232.86	1388.31
	%CV	43.48	39.91	19.58	24.12
Tmax h	Mean	3.74	4.96	1.44	2.67
	SD	1.73	2.15	0.59	1.27
	%CV	46.48	43.49	41.11	47.46

Summary of Fecal Salicylates Elimination Results:

Treatment	Free 5-ASA mg	Free Salicylates mg	Total Salicylates	
			mg	% Dose
Pentasa™ Fasting (A)	98.0 (59)	232.2 (58)	399.5 (43)	40.0 (43)
Pentasa™ Nonfasting (B)	65.4 (74)	194.4 (65)	460.4 (55)	46.0 (55)
5-ASA Susp. Fasting (C)	8.9 (192)	80.1 (82)	130.0 (58)	13.0 (58)
5-ASA Susp. Nonfasting (D)	4.4 (161)	147.7 (55)	276.7 (50)	27.7 (50)

KEY ()= (%CV)

PENTASA™

Summary of Total Salicylate Renal Elimination Results:

Treatment	Acetyl 5-ASA		5-ASA	
	mg	% Dose	mg	% Dose
Pentasa™ Fasting (A)	374.7 (27)	29.2	1.85 (144)	0.185
Pentasa™ Nonfasting (B)	284.3 (29)	22.2	0.36 (273)	0.036
5-ASA Susp. (C)	732.1 (14)	57.1	212.0 (27)	21.2
5-ASA Susp. Nonfasting (D)	529.1 (24.2)	41.3	63.9 (64)	6.39

KEY ()=%CV

From the data on the fecal elimination it can be seen that after food the amount of free salicylates (after Pentasa™) decreases from a mean of 232.2 mg to a mean of 194.4 mg hence possibly the local exposure decreases, whilst after the suspension the exposure to free salicylates increases from a mean of 80.1 mg to a mean of 147.7 mg (before and after food). From a safety viewpoint the effect of food intake is to decrease the absorption of 5-ASA to the same extent as shown by urine excretion data irrespective of the form of the drug. Therefore food possibly alters the local exposure of the tissues to 5-ASA as shown by fecal data and decreases the plasma levels of 5-ASA after administration of Pentasa™.

STATISTICAL ANALYSIS:
Summary of statistical analysis of 5-ASA in plasma:

Table V 5-ASA in Plasma

Pharmacokinetic Parameter	Treatment Comparison	90% CI% 2 one-sided t test	Conclusion
**$AUC_{(0-n)}$	B/A	-3.7 , 29.0	Not BE
	C/A	-76.2, -68.2	Not BE
**C_{max}	B/A	-20.4, 26.6	Not BE
	C/A	-78.1, 65.2	Not BE
T_{max}	B/A	-31.6, 7.9	Not BE
	C/A	-1.7, 37.9	Not BE

** Log Transformed

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Table VI Acetyl 5-ASA in plasma

Pharmacokinetic Parameter	Treatment Comparison	90% CI 2 one-sided t-test	Conclusion
**$AUC_{(0-n)}$	B/A	-6.0, 19.5	BE
	C/A	-31.9, 23.3	Not BE
C_{max}	B/A	-10.0, 19.1	BE
	C/A	-38.6, 18.7	Not BE
T_{max}	B/A	-23.0, 7.5	Not BE
	C/A	-8.8, 21.7	Not BE

** Log Transformed

Table VII 5-ASA and Acetyl 5-ASA in Urine

Pharmacokinetic Parameter	Treatment Comparison	90% CI 2 one-sided t test	Conclusion
5-ASA:			
Total Urinary Excretion	B/A	-3.9 , 57.3	Not BE
	C/A	-95.2, 34.0	Not BE
Acetyl 5-ASA			
Total Urinary Excretion	B/A	-4.7, 16.9	BE
	C/A	-38.0, 25.9	Not BE

Statistical summary for 5-ASA and Acetyl 5-ASA in feces:

Table VIII 5-ASA, Acetyl 5-ASA and Total in Feces

Pharmacokinetic Parameter	Treatment Comparison	90% CI 2 one-sided t test	Conclusion
5-ASA:			
Free	B/A	-42.9, 59.7	Not BE
Total	B/A	-5.8, 62.1	Not BE
Acetyl 5-ASA			
Free	B/A	-54.6, 35.0	Not BE
Total	B/A	-36.6, 45.2	Not BE

COMMENTS:

One gram of 5-ASA in the form of a suspension

was rapidly absorbed. Mean C_{max}'s following administration of this suspension were 14.72 μg/mL (%CV 26%) and 11.4 μg/mL (%CV 20%) for 5-ASA and acetyl 5-ASA respectively. The mean $T_{max's}$ for 5-ASA and acetyl 5-ASA from the suspension were 0.98 h (%CV 54) and 1.44 h (%CV 41%) respectively. About 21% of 5-ASA was excreted unchanged in the urine and 57% was excreted as the metabolite acetyl 5-ASA: 13% was eliminated in the feces chiefly as acetyl 5-ASA when given as a suspension. When given as Pentasa™ capsules, the mean $C_{max's}$ were 0.98 μg/mL (%CV 53%) and 1.83 μg/mL (%CV 46%) for 5-ASA and acetyl 5-ASA respectively and mean $T_{max's}$ were 3.8 h (%CV 52%) and 3.7 h (%CV 46%) for 5-ASA and acetyl 5-ASA respectively. The variability in the $C_{max's}$ were higher for Pentasa™ than for the suspension. Urinary recovery accounted for 29% of the dose as 5-ASA and less than 1% was recovered as the metabolite, acetyl 5-ASA. 40% of the dose was eliminated in the feces. Again %CV's were high.

Individual ratio analysis of the dosage form under fasting and non-fasting conditions revealed that 91% of the subjects had AUC's lower under nonfasting condition than under the fasting condition whilst none of the subjects had AUC's higher under nonfasting compared to fasting condition. The C_{max} for the subjects was lower after food in 65% of the subjects and T_{max} was

prolonged in 70% of the subjects after food (See full results of ratio analysis in the appendix). Ratio analysis of the immediate release suspension under the two conditions of fasting and non-fasting showed that the AUC's were lower after food for all subjects. The C_{max}'s were lower in 91% of the subjects and T_{max}'s were prolonged in 57% of the subjects after food.

The formulation used was not the final "to be marketed" formulation of mesalamine.

CONCLUSIONS:

1. The effect of food in reducing the mean AUC and Cmax of mesalamine was shown not to be due to food effect on the formulation as the same reduction occurred when mesalamine was in the form of a suspension. However the % decrease in mean AUC was not to the same degree comparing the suspension to the capsule form; there was a greater % decrease with Pentasa™ than the suspension.

2. However closer examination of the data showed that the local exposure to 5-ASA as indicated by the free salicylates determined in the feces was reduced after food intake with Pentasa™ which was the opposite for 5-ASA suspension. This may be indicative of release of 5-ASA being affected with Pentasa™ and not necessarily food binding the free salicylates.

- 5-ASA PLASMA RESULTS (all subjects)

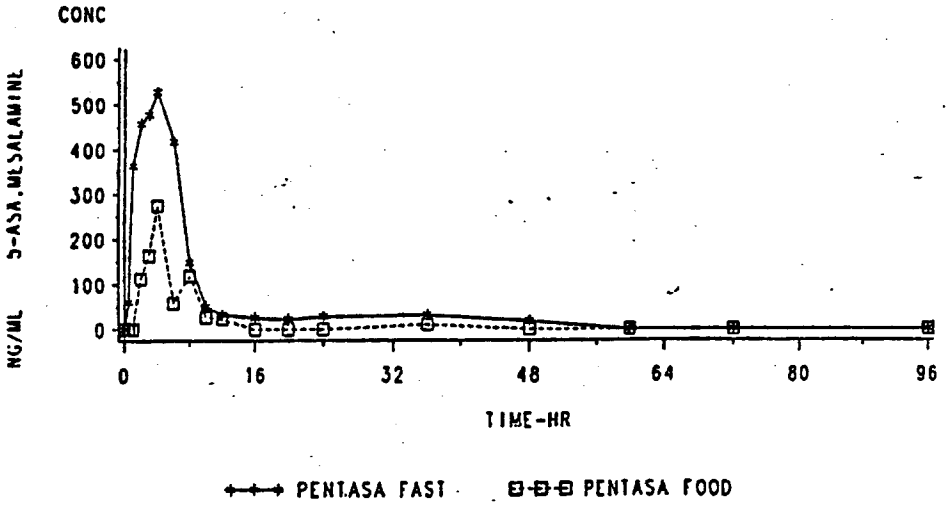

Figure 2-22. Mean 5-ASA Plasma Concentration Profile (Pentasa Capsules only).
Study No. PAST0348

References to Supporting Data:	Vol	Page
Full Report, Tables 1 and 2	1.37	6-6131

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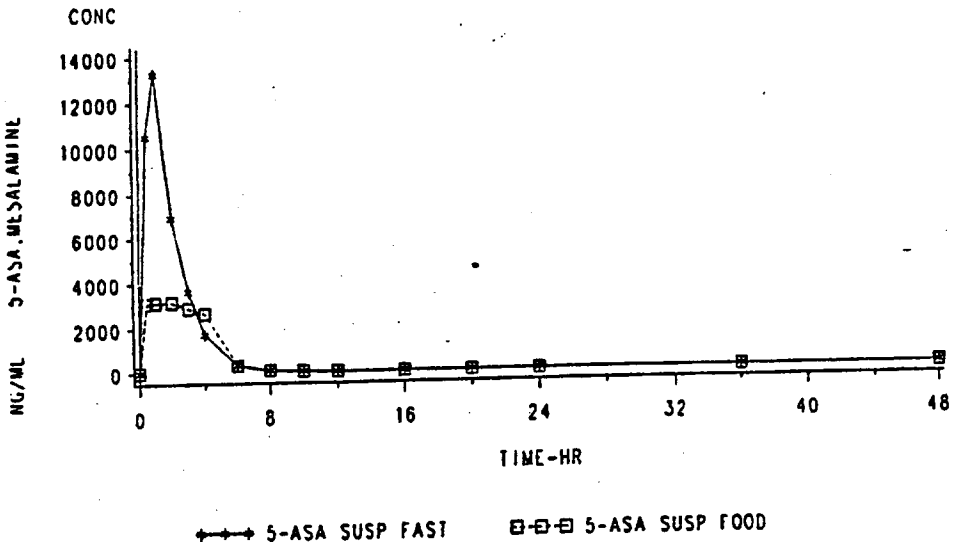

Figure 2-23. Mean 5-ASA Plasma Concentration Profile (Suspension only). Study No. PAST0348

References to Supporting Data:	**Vol**	**Page**
Full Report, Tables 3 and 4	**1.37**	**6-6135**

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- ACETYL 5-ASA PLASMA RESULTS (all subjects)

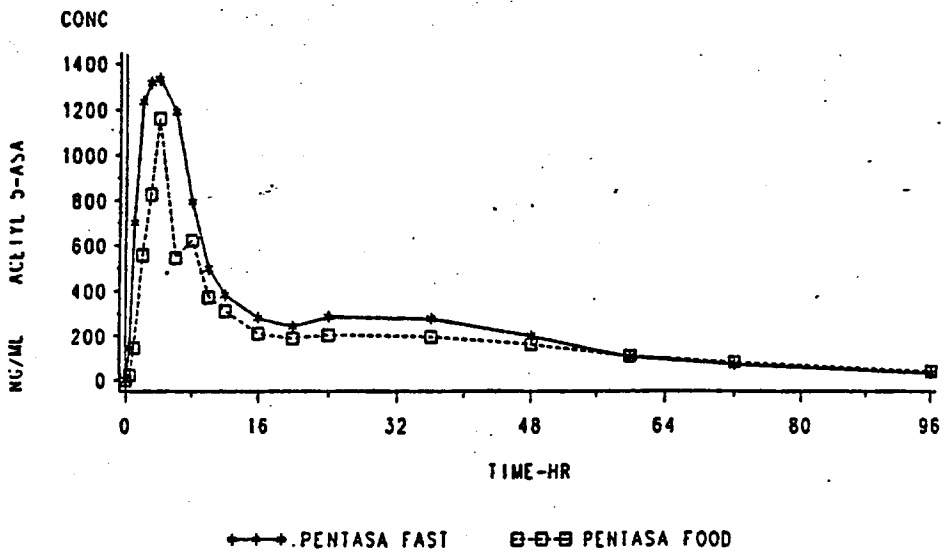

Figure 2-24. Mean Acetyl 5-ASA Plasma Concentration Profile (Pentasa capsules).
Study No. PAST0348

References to Supporting Data:	Vol	Page
Full Report, Tables 11 and 12	1.37	6-6149

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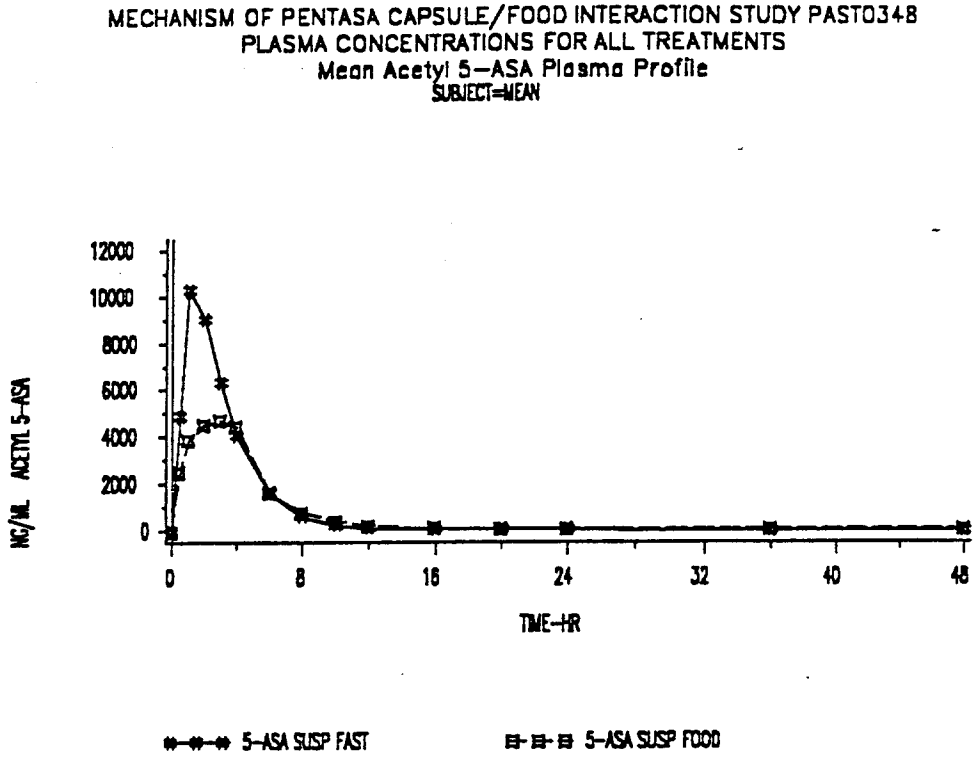

Figure 2-25. Mean Acetyl 5-ASA Plasma Concentration Profile (Suspensions only)

References to Supporting Data:	**Vol**	**Page**
Full Report, Tables 13 and 14	**1.37**	**6-6153**

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F. Human Pharmacokinetics and Bioavailability Summary
3. Biopharmaceutics Studies of Pentasa Capsules (Marion Laboratories, Inc.)

- TOTAL SALICYLATE URINARY ELIMINATION RESULTS (all subjects)

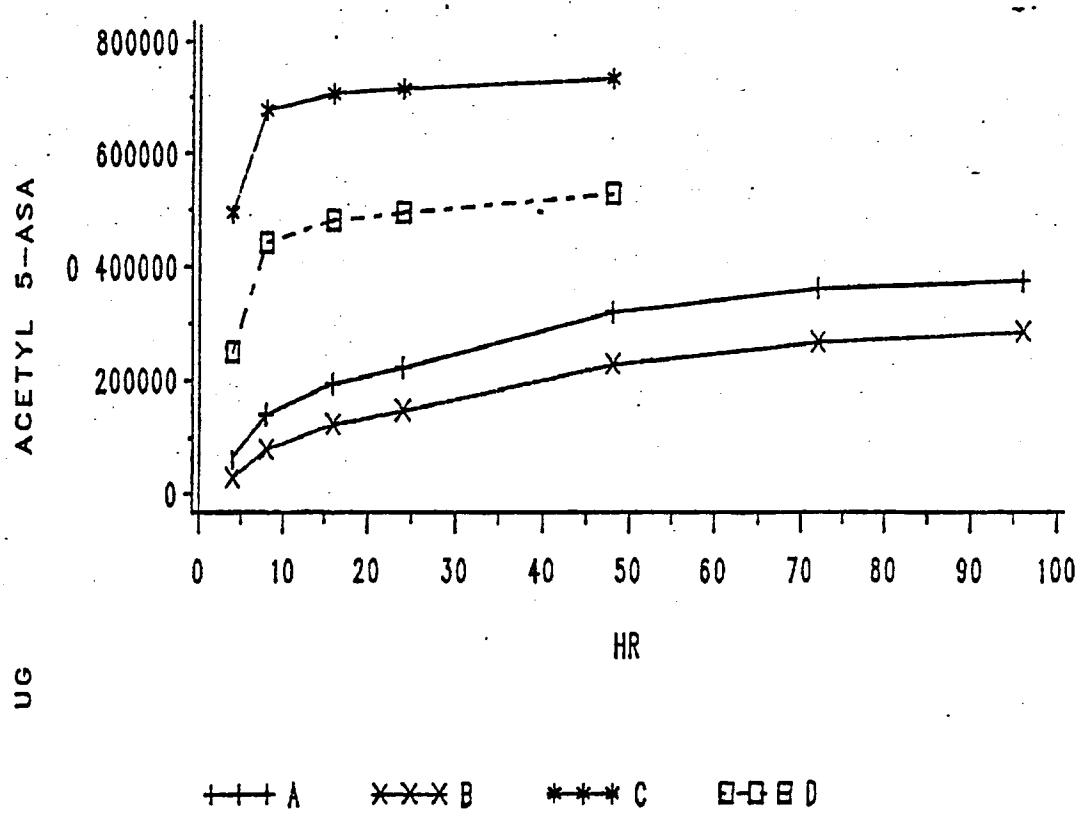

Figure 2-27. Mean Cumulative Acetyl 5-ASA Urinary Excretion Results. Study No. PAST0348

Treatment A = Pentasa Fasting
Treatment B = Pentasa with Food
Treatment C = 5-ASA Suspension Fasting
Treatment D = 5-ASA Suspension with Food
ug = microgram

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References to Supporting Data:	Vol	Page
Full Report, Tables 29 to 32	1.37	6-6175

- MEAN SALICYLATES FECAL ELIMINATION RESULTS (without slow GI transit subjects)

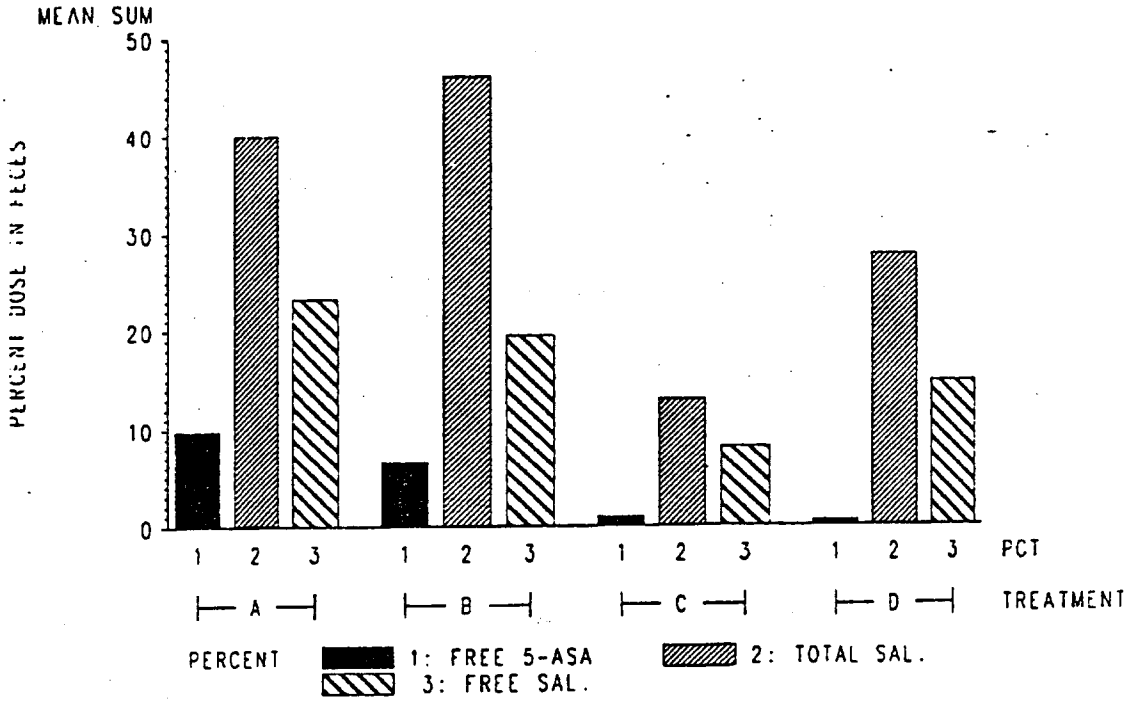

Figure 2-26. Mean Salicylates Fecal Elimination (No Slow GI Transit Subjects).
Study No. PAST0348

Treatment A = Pentasa Fasting
Treatment B = Pentasa with Food
Treatment C = 5-ASA Suspension Fasting
Treatment D = 5-ASA Suspension with Food
Free 5-ASA = formulation released 5-ASA
Total Sal. = formulation bound and released 5-ASA and acetyl 5-ASA
Free Sal. = formulation released 5-ASA and acetyl 5-ASA

References to Supporting Data:		Vol	Page
Full Report, Tables 21 to 24	APPEARS THIS WAY ON ORIGINAL	1.37	6-6167

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