

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**ANDA 77-883**

**Name:** Balsalazide Disodium Capsules  
750 mg

**Sponsor:** Apotex Inc.

**Approval Date:** December 28, 2007

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 77-883**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 77-883**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Rockville, MD 20857

ANDA 77-883

Apotex Inc.  
US Agent: Apotex Corp.  
Attention: Kiran Krishnan  
                    Manager, Regulatory Affairs  
2400 North Commerce Parkway, Suite 400  
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 3, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Balsalazide Disodium Capsules, 750 mg.

Reference is also made to your amendment dated October 16, and November 8, 2006, August 22, September 21 and 24, October 31, and November 9, 2007.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Balsalazide Disodium Capsules, 750 mg to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Colazal Capsules, 750 mg, of Salix Pharmaceuticals, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Amundson Road  
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

*(See appended electronic signature page)*

Gary Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Robert L. West  
12/28/2007 10:09:14 AM  
for Gary Buehler

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 77-883**

**LABELING**

Material	00000	Description	INS USA BALSALAZIDE DISODIUM CAP 750MG	Effective Date:	
Change	NEW FINISHED GOODS	C of A	PKGP-CA-INSERT	CCF#	
Previous Code	N/A	Label Draft#	CUSTOMER APPROVED	Dimensions	FLAT: 210mm x 355mm FOLD: 105mm x 35.5mm
Pantone Colours	(b) (4)	Minimum Font Size	7 POINT	Customer Approval:	QA Approval:
Prepared by:	(b) (4)	Reviewed by:		Date:	
Date:	Nov 08, 2007	Date:		Date:	



**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use Balsalazide Disodium Capsules safely and effectively. See full prescribing information for balsalazide.

**Balsalazide Disodium Capsules**

Initial U.S. Approval: 2000

**RECENT MAJOR CHANGES**

Dosage and Administration, Administration Alternatives (2.2)	9/2006
Warnings and Precautions, Exacerbations of Ulcerative Colitis (5.1)	12/2006
Drug Interactions (7)	2/2007

**INDICATIONS AND USAGE**

- Balsalazide is a locally acting aminosalicylate indicated for the treatment of mildly to moderately active ulcerative colitis in adults (1)
- Safety and effectiveness of balsalazide beyond 12 weeks in adults have not been established. (1)

**DOSE AND ADMINISTRATION**

- Adult dose is three 750 mg balsalazide disodium capsules 3 times a day (6.75 g/day) with or without food for 8 weeks. Some adult patients required treatment for up to 12 weeks. (2,1)
- Capsules may be swallowed whole or may be opened and sprinkled on applesauce, then chewed or swallowed immediately. (2.2, 12.3)

**DOSE FORMS AND STRENGTHS**

Capsules: 750 mg (3)

**CONTRAINDICATIONS**

Patients with hypersensitivity to salicylates or to any of the components of balsalazide disodium capsules or balsalazide metabolites. Hypersensitivity reactions may include, but are not limited to the following: anaphylaxis, bronchospasm, and skin reaction. (4)

**WARNINGS AND PRECAUTIONS**

- Exacerbation of the symptoms of ulcerative colitis in adult patients. Observe patients closely for worsening of these symptoms while on treatment. (5.1)
- Prolonged gastric retention of balsalazide may occur in patients with pyloric stenosis. (5.2)

**ADVERSE REACTIONS**

Most common adverse reactions in adults (incidence  $\geq 3\%$ ) are headache, abdominal pain, diarrhea, nausea, vomiting, respiratory infection, and arthralgia. Adverse reactions in children were similar. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTION**

In an *in vitro* study using human liver microsomes, balsalazide and its metabolites were not shown to inhibit the major CYP enzymes evaluated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). (7)

**USE IN SPECIFIC POPULATIONS**

Renal Impairment: Use balsalazide with caution in patients with a history of renal disease. (5.3)  
Pediatric: Pediatric use information is protected by marketing exclusivity. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

**FULL PRESCRIBING INFORMATION: CONTENTS\***

- INDICATIONS AND USAGE
- DOSE AND ADMINISTRATION
- DOSE FORMS AND STRENGTHS
- CONTRAINDICATIONS

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

Balsalazide disodium capsules are indicated for the treatment of mildly to moderately active ulcerative colitis in adults. Safety and effectiveness of balsalazide beyond 12 weeks in adults have not been established.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Adult Dose**

For treatment of active ulcerative colitis in adult patients, the usual dose is three 750 mg balsalazide disodium capsules to be taken 3 times a day (6.75 g per day) for up to 8 weeks. Some patients in the adult clinical trials required treatment for up to 12 weeks.

**2.2 Administration Alternatives**

Balsalazide disodium capsules may also be administered by carefully opening the capsule and sprinkling the capsule contents on applesauce. The entire drug/applesauce mixture should be swallowed immediately; the contents may be chewed, if necessary, since contents of balsalazide disodium capsules are NOT coated beads/granules. Patients should be instructed not to store any drug/applesauce mixture for future use.

If the capsules are opened for sprinkling, color variation of the powder inside the capsules ranges from orange to yellow and is expected due to color variation of the active pharmaceutical ingredient. Teeth and/or tongue staining may occur in some patients who use balsalazide disodium capsules in sprinkle form with food.

**3 DOSAGE FORMS AND STRENGTHS**

Balsalazide is available as opaque white capsules containing 750 mg balsalazide disodium imprinted with "APD 0750" in red ink.

**4 CONTRAINDICATIONS**

Patients with hypersensitivity to salicylates or to any of the components of balsalazide disodium capsules or balsalazide metabolites. Hypersensitivity reactions may include, but are not limited to the following: anaphylaxis, bronchospasm and skin reaction.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Exacerbation of Ulcerative Colitis**

In the adult clinical trials, 3 out of 250 patients reported exacerbation of the symptoms of ulcerative colitis.

Observe patients closely for worsening of these symptoms while on treatment.

**5.2 Pyloric Stenosis**

Patients with pyloric stenosis may have prolonged gastric retention of balsalazide disodium capsules.

**5.3 Renal**

Renal toxicity has been observed in animals and patients given other mesalamine products. Therefore, caution should be exercised when administering balsalazide capsules to patients with known renal dysfunction or a history of renal disease. [See Nonclinical Toxicology (13.2)]

**6 ADVERSE REACTIONS**

**6.1 Clinical Studies Experience**

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

**Adult Ulcerative Colitis**

During clinical development, 259 adult patients with active ulcerative colitis were exposed to 6.75 g/day balsalazide in 4 controlled trials.

In the 4 controlled clinical trials patients receiving a balsalazide dose of 6.75 g/day most frequently reported the following adverse reactions: headache (8%), abdominal pain (6%), diarrhea (5%), nausea (5%), vomiting (4%), respiratory infection (4%), and arthralgia (4%). Withdrawal from therapy due to adverse reactions was comparable among patients on balsalazide and placebo.

Adverse reactions reported by 1% or more of patients who participated in the four controlled Phase 3 trials are presented by treatment group in Table 1.

The number of placebo patients (35), however, is too small for valid comparisons. Some adverse reactions, such as abdominal pain, fatigue, and nausea were reported more frequently in women than in men. Abdominal pain, rectal bleeding, and anemia can be part of the clinical presentation of ulcerative colitis.

**Table 1: Adverse Reactions occurring in  $\geq 1\%$  of Adult Balsalazide Patients in Controlled Trials\***

Adverse Reaction	Balsalazide Capsules	
	6.75 g/day (N=259)	Placebo (N=35)
Abdominal pain	16 (6%)	1 (3%)
Diarrhea	14 (5%)	1 (3%)
Arthralgia	9 (4%)	0%
Rhinitis	6 (2%)	0%
Insomnia	5 (2%)	0%
Fatigue	5 (2%)	0%
Flatulence	5 (2%)	0%
Fever	5 (2%)	0%
Dyspepsia	5 (2%)	0%
Pharyngitis	4 (2%)	0%
Coughing	4 (2%)	0%
Anorexia	4 (2%)	0%
Urinary tract infection	3 (1%)	0%
Myalgia	3 (1%)	0%
Flu-like disorder	3 (1%)	0%
Dry mouth	3 (1%)	0%
Cramps	3 (1%)	0%
Constipation	3 (1%)	0%

\*Adverse events occurring in at least 1% of Balsalazide Patients which were less frequent than placebo for the same event were not included in the table.

**6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use in clinical practice of products which contain (or are metabolized to) mesalamine. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine.

**Hepatic**

Postmarketing adverse reactions of hepatotoxicity have been reported, including elevated liver function tests (SGOT/AST, SGP/ALT, GGT, LDH), alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal, however, no fatalities associated with these adverse reactions were reported in balsalazide clinical trials. One case of Kawasaki-like syndrome which included hepatic function changes was also reported, however, this adverse reaction was not reported in balsalazide clinical trials.

Several cases of alopecia in patients taking balsalazide have been reported.

**7 DRUG INTERACTIONS**

In an *in vitro* study using human liver microsomes, balsalazide and its metabolites [5-aminosalicylic acid (5-ASA), N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), 4-aminobenzoic acid (4-ABA) and N-acetyl-4-aminobenzoic acid (N-Ac-4-ABA)] were not shown to inhibit the major CYP enzymes evaluated (CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Therefore, balsalazide and its metabolites are not expected to inhibit the metabolism of other drugs with are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category B. Reproduction studies were performed in rats and rabbits at oral doses up to 2 g/kg/day, 2.4 and 4.7 times the recommended human dose based on body surface area for the rat and rabbit, respectively, and revealed no evidence of impaired fertility or harm to the

**5 WARNINGS AND PRECAUTIONS**

**5.1 Exacerbations of Ulcerative Colitis**

**5.2 Pyloric Stenosis**

**5.3 Renal**

**6 ADVERSE REACTIONS**

**6.1 Clinical Studies Experience**

**6.2 Postmarketing Experience**

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**8.3 Nursing Mothers**

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**13.2 Animal Toxicology**

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**14.1 Adult Studies**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

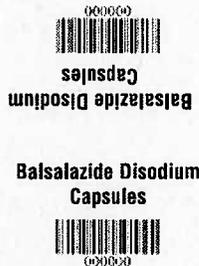
**17 PATIENT COUNSELING INFORMATION**

**17.1 Important Precautions Regarding Balsalazide**

**17.2 What Patients Should Know About Adverse Reactions**

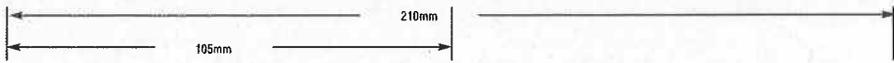
**17.3 What Patients Should Know About Taking Balsalazide With Other Medication**

\*Sections or subsections omitted from the full prescribing information are not listed.



355mm

Material	000000	Description	INS USA BALSALAZIDE DISODIUM CAP 750MG	Effective Date:	
Change	CUSTOMER TEXT REVISION	C of A	PKG-CA-INSERT	CCF#	
Previous Code	N/A	Label Draft#	CUSTOMER APPROVED	Dimensions	FLAT: 210mm x 355mm FOLD: 105mm x 35.5mm
Pantone Colours	(b) (4)	Reviewed by:		Customer Approval:	
Prepared by:	(b) (4)	Date:	Nov 08, 2007	QA Approval:	
Date:	Nov 08, 2007	Date:		Date:	



etus due to balsalazide disodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**3.3 Nursing Mothers**

It is not known whether balsalazide disodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when balsalazide is administered to a nursing woman.

**3.4 Pediatric Use**

Pediatric use information is protected by marketing exclusivity.

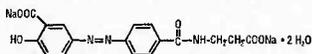
**10 OVERDOSEAGE**

No cases of overdose have occurred with balsalazide. A 3-year-old boy is reported to have ingested 9 g of another mesalamine product. He was treated with gastric and activated charcoal with no adverse reactions.

If an overdose occurs with balsalazide, treatment should be supportive, with particular attention to correction of electrolyte abnormalities.

**11 DESCRIPTION**

Each balsalazide disodium capsule contains 750 mg of balsalazide disodium, a prodrug that is enzymatically cleaved in the colon to 5-aminosalicylic acid or 5-ASA, an anti-inflammatory drug. Each capsule of balsalazide (750 mg) is equivalent to 267 mg of mesalamine. Balsalazide disodium has the chemical name [E]-5-[4-[[2-(carboxyethyl) amino]carbonyl] phenylazo]-2-hydroxybenzoic acid disodium salt, dihydrate. Its structural formula is:



Molecular Weight: 437.32

Molecular Formula: C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>Na<sub>2</sub>•2H<sub>2</sub>O

Balsalazide disodium is a stable, odorless orange to yellow microcrystalline powder.

It is freely soluble in water and isotonic saline, sparingly soluble in methanol and ethanol, and practically insoluble in all other organic solvents.

Inactive Ingredients: Each hard gelatin capsule contains colloidal silicon dioxide, magnesium stearate and titanium dioxide. The capsule imprinting ink contains polyethylene glycol, strong ammonia solution, shellac and red iron oxide. The sodium content of each capsule is approximately 86 mg.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreductase to release equimolar quantities of mesalamine, which is the therapeutically active portion of the molecule and the 4-aminobenzoyl-β-alanine carrier moiety. The carrier moiety released when balsalazide disodium is cleaved is only minimally absorbed and is largely inert.

The mechanism of action of 5-ASA is unknown, but appears to be local to the colonic mucosa rather than systemic. Mucosal protection of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanooids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyacids, is increased in patients with chronic inflammatory bowel disease, and it is possible that 5-ASA diminishes inflammation by blocking production of arachidonic acid metabolites in the colon.

**12.3 Pharmacokinetics**

Balsalazide disodium capsules contain a powder of balsalazide disodium that is insoluble in acid and designed to be delivered to the colon as the intact prodrug. Upon reaching the colon, bacterial azoreductases cleave the compound to release 5-ASA, the therapeutically active portion of the molecule, and 4-aminobenzoyl-β-alanine. The 5-ASA is further metabolized to yield N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), a second key metabolite.

**Absorption**

The plasma pharmacokinetics of balsalazide and its key metabolites from a crossover study in healthy volunteers are summarized in Table 2. In this study a single oral dose of balsalazide 2.25 g was administered to healthy volunteers as intact capsules (3 x 750 mg) under fasting conditions, as intact capsules (3 x 750 mg) after a high-fat meal, and unencapsulated (3 x 750 mg) as sprinkles on applesauce.

**Table 2: Plasma Pharmacokinetics for Balsalazide and Key Metabolites (5-ASA and N-Ac-5-ASA) with Administration of Balsalazide Following a Fast, a High-Fat Meal, and Drug Contents Sprinkled on Applesauce (Mean ± SD)**

	Fasting n=17	High-Fat Meal n=17	Sprinkled n=17
<i>C<sub>max</sub></i> (mcg/mL)			
Balsalazide	0.51 ± 0.32	0.45 ± 0.39	0.21 ± 0.12
5-ASA	0.22 ± 0.12	0.11 ± 0.10	0.29 ± 0.17
N-Ac-5-ASA	0.88 ± 0.39	0.64 ± 0.534	1.04 ± 0.57
<i>AUC<sub>0-24</sub></i> (mcg•hr/mL)			
Balsalazide	1.25 ± 0.73	1.52 ± 1.01	0.87 ± 0.48
5-ASA	2.59 ± 1.46	2.10 ± 2.58	2.99 ± 1.70
N-Ac-5-ASA	17.8 ± 8.14	17.7 ± 13.7	20.0 ± 11.4
<i>t<sub>1/2α</sub></i> (h)			
Balsalazide	0.8 ± 0.85	1.2 ± 1.11	1.6 ± 0.44
5-ASA	8.2 ± 1.98	22.0 ± 8.23	8.7 ± 1.99
N-Ac-5-ASA	9.9 ± 2.49	20.2 ± 8.94	10.8 ± 5.39

A relatively low systemic exposure was observed under all three administered conditions (fasting, fed with high-fat meal, sprinkled on applesauce), which reflects the variable, but minimal absorption of balsalazide disodium and its metabolites. The data indicate that both *C<sub>max</sub>* and *AUC<sub>0-24</sub>* were lower, while *t<sub>1/2α</sub>* was markedly prolonged under fed (high-fat meal) compared to fasted conditions. Moreover, the data suggest that taking balsalazide disodium as a sprinkle or as a capsule provides highly variable, but relatively similar mean pharmacokinetic parameter values. No inference can be made as to how the systemic exposure differences of balsalazide and its metabolites in this study might predict the clinical efficacy under different dosing conditions (i.e., fasted, fed with high-fat meal, or sprinkled on applesauce) since clinical efficacy after balsalazide disodium administration is presumed to be primarily due to the local effects of 5-ASA on the colonic mucosa.

In a separate study of adult patients with ulcerative colitis, who received balsalazide, 1.5 g twice daily for over 1 year, systemic drug exposure, based on mean *AUC* values, was up to 60 times greater (0.028 mcg•hr/mL to 0.480 mcg•hr/mL) when compared to that obtained in healthy subjects who received the same dose.

**Distribution**

The binding of balsalazide to human plasma proteins was >99%.

**Metabolism**

The products of the azoreduction of this compound, 5-ASA and 4-aminobenzoyl-β-alanine, and their N-acetylated metabolites have been identified in plasma, urine and feces.

**Elimination**

Following single-dose administration of 2.25 g balsalazide (three 750 mg capsules) under fasting conditions in healthy subjects, mean urinary recovery of balsalazide, 5-ASA and N-Ac-5-ASA was 0.28%, 0.22% and 10.2%, respectively.

In a multiple-dose study in healthy subjects receiving a balsalazide dose of two 750 mg capsules twice daily (3 g/day) for 10 days, mean urinary recovery of balsalazide, 5-ASA, and N-Ac-5-ASA was 0.1%, 0%, and 11.3%, respectively. During this study, subjects received their morning dose 0.5 hours after being fed a standard meal, and subjects received their evening dose 2 hours after being fed a standard meal.

In a study with 10 healthy volunteers, 85% of a single 2.25-g dose of balsalazide was recovered as 5-ASA, 4-aminobenzoyl-β-alanine, and the N-acetylated metabolites in feces, while <1% of the dose was recovered as parent compound.

In a study that examined the disposition of balsalazide in patients who were taking 3 to 6 g of balsalazide daily for more than 1 year and who were in remission from ulcerative colitis, less

than 1% of an oral dose was recovered as intact balsalazide in the urine. Less than 4% of the dose was recovered as 5-ASA, while virtually no 4-aminobenzoyl-β-alanine was detected in urine. The mean urinary recovery of N-Ac-5-ASA and N-acetyl-4-aminobenzoyl-β-alanine comprised <16% and <12% of the balsalazide dose, respectively. No fecal recovery studies were performed in this population.

All pharmacokinetic studies with balsalazide are characterized by large variability in the plasma concentration versus time profiles for balsalazide and its metabolites; thus half-life estimates of these analytes are indeterminate.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 24-month rat (Sprague Dawley) carcinogenicity study, oral (dietary) balsalazide disodium at doses up to 2 g/kg/day was not tumorigenic. For a 50-kg person of average height this dose represents 2.4 times the recommended human dose on a body surface area basis. Balsalazide disodium was not genotoxic in the following *in vitro* or *in vivo* tests: Ames test, human lymphocyte chromosomal aberration test, and mouse lymphoma cell (L5178Y/TK<sup>+</sup>) forward mutation test; *in vitro* micronucleus test. However, it was genotoxic in the *in vitro* Chinese hamster lung cell (CH V79/HPF1) forward mutation test.

4-aminobenzoyl-β-alanine, a metabolite of balsalazide disodium, was not genotoxic in the Ames test and the mouse lymphoma cell (L5178Y/TK<sup>+</sup>) forward mutation test but was positive in the human lymphocyte chromosomal aberration test. N-acetyl-4-aminobenzoyl-β-alanine, a conjugated metabolite of balsalazide disodium, was not genotoxic in Ames test, the mouse lymphoma cell (L5178Y/TK<sup>+</sup>) forward mutation test, or the human lymphocyte chromosomal aberration test. Balsalazide disodium at oral doses up to 2 g/kg/day, 2.4 times the recommended human dose based on body surface area, was found to have no effect on fertility and reproductive performance in rats.

**13.2 Animal Toxicology**

**Renal Toxicity**

In animal studies conducted at doses up to 2000 mg/kg (approximately 21 times the recommended 6.75 g/day dose on a mg/kg basis for a 70 kg person), balsalazide demonstrated no nephrotoxic effects in rats or dogs.

**Overdose**

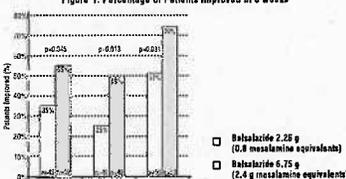
A single oral dose of balsalazide disodium of 5 g/kg or 4-aminobenzoyl-β-alanine, a metabolite of balsalazide disodium, at 1 g/kg was non-lethal in mice and rats. No symptoms of acute toxicity were seen at these doses.

**14 CLINICAL STUDIES**

**14.1 Adult Studies**

Two randomized, double-blind studies were conducted in adults. In the first trial, 103 patients with active mild-to-moderate ulcerative colitis with sigmoidoscopy findings of friable or spontaneously bleeding mucosa were randomized and treated with balsalazide 6.75 g/day or balsalazide 2.25 g/day. The primary efficacy endpoint was reduction of rectal bleeding and improvement of at least one of the other assessed symptoms (stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment [PGA]). Outcome assessment for rectal bleeding at each interim period (week 2, 4, and 8) encompassed a 4-day period (96 hours). Results demonstrated a statistically significant difference between high and low dose (Figure 1).

**Figure 1: Percentage of Patients Improved at 8 weeks**



A second study conducted in Europe confirmed findings of symptomatic improvement.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

Balsalazide Disodium Capsules are available as white, opaque capsules imprinted "APO 8750" in red ink.

Balsalazide Disodium Capsules are supplied as follows:

- Bottles of 30 (NDC 66505-2575-3)
- Bottles of 280 (NDC 66505-2575-7)
- Bottles of 350 (NDC 66505-2575-1)
- Unit Dose Blister Packs of 10 strips of 10 capsules (NDC 66505-2575-0)

**Storage**

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). See USP Controlled Room Temperature.

**17 PATIENT COUNSELING INFORMATION**

**17.1 Important Precautions Regarding Balsalazide Disodium Capsules**

- Instruct patients not to take balsalazide if they have a hypersensitivity to salicylates (e.g., aspirin).
- Patients should be instructed to contact their health care provider under the following circumstances:
  - If they experience a worsening of their ulcerative colitis symptoms.
  - If they are diagnosed with pyloric stenosis, because balsalazide disodium capsules may be slow to pass through their digestive tract.
  - If they are diagnosed with renal dysfunction. Damage to the kidney has been observed in people given medications similar to balsalazide.

**17.2 What Patients Should Know About Adverse Reactions**

- In adult clinical trials the most common adverse reactions were headache, abdominal pain, diarrhea, nausea, vomiting, respiratory infection, and arthralgia.
- Inform patients that this listing of adverse reactions is not complete and not all adverse reactions can be anticipated. If appropriate, a more comprehensive list of adverse reactions can be discussed with patients.

**17.3 What Patients Should Know About Taking Balsalazide Disodium Capsules with Other Medication**

- Based upon limited studies conducted in a test tube, balsalazide is not believed to interfere with other drugs by preventing how the liver functions. However, as the studies were limited in scope, you should always consult your doctor and discuss potential interactions prior to initiating any new drug.

**APOTEX INC.**

**BALSALAZIDE DISODIUM CAPSULES 750 mg**

Manufactured by: Apotex Inc., Toronto, Ontario M9L 1T9  
 Manufactured for: Apotex Corp., Weston, Florida Canada USA 33326  
 (BALSALAZIDE-CAP-210X355-INS-11082007)

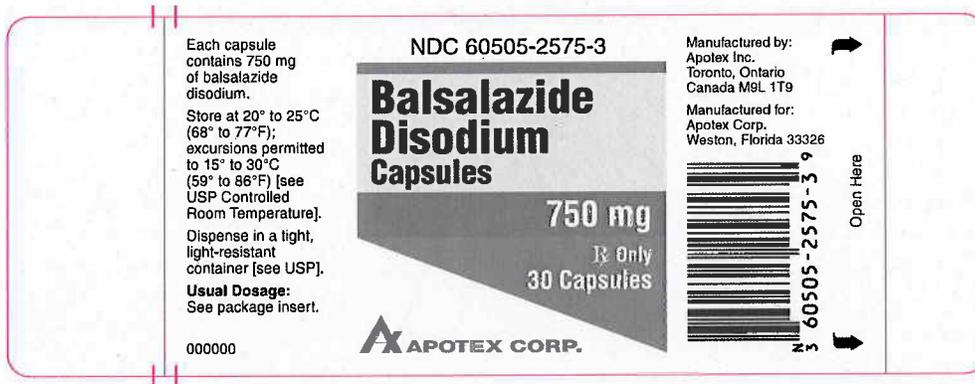
Revision: 03  
 Revised: November 2007



**PRINTED PACKAGING MATERIAL MASTER**

Copy of

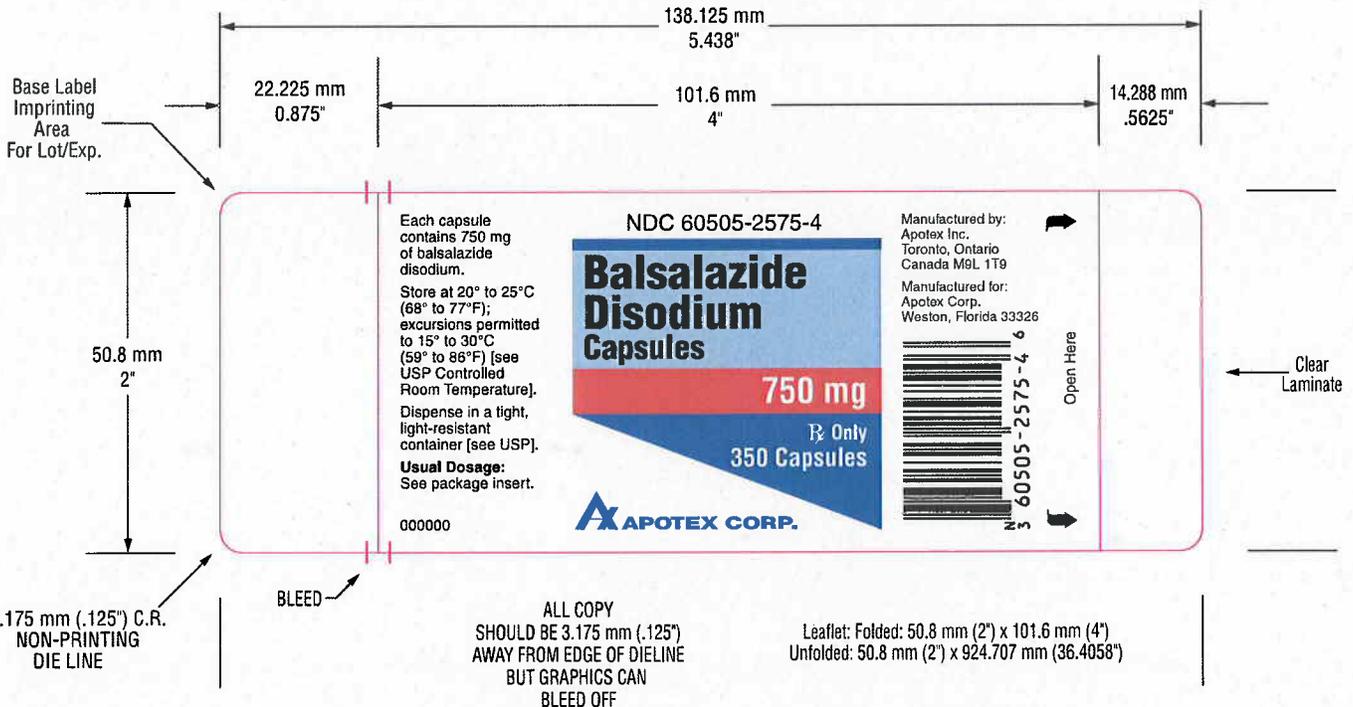
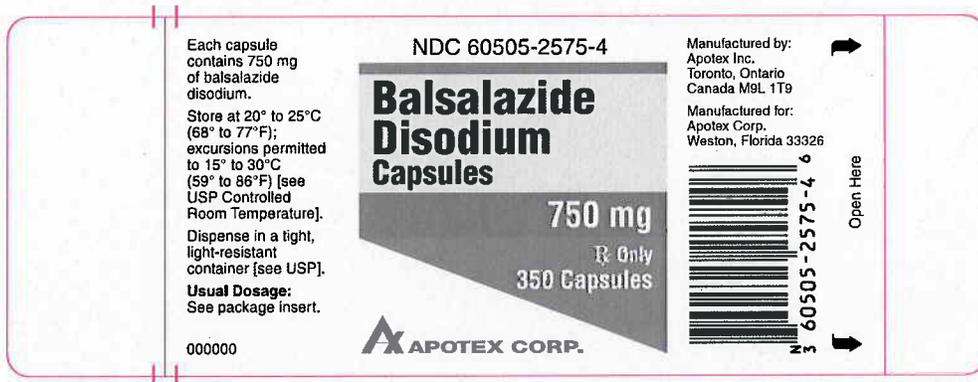
Material 000000	Description LBL USABALSALZIDE DISODIUM CAP 750MG 30	Effective Date:
Change NEW FINISHED GOODS	C of A PKGP-CA-LABEL	CCF#
Previous Code N/A	Label Draft# CUSTOMER APPROVED	Dimensions Composite: 50.8mm x 138.125 mm
Pantone Colours	(b) (4)	
Prepared by: (b) (4)	Reviewed by:	Customer Approval:
Date: Oct 30, 2007	Date:	QA Approval: Date:



**PRINTED PACKAGING MATERIAL MASTER**

Copy of

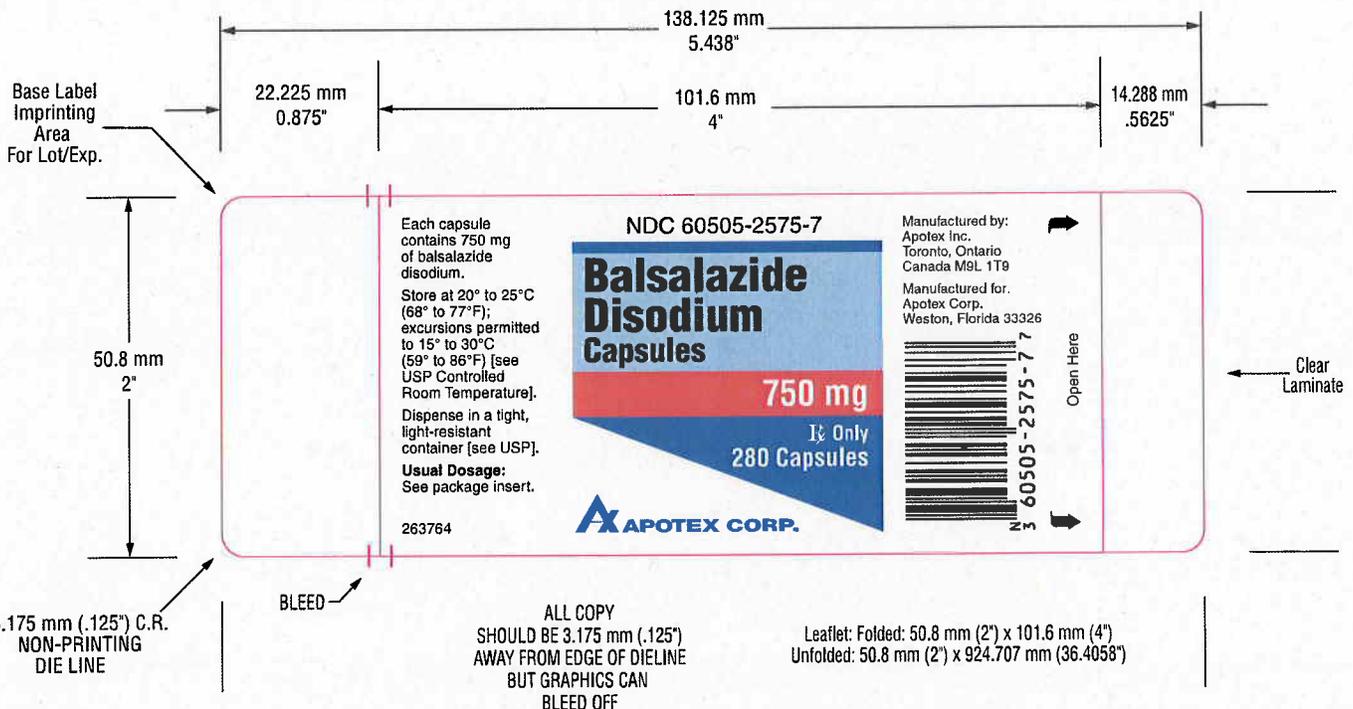
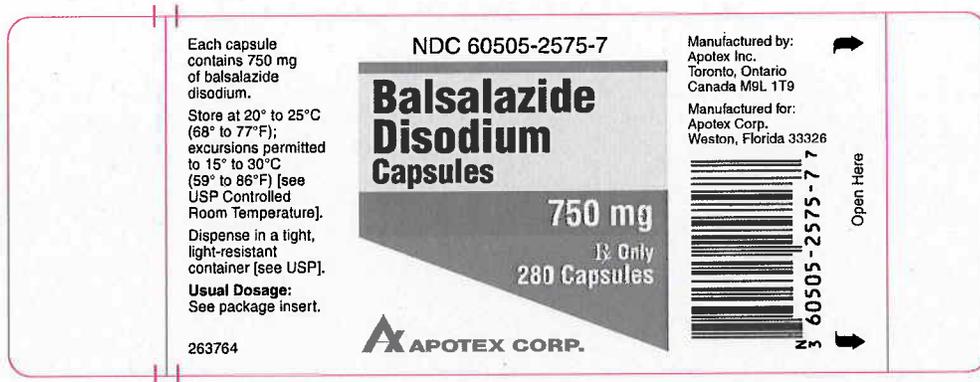
Material 000000	Description LBL USABALSALZIDE DISODIUM CAP 750MG 350	Effective Date:
Change NEW FINISHED GOODS	C of A PKGP-CA-LABEL	CCF#
Previous Code N/A	Label Draft# CUSTOMER APPROVED	Dimensions Composite: 50.8mm x 138.125 mm
Pantone Colours	(b) (4)	
Prepared by: (b) (4)	Reviewed by:	Customer Approval:
Date: Oct 30, 2007	Date:	QA Approval: Date:



**PRINTED PACKAGING MATERIAL MASTER**

Copy of

Material 263764	Description LBL USABALSALZIDE DISODIUM CAP 750MG 280	Effective Date:
Change CUSTOMER TEXT REVISION	C of A PKGP-CA-LABEL	CCF#
Previous Code 251621	Label Draft# CUSTOMER APPROVED	Dimensions Composite: 50.8mm x 138.125 mm
Pantone Colours	(b) (4)	
Prepared by: (b) (4)	Reviewed by:	Customer Approval:
Date: Oct 30, 2007	Date:	QA Approval: Date:

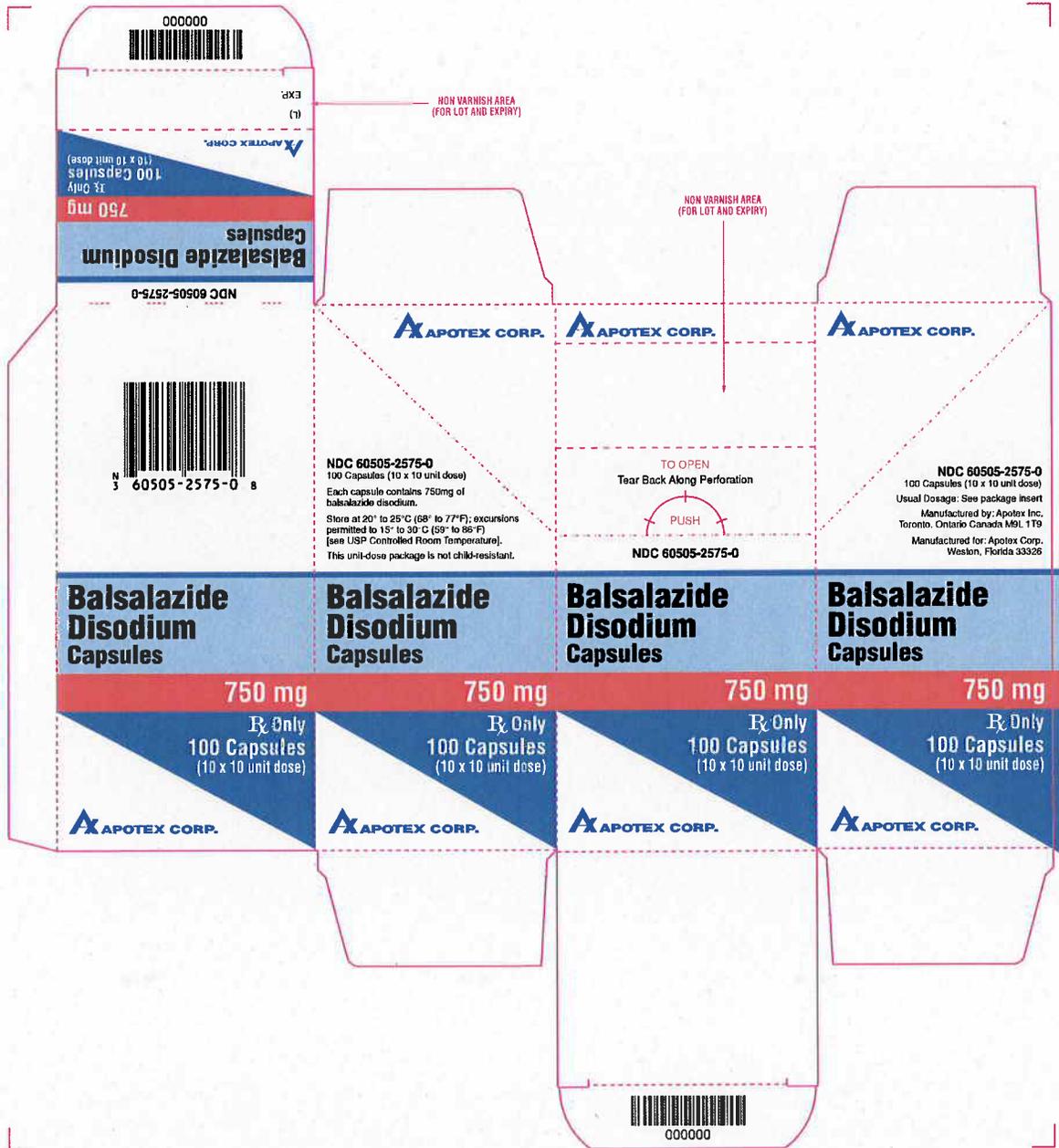




**PRINTED PACKAGING MATERIAL MASTER**

Copy of

Material: 000000	Description: CTN USA BALSALAZIDE DISODIUM CAP 750MG 100		Effective Date:
Change: NEW FINISHED GOODS	C of A: PKGP-CA-CARTON		CCF#:
Previous Code: N/A	Label Draft#: CUSTOMER APPROVED	Dimensions: 1NG2027 67 mm x 62 mm x 141.5 mm	Minimum Font Size: 7 POINT
Pantone Colours: (b) (4)			
Prepared by: (b) (4) Date: Oct 30, 2007	Reviewed by: Date:	Customer Approval: Date:	OA Approval: Date:



Material: 000000	Description: PPADBSUSA BALSALAZIDE DISODIUMCAP 750MG 10	Effective Date:
Change: NEW FINISHED GOODS	C of A: PKGP-CA-PAD	CCF#:
Previous Code: N/A	Label Draft#: CUSTOMER APPROVED	Dimensions: TOOLING TO01N 62.3 mm x 135 mm
Pantone Colours: (b) (4)	Minimum Font Size: 4 POINTS	
Prepared by: (b) (4)	Reviewed by:	Customer Approval:
Date: Oct 30, 2007	Date:	QA Approval:

**Balsalazide Disodium Capsules**  
750 mg

Each capsule contains 750 mg of balsalazide disodium. See package enclosure for prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room].

000000

**Balsalazide Disodium Capsule**  
750 mg

MFD. FOR APOTEX CORP.  
WESTON, FL 33326

(01)00360505257508  
EXP. 10 2008

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 77-883**

**LABELING REVIEWS**

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

ANDA Number: 77-883      Dates of Submission: November 3, 2005, September 24, 2007

Applicant's Name: Apotex, Inc.

Established Name: Balsalazide Disodium Capsules, 750 mg

---

Labeling Deficiencies:

1. CONTAINER (Bottles of 30s, 280s, and 350s):

Please separate the strength from the net quantity statement by inserting "Rx only" statement between them.

2. CARTON (10 X 10)

See CONTAINER comment above.

3. BLISTER

Please revise the individual blister to read "Balsalazide Disodium Blister" since only one capsule will be packaged in one blister.

2. INSERT:

a. GENERAL COMMENTS:

- i. Please use italicized font for phrases such as "*in vivo*" and "*in vitro*" throughout the text.
- ii. Revise "µg" to "mcg".
- iii. Please justify the amount of sodium (approximately 86 mg) on the label.

b. HIGHLIGHTS

- i. Add "Initial U.S. Approval: 2000" please refer to the template.
- ii. Add the "RECENT MAJOR CHANGES" section, please refer to the template.

c. FULL PRESCRIBING INFORMATION: CONTENTS\*

Please separate this section from the HIGHLIGHTS and FULL PRESCRIBING INFORMATION sections by lines. Please refer to the template.

d. FULL PRESCRIBING INFORMATION

i. 1 INDICATIONS AND USAGE

Revise "Balsalazide" to "Balsalazide disodium capsules"

- ii. Add margin markers to 2.2 and 5.1.

iii. 11 DESCRIPTION

Please add components of printing ink and "titanium dioxide" to the list of inactive ingredients

iv. 12.3 Pharmacokinetics

Elimination, penultimate paragraph, revise "3-6 g" to "3 to 6 g".

Submit labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

**NOTES/QUESTIONS TO THE CHEMIST:**

**5/31/06- Emailed chemist Shanaz Read about the sodium content of this drug product. The PI state approximately 86 mg of sodium. I need her to verify this amount.**

**FOR THE RECORD:**

1. MODEL LABELING- This review is partially based on the labeling of Colazal® Capsules of Salix Pharmaceuticals, Inc., NDA 20-610/S-016 approved December 20, 2006. Salix received PED exclusivity and then the ODE exclusivity. Because the ODE overrides the Waxman-Hatch exclusivity, all information relating to this indication in pediatric patients was carved out of the labeling. No BPCA statements was used except in the Use in Specific Populations section of the Highlighted area as well as the Pediatrics section (8.4). A labeling template was created to reflect the ODE exclusivity and PEDs, OND and OCC were consulted. Kim Dettelbach (OCC) okay the carve out template on 9/12/07. The labeling template was emailed to the participating firms on 9/13/07.

2. PATENT/ EXCLUSIVITIES

**Patent Data – for NDA 20-610**

No	Expiration	Use Code	Use	File	Labeling Impact
4412992	July 8, 2006			III	None
4,412,992 *PED	Jan 8, 2007				

**Exclusivity Data – for NDA 20-610**

Code/sup	Expiration	Use Code	Description	Labeling Impact
PED	Jun 20, 2010			Carve out
NPP	Dec 20, 2009		New patient population (pediatric)	Carve out
ODE	Dec 20, 2013		Orphan Drug Exclusivity (pediatric)	Carve out
PED	Jun 20, 2014		Associated with ODE exclusivity	Carve out

3. MANUFACTURING FACILITY

Apotex Inc.  
150 Signet Drive  
Toronto, Ontario M9L 1T9  
Canada

[Chemist review #1]

4. SCORING:

NDA - N/A  
ANDA - N/A

5. STORAGE CONDITIONS:

NDA - Store at 25°C (77°); excursions permitted between 15° and 30°C (59° and 86°F). See USP Controlled Room Temperature.

ANDA - Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). See USP Controlled Room Temperature.

6. DISPENSING RECOMMENDATIONS:

NDA - None listed in labeling.

ANDA - Dispense in a tight, light-resistant container [see USP].

7. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert is not consistent with the listing of inactive ingredients found in the statement of components and composition.

[Chemist review #1]

The inactive ingredients for the drug product are:

Capsule shell- titanium dioxide, gelatin

Capsule content- colloidal silicon dioxide, magnesium stearate, (b) (4)

Printing ink: shellac, (b) (4) propylene glycol, red iron oxide, strong ammonia solution

Since only the printing ink contain iron oxide, the calculations for elemental iron intake is not necessary.

I ask firm to add the components of the printing ink and titanium dioxide.

8. PACKAGING CONFIGURATIONS:

NDA- Bottles of 280

Bottles of 500

ANDA- Bottles of 30s, 280s, 350s and unit dose blister packs (10 x 10)

9. CONTAINER/CLOSURE SYSTEM: [Chemist review 1]

Fill Size	Bottle Type	Cap Type
30	120 cc White round HDPE bottles	Seal CRC
280	750 cc White round HDPE bottles	Seal-non CRC
350	950 cc White round HDPE bottles	Seal- non CRC
U-D	(b) (4) clear film from (b) (4) and aluminum foil from (b) (4)	

10. The capsule debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

ANDA- white, opaque body and white opaque cap, imprinted "APO B750" in red ink.

11. Insert states that effect of food intake was not studied (PHARMACOKINETICS, Absorption) Bioequivalence review is acceptable as of 10/17/07.

12. NDC numbers: 30 capsules- NDC 60505-2575-3  
NDC numbers: 280 capsules- NDC 60505-2575-7  
NDC numbers: 350 capsules- NDC 60505-2575-4  
Unit dose bliser packs- NDC 60505-2575-0

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Date of Review: October 17, 2007

Dates of Submission: November 3, 2005 and September 24, 2007

Primary Reviewer: Thuyanh Vu

Date:

Team Leader: Lillie Golson

Date:

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Thuyanh Vu  
10/24/2007 08:37:39 AM  
LABELING REVIEWER

Lillie Golson  
10/25/2007 04:49:33 PM  
LABELING REVIEWER

**APPROVAL SUMMARY  
REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

ANDA Number: 77-883      Dates of Submission: October 31 and November 9, 2007

Applicant's Name: Apotex, Inc.

Established Name: Balsalazide Disodium Capsules, 750 mg

---

**BASIS OF APPROVAL:**

**APPROVAL SUMMARY**

Container Labels: (Bottles of 30s, 280 and 350s)  
**Satisfactory in final print as of October 31, 2007**

Carton Label: (10 x10)  
**Satisfactory in final print as of October 31, 2007**

Blister Label:  
**Satisfactory in final print as of October 31, 2007**

Professional Package Insert Labeling:  
**Satisfactory in final print as of November 9, 2007, blister-labeling insert.**

Revisions needed post-approval: None

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Colazal

NDA Number: 20-610

NDA Drug Name: Colazal

NDA Firm: Salix Pharmaceuticals, Inc.

Date of Approval of NDA Insert and supplement #: November 2, 2007/ S-017

Has this been verified by the MIS system for the NDA? yes

Was this approval based upon an OGD labeling guidance? no

Basis of Approval for the Container Labels: side-by-side

Other Comments: Colazal had pediatric exclusivity and then orphan drug exclusivity. Pediatric indication, study and dosing were "carved out" from the generic labeling. Consults were submitted to the PEDs, Division and OCC for clearance. Read FTR below.

**NOTES/QUESTIONS TO THE CHEMIST:**

**5/31/06- Emailed chemist Shanaz Read about the sodium content of this drug product. The PI state approximately 86 mg of sodium. I need her to verify this amount.**

---

**FOR THE RECORD:**

1. MODEL LABELING- This review is partially based on the labeling of Colazal ® Capsules of Salix Pharmaceuticals, Inc., NDA 20-610/S-017, approved 11/2/07. Salix received PED exclusivity and then the ODE exclusivity. Because the ODE overrides the Waxman-Hatch exclusivity, all information relating to this indication in pediatric patients was carved out of the labeling. No BPCA statements was used except in the Use in Specific Populations section of the Highlighted area as well as the Pediatrics section (8.4). A labeling template was created to reflect the ODE exclusivity and PEDs, OND and OCC were consulted. Kim Dettelbach (OCC) okay the carve out template on 9/12/07. The labeling template was emailed to the participating firms on 9/13/07.

2. PATENT/ EXCLUSIVITIES

**Patent Data – for NDA 20-610**

No	Expiration	Use Code	Use	File	Labeling Impact
4412992	July 8, 2006			III	None
4,412,992 *PED	Jan 8, 2007				

**Exclusivity Data – for NDA 20-610**

Code/sup	Expiration	Use Code	Description	Labeling Impact
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NPP	Dec 20, 2009		New patient population (pediatric)	Carve out
ODE	Dec 20, 2013		Orphan Drug Exclusivity (pediatric)	Carve out
PED	Jun 20, 2014		Associated with ODE exclusivity	Carve out

3. MANUFACTURING FACILITY

Apotex Inc.  
150 Signet Drive  
Toronto, Ontario M9L 1T9  
Canada

[Chemist review #1]

4. SCORING:

NDA - N/A  
ANDA - N/A

5. STORAGE CONDITIONS:

NDA - Store at 25°C (77°); excursions permitted between 15° and 30°C (59° and 86°F). See USP Controlled Room Temperature.  
ANDA - Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). See USP Controlled Room Temperature.

6. DISPENSING RECOMMENDATIONS:

NDA - None listed in labeling.  
ANDA - Dispense in a tight, light-resistant container [see USP].

7. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert is not consistent with the listing of inactive ingredients found in the statement of components and composition.

[Chemist review #1]

The inactive ingredients for the drug product are:

Capsule shell- titanium dioxide, gelatin

Capsule content- colloidal silicon dioxide, magnesium stearate, (b) (4)

Printing ink: shellac, (b) (4), propylene glycol, red iron oxide, strong ammonia solution

Since only the printing ink contain iron oxide, the calculations for elemental iron intake is not necessary.

I ask firm to add the components of the printing ink and titanium dioxide.

8. PACKAGING CONFIGURATIONS:

NDA- Bottles of 280  
Bottles of 500

ANDA- Bottles of 30s, 280s, 350s and unit dose blister packs (10 x 10)

9. CONTAINER/CLOSURE SYSTEM: [Chemist review 1]

Fill Size	Bottle Type	Cap Type
30	120 cc White round HDPE bottles	Seal CRC
280	750 cc White round HDPE bottles	Seal-non CRC
350	950 cc White round HDPE bottles	Seal- non CRC

U-D	(b) (4) clear film from (b) (4) and aluminum foil from (b) (4)	
-----	---	--

10. The capsule debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

ANDA- white, opaque body and white opaque cap, imprinted "APO B750" in red ink.

11. Insert states that effect of food intake was not studied (PHARMACOKINETICS, Absorption) Bioequivalence review is acceptable as of 10/17/07.

12. NDC numbers: 30 capsules- NDC 60505-2575-3  
NDC numbers: 280 capsules- NDC 60505-2575-7  
NDC numbers: 350 capsules- NDC 60505-2575-4  
Unit dose bliser packs- NDC 60505-2575-0

13. In AF dated 10/31/07- Apotex provided justification of their sodium content. The sodium content of their capsule is approximately 86 mg.

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Date of Review:	November 15, 2007	Dates of Submission:	October 31, 2007 and November 9, 2007
Primary Reviewer:	Thuyanh Vu	Date:	
Team Leader:	Lillie Golson	Date:	

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Thuyanh Vu  
11/19/2007 09:12:54 AM  
LABELING REVIEWER

Koung Lee  
11/19/2007 09:42:38 AM  
LABELING REVIEWER  
Signing for Lillie Golson

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 77-883**

**CHEMISTRY REVIEWS**



**ANDA 77-883**

**Balsalazide Disodium Capsules, 750 mg**

**Apotex Inc.**

**Shahnaz Read  
Chemistry Division II**



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# Chemistry Review Data Sheet

1. ANDA 77-883
2. REVIEW #: 1
3. REVIEW DATE: September 26, 2006
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS: NA
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission

Amendment in response to "Refuse to Receive Letter"

Document Date

November 3, 2005

June 15, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Apotex Inc.  
Address: 380 Elgin Mills Road East  
Richmond Hills, Ontario  
Canada L4C 5H2  
U.S. Representative: Tammy McIntire  
Apotex Corp.  
2400 North Commerce Parkway, Suite 400  
Weston, FL 33326  
Telephone: 954-349-4217  
Fax: 954-349-4233

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
- b) Non-Proprietary Name (USAN): Balsalazide Disodium
- c) British adopted name (BAN): Balzazide



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Colazal® (Balsalazide Disodium) Capsules (NDA 20-610) held by Salix Pharmaceuticals. The applicant has filed Paragraph III certification for U.S. patent 4,412,992 which was to expire on July 8, 2006 but has been granted pediatric exclusivity up to January 8, 2007 and seeks approval after expiration of the patent. The applicant also certifies that according to the "Orange Book" the drug does not have any unexpired marketing exclusivity.

10. PHARMACOL. CATEGORY: For Treatment of Active Ulcerative Colitis

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 750 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  X  Rx   OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

x  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (E)-5-[[4-[(2-carboxyethyl)amino]carbonyl]phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate.

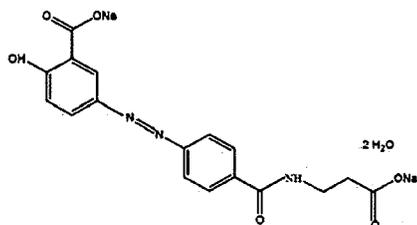
(E)-5-[[p-[(2-carboxyethyl)carbamoyl]phenyl]azo}salicylic acid, disodium salt, dihydrate. Molecular Formula: C<sub>10</sub>H<sub>7</sub>Cl<sub>2</sub>N<sub>3</sub>O.HCl.H<sub>2</sub>O;

Molecular Weight: 401.32 (437.32 for the dihydrate)



## Chemistry Review Data Sheet

## Chemical Structure:



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	Sept 25, 2006	DMF holder has been notified
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	8/29/06	S. Adams
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	Satisfactory		
Radiopharmaceutical	NA		

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

# The Chemistry Review for ANDA 77-883

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Not Approvable

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance and drug product are not compendial. Balsalazide Disodium Dihydrate is a stable, odorless, orange to yellow microcrystalline powder. It is freely soluble in water and isotonic saline, sparingly soluble in methanol and ethanol, and practically insoluble in all other organic solvents. It is delivered intact to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine which is the therapeutically active portion of the molecule and 4-aminobenzoyl- $\beta$ -alanine which is inert. The mechanism of action of mesalamine is unknown, but it is believed to be topical rather than systemic.

The product is a hard gelatin capsule containing 750 mg of Balsalazide Sodium Dihydrate and excipients. The process consists of comprises of (b) (4)

encapsulation and packaging. The capsules are available in bottles of 30, 280 and 350 capsules and 10x10 blister packs.

#### B. Description of How the Drug Product is Intended to be Used

For Treatment of Active Ulcerative Colitis, the usual dose in adults is three 750 mg capsules be taken three times a day for a total daily dose of 6.75 grams for a duration of 8 weeks. The capsules contain granules of balsalazide disodium which are insoluble in acid and designed to be delivered to the colon intact where the bacterial azoreductases cleave the compound to release mesalamine and 4-aminobenzoyl- $\beta$ -alanine. The recommended dose of 6.75 g/day provides 2.4 g of free 5-aminosalicylic acid (mesalamine).

#### C. Basis for Approvability or Not-Approval Recommendation

The firm needs to resolve issues related to drug product specifications and other deficiencies as noted in the deficiency letter.

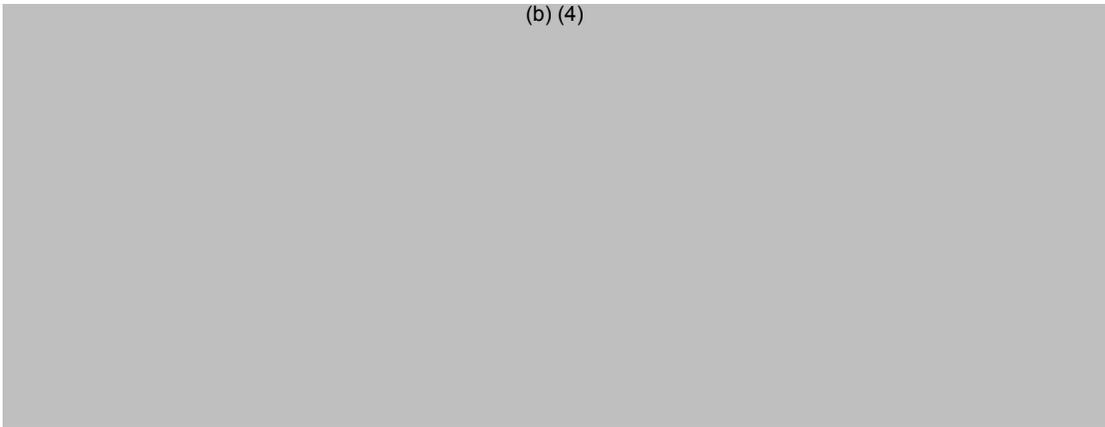


## CHEMISTRY REVIEW



### Chemistry Assessment Section

(b) (4)



**30. MICROBIOLOGY**

NA

**31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

NA

**32. LABELING**

Pending

**33. ESTABLISHMENT INSPECTION**

Acceptable 8/29/06.

**34. BIOEQUIVALENCE**

Pending

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).



**36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 77-883

APPLICANT: Apotex Inc.

DRUG PRODUCT: Balsalazide Disodium Capsules, 750 mg

A. The deficiencies presented below represent MINOR deficiencies.

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.
- 9.
- 10.

(b) (4)





## CHEMISTRY REVIEW



### Chemistry Assessment Section

B. Comments:

1. Please provide updated stability data for the exhibit batches.
2. The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

Sincerely yours,

*{See appended electronic signature page}*

Florence S. Fang  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research



Chemistry Assessment Section

cc: ANDA 77-883  
DIV FILE  
Field Copy

Endorsements:

HFD-645/SRead/9-26-06

HFD-645/SFurness/10-6-06

HFD-617/YKong/10-11-06

F/T by:

V:\FIRMSAM\APOTEX\LTRS&REV\77883R1.doc

**TYPE OF LETTER: MINOR**

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

-----  
Shanaz Read  
10/11/2006 01:08:18 PM  
CHEMIST

Yoon Kong  
10/11/2006 02:02:54 PM  
CSO

Michael S Furness  
10/11/2006 02:19:57 PM  
CHEMIST

**ANDA 77-883**

**Balsalazide Disodium Capsules, 750 mg**

**Apotex Inc.**

**Shahnaz Read  
Chemistry Division II**



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# Chemistry Review Data Sheet

1. ANDA 77-883

2. REVIEW #: 2

3. REVIEW DATE: February 26, 2007

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed

Original Submission

Amendment in response to "Refuse to Receive Letter"

Document Date

November 3, 2005

June 15, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Minor Amendment

Document Date

November 8, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Apotex Inc.  
Address: 380 Elgin Mills Road East  
Richmond Hills, Ontario  
Canada L4C 5H2  
U.S. Representative: John G. Lay  
Apotex Corp.  
2400 North Commerce Parkway, Suite 400  
Weston, FL 33326  
Telephone: 954-349-4217  
Fax: 954-349-4233

8. DRUG PRODUCT NAME/CODE/TYPE:

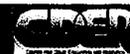
a) Proprietary Name: (b) (4)

b) Non-Proprietary Name (USAN): Balsalazide Disodium

c) British adopted name (BAN): Balzazalazide



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Colazal® (Balsalazide Disodium) Capsules (NDA 20-610) held by Salix Pharmaceuticals. The applicant has filed Paragraph III certification for U.S. patent 4,412,992 which was to expire on July 8, 2006 but has been granted pediatric exclusivity up to January 8, 2007 and seeks approval after expiration of the patent. The applicant also certifies that according to the "Orange Book" the drug does not have any unexpired marketing exclusivity.

10. PHARMACOL. CATEGORY: For Treatment of Active Ulcerative Colitis

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 750 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  X  Rx   OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

x  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (E)-5-[[4-[[2-carboxyethyl]amino]carbonyl]phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate.

(E)-5-[[p-[(2-carboxyethyl)carbamoyl]phenyl]azo]salicylic acid, disodium salt, dihydrate. Molecular Formula:  $C_{10}H_7Cl_2N_3O \cdot HCl \cdot H_2O$ ;

Molecular Weight: 401.32 (437.32 for the dihydrate)

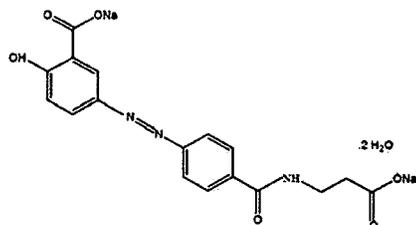


# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

Chemical Structure:



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	February 26, 2007	
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	10/24/06	S. Adams
Methods Validation	NA		
Labeling	Acceptable	11/20/07	
Bioequivalence	Acceptable	10/24/07	
EA	Satisfactory		
Radiopharmaceutical	NA		

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:



# The Chemistry Review for ANDA 77-883

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Approvable for CMC

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance and drug product are not compendial. Balsalazide Disodium Dihydrate is a stable, odorless, orange to yellow microcrystalline powder. It is freely soluble in water and isotonic saline, sparingly soluble in methanol and ethanol, and practically insoluble in all other organic solvents. It is delivered intact to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine which is the therapeutically active portion of the molecule and 4-aminobenzoyl- $\beta$ -alanine which is inert. The mechanism of action of mesalamine is unknown, but it is believed to be topical rather than systemic.

The product is a hard gelatin capsule containing 750 mg of Balsalazide Sodium Dihydrate and excipients. The process consists of comprises of (b) (4)

encapsulation and packaging. The capsules are available in bottles of 30, 280 and 350 capsules and 10x10 blister packs.

#### B. Description of How the Drug Product is Intended to be Used

For Treatment of Active Ulcerative Colitis, the usual dose in adults is three 750 mg capsules be taken three times a day for a total daily dose of 6.75 grams for a duration of 8 weeks. The capsules contain granules of balsalazide disodium which are insoluble in acid and designed to be delivered to the colon intact where the bacterial azoreductases cleave the compound to release mesalamine and 4-aminobenzoyl- $\beta$ -alanine. The recommended dose of 6.75 g/day provides 2.4 g of free 5-aminosalicylic acid (mesalamine).

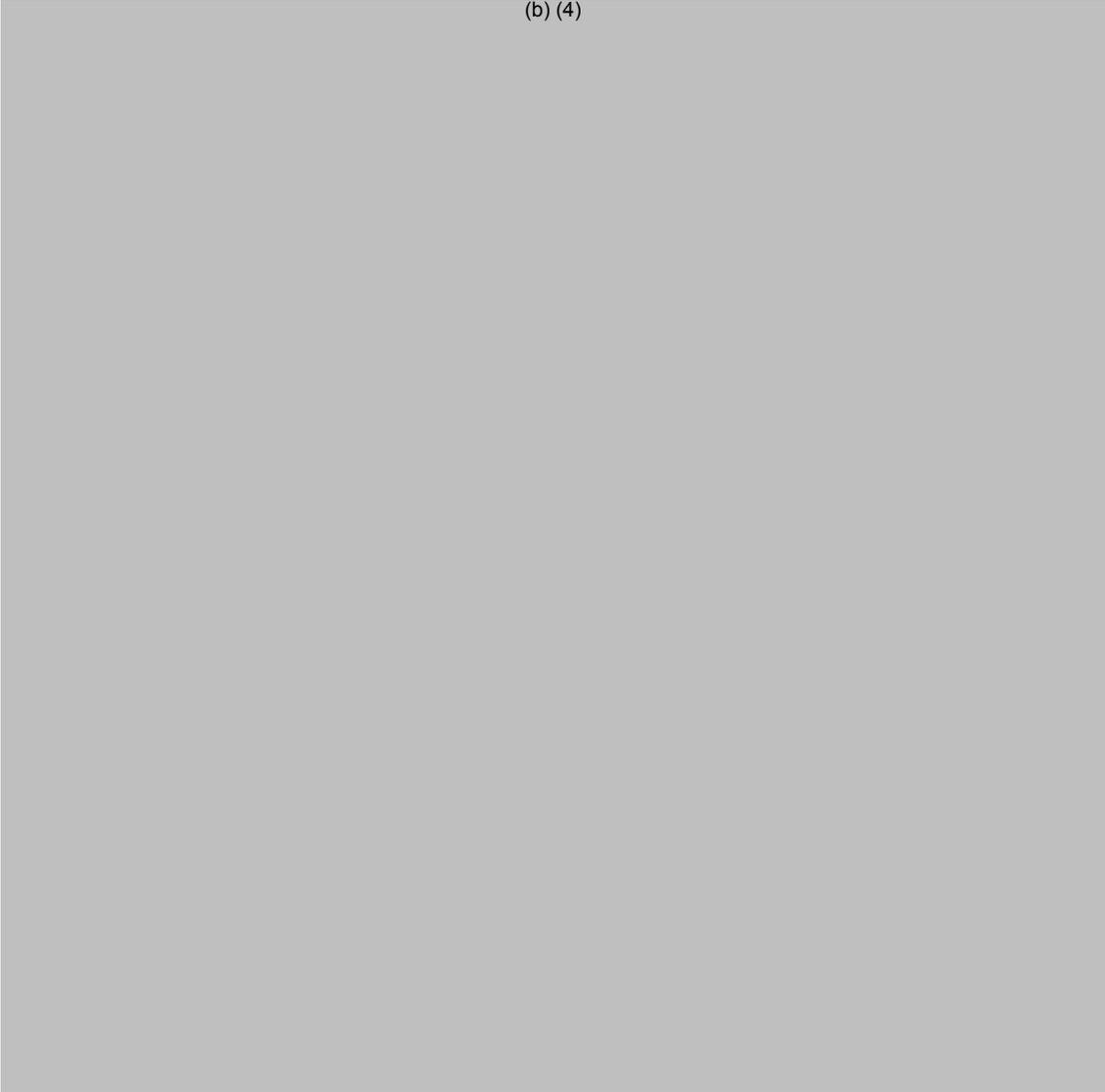
#### C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been resolved



Chemistry Assessment Section

(b) (4)



**30. MICROBIOLOGY**

NA

**31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

NA

**32. LABELING**

Acceptable 11/20/07.

**33. ESTABLISHMENT INSPECTION**

Acceptable 10/24/06.



## CHEMISTRY REVIEW



### Chemistry Assessment Section

**34. BIOEQUIVALENCE**

Acceptable 10/24/07.

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

A categorical exclusion from the requirement of an Environmental Assessment or Environmental Impact Statement is requested in accordance with 21 CFR 25.31(a).

**36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

None



Chemistry Assessment Section

cc: ANDA 77-883  
DIV FILE  
Field Copy

Endorsements:

HFD-645/SRead/2/26/07

HFD-645/SFurness/3/1/07

HFD-617/thinchliffe/3/2/07;TLiu/11/23/07

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

-----  
Shanaz Read  
11/30/2007 12:01:26 PM  
CHEMIST

Sema Basaran  
11/30/2007 01:26:32 PM  
CHEMIST  
Signing for Scott Furnes as a acting team leader.

Simon Eng  
12/4/2007 12:10:28 PM  
CSO

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 77-883**

**BIOEQUIVALENCE REVIEWS**

**DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW**

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<b>ANDA No.</b>	77-883
<b>Drug Product Name</b>	Balsalazide Disodium Capsules
<b>Strength</b>	750 mg
<b>Applicant Name</b>	Apotex Inc.
<b>Submission Date(s)</b>	November 3, 2005
<b>Amendment Date</b>	June 15, 2006
<b>First Generic</b>	No
<b>Reviewer</b>	Devvrat Patel, Pharm.D.
<b>File Location</b>	V:\firmsam\Apotex\ltrs&rev\77883D1105.doc

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**EXECUTIVE SUMMARY**

This is a review of the dissolution testing data only.

There is no USP method for this product, but there is an FDA-recommended method. The firm conducted dissolution testing with a non-FDA-recommended method. The firm should conduct dissolution testing with the FDA-recommended method.

The firm also submitted additional dissolution testing (as recommended per P05-006.doc) using 900 ml of 4 different media (0.1N HCl, pH 4.5 Buffer, pH 6.8 Buffer, and pH 7.4 Buffer) with apparatus 1 (basket) at 100 rpm. Although this method differs from the current FDA-recommended dissolution method with respect to apparatus and speed, the additional dissolution testing is acceptable and need not be repeated (see comments on page 4).

The firm has not submitted all electronic summary tables.

The DBE will review the fasted BE study at a later date.



TABLE 1. SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Did the firm use the USP dissolution method			<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Did the firm use 12 units of both test and reference in dissolution testing			<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Did the firm conduct dissolution testing with its own proposed method			<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Is FDA method in the public dissolution database (on the web)			<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Plasma concentrations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Fed BE study	PK parameters	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Plasma concentrations	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	Other study	PK parameters	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Plasma concentrations	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Are all eight electronic summary biotables present			<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Are electronic summary biotables in pdf format			<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

If the answer to either of the last two questions is no, indicate which summary biotables are

- Not present: 3,5,6
- Not in pdf format: N/A

**Reviewer's Comment:** In future applications, to facilitate the review process, the firm should submit all CTD electronic summary biotables in word format.

**RLD METHOD**

<b>Medium</b>	Potassium Phosphate buffer, pH 6.8
<b>Volume</b>	900 ml
<b>Temperature</b>	37°C
<b>Apparatus</b>	2 (paddle) with sinkers
<b>Rotational Speed</b>	50 rpm
<b>Specification</b>	NLT $\frac{(b)}{(4)}$ % (Q) in 30 minutes

Source of Method: NDA # 20-610/SCS-011 Chemistry Review-Jul 20, 2005.

**ADDITIONAL RECOMMENDED DISSOLUTION METHODS (as per P05-006.doc)**

<b>Medium</b>	0.1N HCl, pH 4.5 Buffer, pH 6.8 Buffer, and pH 7.4 Buffer
<b>Volume</b>	900 ml
<b>Temperature</b>	37°C
<b>Apparatus</b>	1 (Basket)
<b>Rotational Speed</b>	100 rpm
<b>Submitted by Firm?</b>	Yes

**Table 1. Summary of In Vitro Dissolution Data**

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)						Study Report Location
					5 min	10 min	15 min	20 min	30 min	45 min	
50256	Apotex / 043-11	750 mg Caps	Dissolution: Apparatus 1 (basket)	12	31 (22-45)	59 (46-73)	80 (68-85)	94 (88-98)	101 (96-103)	101 (97-104)	5.3.1.3
50256	Colazal® / 311208	750 mg Caps	Speed of Rotation: 100 rpm Medium: Water Volume: 900 mL Temperature: 37°C Specification: Not provided	12	21 (0-36)	58 (42-74)	79 (61-90)	94 (79-102)	102 (94-106)	102 (95-106)	

**COMMENTS:**

1. The DBE recommended the following dissolution testing for Balsalazide Capsules in a review of protocol, P05-006:

- a. Because balsalazide acts locally in the GI tract (not systemically), evaluation of dissolution is important in determining whether an equivalent amount of drug from each formulation (test and reference), is delivered to the sites of activity in the GI tract. The OGD recommends that the applicant compare the dissolution performance of its Balsalazide Disodium Capsules to that of Colazal® in dissolution media of varying pH. Varying pH conditions should be studied to approximate the varying pH conditions that balsalazide disodium capsules will be subjected to throughout the GI tract. Therefore, the OGD asks that the dissolution of Balsalazide Disodium Capsules be compared to that of Colazal® under the following pH conditions:

- (1) 0.1N HCl
- (2) a pH 4.5 buffer
- (3) a pH 6.8 buffer
- (4) a pH 7.4 buffer

Since this is a capsule product, the OGD asks that the dissolution testing be conducted using USP apparatus 1 (Basket) at 100 rpm using 900 ml of the above dissolution media.

- b. For its stability and quality controls program, the applicant should perform dissolution testing of its Balsalazide Disodium Capsules using the FDA-recommended dissolution method:

Medium	Water
Volume	900 mL
Temperature	37°C
Apparatus	Basket
Rotational Speed	100 rpm

- c. Because of the rapid rate of dissolution of mesalamine at neutral pH, the applicant should use sampling times of 5, 10, 15, 20, 30, 45, and 60 minutes during dissolution testing. This will help ensure that the investigator will be able to calculate the similarity factor (f2) to compare test and reference dissolution profiles. To determine f2, it is necessary that at least two of the dissolution values obtained before the plateau of the dissolution profile (% of labeled amount dissolved versus time) is reached.

2. Recently, the dissolution method for the RLD was revised as follows:

<b>Medium</b>	Potassium Phosphate buffer, pH 6.8
<b>Volume</b>	900 ml
<b>Temperature</b>	37°C
<b>Apparatus</b>	2 (paddle) with sinkers
<b>Rotational Speed</b>	50 rpm
<b>Sampling Times</b>	10, 20 and 30 minutes
<b>Specification</b>	NLT $\frac{(b)}{(4)}\%$ (Q) in 30 minutes

**Source of Method:** NDA# 20-610/SCS-011 Chemistry Review-Jul 20, 2005.

The firm conducted dissolution testing for their Balsalazide disodium capsules, 750 mg, and Colazal® Capsules, 750 mg, in 900 ml of water using apparatus 1 (basket) at 100 rpm as per old RLD method. The firm should therefore conduct dissolution testing using the current RLD method: 900 ml of potassium phosphate buffer pH 6.8 using apparatus 2 (paddle) with sinkers at 50 rpm.

3. The firm also submitted additional dissolution testing (as recommended per P05-006.doc) using 900 ml of 4 different media (0.1N HCl, pH 4.5 Buffer, pH 6.8 Buffer, and pH 7.4 Buffer) with apparatus 1 (basket) at 100 rpm. Although this method differs from the current FDA-recommended dissolution method with respect to apparatus and speed (basket at 100 rpm vs. paddle at 50 rpm), the additional dissolution testing is acceptable and need not be repeated because this testing is to evaluate if an equivalent amount of drug from each formulation (test and reference) is delivered to the sites of activity in the GI tract. The dissolution performance of the test product is comparable to the reference product under these conditions.

Dissolution data submitted by the firm is attached below:



Dissol.pdf

#### **DEFICIENCY COMMENTS:**

1. The firm should conduct dissolution testing using the FDA-recommended method: 900 ml of potassium phosphate buffer pH 6.8 using apparatus 2 (paddle) with sinkers at 50 rpm. The samples should be taken at 5, 10, 15, 20, 30, 45, 60, 80 and 120 minutes.

**RECOMMENDATIONS:**

The *in vitro* dissolution testing conducted by Apotex Inc., on its test product, Balsalazide Disodium Capsules, 750 mg, comparing it to Salix Pharma's Colazal® Capsules, 750 mg, is incomplete.

Devvrat Patel 9/13/2006  
Date  
Devvrat Patel, Pharm.D.  
Reviewer, Branch V  
Division of Bioequivalence

Kuldeep R. Dhariwal 9/13/06  
Date  
Kuldeep R. Dhariwal, Ph.D.  
Team Leader, Branch V  
Division of Bioequivalence

Dale P. Conner 9/18/06  
Date  
Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs

CC: ANDA #: 77-883  
ANDA DUPLICATE  
DIVISION FILE  
HFD-650/ Bio Drug File  
HFD-658/ Patel  
HFD/658/ Thompson

V:\firmsam\Apotex\ltrs&rev\77883D1105.doc

Endorsements: (Final with Dates)

HFD-658/Patel *9/13/06*

HFD-658/Dhariwal *9/13/06*

HFD/658/Thompson

*h* HFD-650/Conner *BMD 9/18/06*

BIOEQUIVALENCE - INCOMPLETE      Submission date: 11/3/2005

[NOTE: The *in vitro* testing is incomplete. The fasting BE study is pending review]

1. BDI

Strength: 750 mg

## DIVISION OF BIOEQUIVALENCE REVIEW

---

<b>ANDA No.</b>	77-883
<b>Drug Product Name</b>	Balsalazide Disodium Capsules
<b>Strength</b>	750 mg
<b>Applicant Name</b>	Apotex Inc.
<b>Applicant Address</b>	50 Steinway Boulevard, Etobicoke, Ontario, Canada M9W 6Y3
<b>Contact Information</b>	Kalpesh Shroff, US Agent – Apotex Corp. PH 954-349-4217 Fax 954-349-4233
<b>Clinical Site</b>	<u>Fasting Study No. 50256 and Re-dosing Fasting Study No. 60045</u> SFBC Anapharm 5160 Boul. Décarie, Suite 800 Montreal (Quebec), Canada H3X 2H9
<b>Analytical Site</b>	<u>Fasting Study No. 50256 and Re-dosing Fasting Study No. 60045</u> SFBC Anapharm 2050 Boul. René-Lévesque Ouest, Sainte-Foy (Québec), Canada G1V 2K8
<b>Submission Date</b>	June 15, 2006 (Refuse to file letter: November 03, 2005)
<b>Amendment Date</b>	October 16, 2006 (Dissolution Amendment)
<b>Reviewer</b>	April C. Braddy, Ph.D.
<b>First Generic</b>	No

---

### Review of Two Bioequivalence Studies and In Vitro Dissolution Testing

#### I. Executive Summary

In this application, the firm, Apotex, Inc. submitted an *in vivo* fasting bioequivalence (BE) study comparing its Balsalazide Disodium Capsules, 750 mg to the reference-listed drug (RLD), Colazal<sup>®</sup> Capsules, 750 mg by Salix Pharmaceuticals, Inc. (NDA #: 20-610). The fasting BE study was designed as a two-way, **two-group** crossover study in healthy, adult males subjects (Treatment Group No. 01, N = 36, Treatment Group No. 02, N =41). The male subjects received a single oral dose of 3 x 750 mg capsules. In this study there was no statistical significant group-by-treatment effect. The subjects were combined into one group for pharmacokinetic and statistical analyses, N=72 (5 subjects voluntarily withdrew).

Statistical analyses of plasma concentration data for the parent compound, balsalazide demonstrates bioequivalence. The balsalazide results including all subjects, N =72 (point estimate, 90% CI) are: LAUC<sub>T</sub> of 1.01, 93.60-108.15%, LAUC<sub>∞</sub> of 1.00, 93.40-108.15%, and LC<sub>max</sub> of 1.00, 91.83-109.69%.

Statistical analyses of plasma concentration data for the metabolite, mesalamine (5-ASA) does not demonstrate bioequivalence. The results for mesalamine including all subjects,

N =72 (point estimate, 90% CI) are: LAUC<sub>T</sub> of 0.88, **73.94-105.42%**, LAUC<sub>∞</sub> of 0.89, **79.16-100.23%**, and LC<sub>max</sub> of 0.86, **74.25-100.30%**.

The firm concluded that Subject No. 34 had aberrant plasma mesalamine concentrations in the fasting BE study. The firm conducted a re-dosing fasting BE study consisting of five (5) subjects (subject Nos. 1, 34, 44, 49 and 61). The *redose* data confirmed that the original data obtained for subject No. 34 was aberrant and supported the exclusion of this subject from the fasting study analysis. So the subject was dropped from the study analysis. The results for mesalamine (5-ASA) after excluding Subject No. 34, N = 71 (point estimate, 90% CI) are: LAUC<sub>T</sub> of 0.95, 82.56-109.24%, LAUC<sub>∞</sub> of 0.89, **79.16-100.23%**, and LC<sub>max</sub> of 0.91, 80.72-103.68%.

The Division of Bioequivalence (DBE) agreed with the firm that Subject No. 34 had an aberrant response to dosing. The DBE used the Studentized Residual Outlier test to identify Subject No. 34 as a candidate for redosing. However, applying the same test indicated that Subject No. 78 may have also had an aberrant response. Therefore, Subject No. 78 should have been re-dosed as well. After excluding Subject Nos. 34 and 78 (N=70) from statistical analyses of the study, plasma concentration data for mesalamine (5-ASA) does not demonstrate bioequivalence. The results (point estimate, 90% CI) are: LAUC<sub>T</sub> of 0.90, 80.20-100.08%, LAUC<sub>∞</sub> of 0.89, **79.16-100.23%**, and LC<sub>max</sub> of 0.87, **78.62-96.85%**.

The firm did not provide a standard operating procedure (SOP) for selecting suspected subjects with anomalous pharmacokinetic parameters for re-dosing study. As mentioned above, based on the Studentized Residual Outlier test, Subject No. 78 is also considered to have aberrant plasma mesalamine concentrations along with Subject No. 34 and should have been re-dosed as well. Subject No. 78 could have been excluded from the re-dosing study with bias toward favorable bioequivalence outcome. Therefore, the firm is advised to re-dose Subject No.78 with several subjects (control group) chosen at random from the same study (study No. 50256). Alternatively, the firm may conduct a new fasting bioequivalence study.

The fasting BE study is considered **incomplete** for the above reasons and due to insufficient analytical reports.

The firm had previously conducted dissolution in four (4) different media: (1) 0.1N HCl, (2) pH 4.5 buffer, (3) pH 6.8 buffer, and (4) pH 7.4 buffer to establish bioequivalency between the test and reference products. Since, this drug acts locally within the GI tract, the evaluation of the dissolution is considered to be critical in assessing whether an equivalent amount of drug from the test and reference formulation will be delivered to the necessary sites of action within the GI tract. In addition the firm conducted dissolution testing using the FDA-recommended method. The *in vitro* dissolution data provided by the firm for its Balsalazide Disodium Capsules, 750 mg are acceptable. However, the firm should acknowledge the FDA-recommended method and specification. Therefore, the dissolution testing is **incomplete**.

On September 21, 2006, the labeling for Colazal<sup>®</sup> (balsalazide disodium) Capsules was amended to include statements pertaining to a food effect on the drug product in the Clinical Pharmacology and Dosing and Administration sections. As the new labeling now has information about the effect food has on absorption or administration, as per the Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance, the firm should perform a fed study to demonstrate that food has the same effect on its test product.

This application is **incomplete** with deficiencies.

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### III. Submission Summary

#### A. Drug Product Information

<b>Test Product</b>	Balsalazide Disodium Capsules
<b>Reference Product</b>	Colazal® (Balsalazide Disodium) Capsules
<b>RLD Manufacturer</b>	Salix Pharmaceuticals, Inc.
<b>NDA No.</b>	20-610
<b>RLD Approval Date</b>	July 18, 2000
<b>Indication</b>	It is indicated for the treatment of mild to moderate active ulcerative colitis.

#### B. PK/PD Information<sup>1</sup>

<b>Mechanism of Action</b>	The balsalazide molecule consists of mesalamine covalently linked to the “carrier” 4-aminobenzoyl-alanine. Balsalazide is insoluble in acidic media. According to the approved Colazal® package insert, about 99% of an ingested dose travels to the colon where the enzyme, azoreductase, produced by colonic bacteria, cleaves the molecule and releases mesalamine for anti-inflammatory activity. The mechanism whereby mesalamine exerts its therapeutic effects in ulcerative colitis is not clear. It is thought that systemic absorption of balsalazide is not likely to be relevant to its therapeutic efficacy because its active moiety mesalamine exerts its effects locally in the colon.
<b>Bioavailability</b>	Balsalazide is administered orally in a capsule formation containing acid-insoluble balsalazide disodium granules. In healthy individuals, the systemic absorption of intact balsalazide is low and variable, but can be higher in ulcerative colitis patients. The absolute bioavailability is unknown. Both balsalazide and mesalamine (5-aminosalicylic acid, 5-ASA) are measurable in plasma following an oral dose of Colazal®.
<b>Food Effect</b>	On September 21, 2006 the labeling for Colazal® (balsalazide disodium) capsules was amended to include statements pertaining to a food effect on the

<sup>1</sup> 1. Online-Physicians' Desk Reference Electronic Library™. (2006). <http://www.thomsonhc.com>. Thomson Micromedex: Keyword Search: Colazal® Tablets. Last accessed: 11/20/2006.

2. Online-Clinical Pharmacology (2006). <http://cpip.gsm.com>. World-Class Drug Information: Monographs: Colazal® Tablets. Last updated: 09/27/2006; Last accessed: 11/20/2006.

	<p>drug product. The effect of food on the absorption of balsalazide has been studied. The data has shown that both the rate of absorption (<math>C_{max}</math>) and the extent of absorption (AUC) are lowered, while the <math>T_{max}</math> is markedly prolonged, when administered along side a high-fat meal as compared to fasting.</p>
<b>Tmax</b>	<p>Peak plasma concentrations of balsalazide occur from 1 to 2 hours after single oral doses of 1.5 grams (2 x 750 mg capsule) or 2.25 grams (3 x 750 mg capsule), whereas peak plasma concentrations of mesalamine occurs at about 10 hours post-dosing.</p>
<b>Metabolism</b>	<p>Balsalazide undergoes extensive colorectal metabolism, the bacterial azoreductases cleave the compound to release mesalamine (5-aminosalicylic acid, 5-ASA), the therapeutically active portion, and 4-amino-beta-alanine. The compounds 5-ASA and 4-amino-beta-alanine are further metabolized to N-acetylated metabolites.</p>
<b>Excretion</b>	<p>The major route of elimination is via the feces. Less than &lt;1% of parent, balsalazide and over 65% of the metabolites is excreted in the feces. Less than 1% of parent, balsalazide and less than 25% of the metabolites are eliminated renally.</p>
<b>Half-life</b>	<p><u>Balsalazide</u> The elimination half-life for balsalazide can not be determined due to large intersubject variability.</p> <p><u>Mesalamine (5-aminosalicylic acid, 5-ASA)</u> The elimination half-life of 5-ASA is approximately 1 hour.</p>
<b>Relevant OGD or DBE History</b>	<p>ANDA #78-883, was originally submitted on November 03, 2005. This application was refused to file on January 09, 2006 on the basis of the criteria set forth in 21 § CFR 314.101 (d) (3). It was a bioequivalency deficiency. The firm was informed that they could not drop the outlier value from the original data set until additional data is submitted. The firm amended its application on June 15, 2006, to provide the re-dosing fasting study report.</p> <p>Presently, there are no generic products on the market for Colazal<sup>®</sup> Capsules, 750 mg.</p> <ol style="list-style-type: none"> <li>1. The OGD convened a working group of CDER scientists and physicians to recommend approaches for bioequivalence assessment of</li> </ol>

locally-active drug products that deliver mesalamine to the GI tract for the treatment of colitis. The working group met on February 22, 2005, and concluded that OGD will request the following data to determine if a generic formulation of Balsalazide Disodium Capsules, 750 mg is bioequivalent to the RLD, Colazal® Capsules, 750 mg. (Source: OGD Protocol 05-006, (V:\FIRMSNZ\ (b) (4) \PROTOCOLS\05006p0105.doc ):

- a. A single-dose fasting *in-vivo* bioequivalence study, in healthy subjects, comparing Balsalazide Disodium Capsules, 750 mg to the RLD, Colazal® Capsules, 750 mg.
- b. **As of September 21, 2006**, a single-dose fed *in-vivo* bioequivalence study, in healthy subjects, comparing Balsalazide Disodium Capsules, 750 mg to the RLD, Colazal® Capsules, 750 mg is also requested.
- c. Please measure, both the parent compound, balsalazide, and its active metabolite mesalamine, (5-aminosalicylic acid, 5-ASA)

\*If balsalazide cannot be reliably measured, 5-ASA can be used for bioequivalence statistics. The usual adult dose of Balsalazide Disodium is three 750 mg capsules. Therefore, you may wish to administer single doses of two or three capsules to achieve measurable plasma concentrations. Since the plasma concentrations of balsalazide and 5-ASA are highly variable, the study should be adequately powered to determine if the generic product is bioequivalent to the RLD.

2. Because balsalazide acts locally in the GI tract (rather than systemically), evaluation of dissolution is important in determining whether an equivalent amount of drug from each formulation, test and reference, is delivered to the sites of activity in the GI tract. The OGD recommends that the applicant compare the dissolution performance of its Balsalazide Disodium Capsules to that of Colazal® in dissolution media of varying pH.

	<p>Varying pH conditions should be studied to approximate the varying pH conditions that balsalazide disodium capsules will be subjected to throughout the GI tract. Therefore, the OGD asks that the dissolution of Balsalazide Disodium Capsules be compared to that of Colazal® under the following pH conditions:</p> <ul style="list-style-type: none"> <li>0.1N HCl</li> <li>pH 4.5 buffer</li> <li>pH 6.8 buffer</li> <li>pH 7.4 buffer</li> </ul> <p>Since this is a capsule product, the OGD asks that the dissolution testing be conducted using USP apparatus 1 (basket) at 100 rpm using 900 ml of the above dissolution media.</p> <p>3. Although neither dissolution nor plasma pharmacokinetics are a complete reflection of drug appearance at the local site(s) of action, these parameters together provide adequate assurance of formulation performance to support a demonstration of bioequivalence.</p> <p>4. For its stability and quality controls program, the applicant should perform dissolution testing of its Balsalazide Disodium Capsules using the FDA-recommended dissolution method* (<b>see No. 06 below</b>):</p> <ul style="list-style-type: none"> <li>Medium: Water</li> <li>Volume: 900 mL</li> <li>Temperature: 37°C</li> <li>Apparatus: USP 1 (Basket) with sinkers</li> <li>Rotational Speed: 50 rpm</li> <li>Specification: NLT <math>\frac{(b)}{(4)}</math>% (Q) in 30 min</li> </ul> <p>5. Because of the rapid rate of dissolution of mesalamine at neutral pH, the applicant should use sampling times of 5, 10, 15, 20, 30, 45, and 60 minutes during dissolution testing. This will help ensure that the investigator will be able to calculate the similarity factor (f2) to compare test and reference dissolution profiles. To determine f2, it is necessary that at least two of the dissolution values obtained before the plateau of the dissolution profile (% of labeled amount</p>
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	<p>dissolved versus time) is reached.</p> <p>6. Recently, the dissolution method for the RLD was revised as follows (V:\firmsam\ (b) (4) \ltrs&amp;rev (b) (4) D0705.doc)*:  Medium: Potassium Phosphate buffer, pH 6.8  Volume: 900 ml  Temperature: 37 °C  Apparatus: USP2 (paddle) with sinkers  Rotational Speed: 50 rpm  Specification: NLT <sup>(b)</sup><sub>(4)</sub>% (Q) in 30 minutes  *Source of Method: NDA # 20-610/SCS-011 Chemistry Review-Jul 20, 2005.</p> <p>The DBE has reviewed numerous controlled documents, protocols, and ANDAs over the last several years. The following ANDAs have been reviewed in 2006: (b) (4) June 19, 2005-1<sup>st</sup> generic), (b) (4) 07/15/2006), (b) (4) (b) (4) 07/18/2005), (b) (4) 07/18/2005), (b) (4) (10/18/2005), #77-806 (Roxane, July 15, 2005), and #77-807 (Mylan, 07/18/2005), and (b) (4) 02/18/2006 – dissolution only).</p>
<b>Agency Guidance</b>	2003 Guidance Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (issued Mar 2003).
<b>Dosage and Administration</b>	The usual dose in adults is three 750 mg Colazal <sup>®</sup> Capsules to be taken 3x a day for a total dose of 6.75 grams for a duration of 8 weeks. Some patients in the clinical trials required treatment for up to 12 weeks.
<b>Drug Specific Issues (if any)</b>	None

**C. Contents of Submission**

<b>Study Types</b>	<b>Yes/No?</b>	<b>How many?</b>
<b>Single-dose fasting</b>	Yes	2
<b>Single-dose fed</b>	No	--
<b>Steady-state</b>	No	--
<b>In vitro dissolution</b>	Yes	1
<b>Waiver requests</b>	No	--
<b>BCS Waivers</b>	No	--
<b>Vasoconstrictor Studies</b>	No	--
<b>Clinical Endpoints</b>	No	--
<b>Failed Studies</b>	No	-
<b>Amendments</b>	Yes	1

**D. Pre-Study Bioanalytical Method Validation****Table D-1. Fasting Study No. 50256: Bioanalytical Method Validation for Balsalazide:<sup>1</sup>**

<b>FAST 50256</b>	<b>DATA</b>
Bioanalytical method validation report location	Section 16.2.5.3 of bioanalytical report
Analyte	Balsalazide*
Internal standard (IS)	(b) (4)
Method description	This method involves the extraction of balsalazide and the internal standard from human EDTA K <sub>3</sub> Plasma by a solid phase extraction. Samples are kept frozen at -20°C prior to analysis and 0.200mL of plasma was used for analysis.
Limit of quantitation (ng/mL)	Balsalazide: 1.00
Average recovery of drug range (%)	Balsalazide: 80.59 to 84.83
Average recovery of IS (%)	78.83
Standard curve concentrations range (ng/mL)	Balsalazide: 1.00 to 500.40
QC concentration (ng/mL)	Balsalazide: QC1: 3.02, QC2: 150.84, QC3: 351.96
QC Intraday precision range (%)	Balsalazide: 3.04 to 7.61
QC Intraday accuracy range (%)	Balsalazide: 98.92 to 105.78
QC Interday precision range (%)	Balsalazide: 3.22 to 5.47
QC Interday accuracy range (%)	Balsalazide: 98.53 to 100.85
Bench-top stability (hrs)	23 hours at room temperature
Stock stability (days)	22 days at -20°C IS: 196 days at -20°C
Processed stability (hrs)	96 hours at room temperature
Freeze-thaw stability (cycles)	4 at -20°C and 4 at -80°C
Long-term storage stability (days)	195 days at -20°C and 5 days at -80°C
Dilution integrity	QC3 diluted 2 fold: CV (%) 3.10 % Nominal (%) 100.56 % DQC diluted 20 fold: CV (%) 2.48 % Nominal (%) 99.23 %
Selectivity	Human plasma samples (EDTA K <sub>3</sub> as anti-coagulant) from 10 different individual human blank sources were tested for interfering peaks at the retention time of balsalazide and the internal standard. None of the sources showed significant interference at the retention time of balsalazide or the internal standard.

<sup>1</sup>: Table provided by firm

**Table D-2. Fasting Study No. 50256: Bioanalytical Method Validation for Mesalamine (5-Aminosalicylic Acid, 5-ASA):<sup>1</sup>**

<b>FAST 50256</b>	<b>DATA</b>
Bioanalytical method validation report location	Section 16.2.5.3 of bioanalytical report
Analyte	5-ASA*
Internal standard (IS)	(b) (4)
Method description	This method involves the extraction of 5-ASA and the internal standard from human EDTA K <sub>3</sub> Plasma by a protein precipitation followed by solid phase extraction. Samples are kept frozen at -20°C prior to analysis and 0.400mL of plasma was used for analysis.
Limit of quantitation (ng/mL)	5-ASA: 2.00
Average recovery of drug range (%)	5-ASA: 70.04 to 71.92
Average recovery of IS (%)	72.12
Standard curve concentrations range (ng/mL)	5-ASA: 2.00 to 601.44
QC concentration (ng/mL)	5-ASA: QC1: 6.06, QC2: 181.87, QC3: 424.37
QC Intraday precision range (%)	5-ASA: 2.15 to 3.50
QC Intraday accuracy range (%)	5-ASA: 93.43 to 97.20
QC Interday precision range (%)	5-ASA: 2.43 to 3.34
QC Interday accuracy range (%)	5-ASA: 92.42 to 96.03
Bench-top stability (hrs)	15 hours at room temperature
Stock stability (days)	5-ASA: 48 days at -20°C (acidified methanol) IS: 98 days at -20°C (acidified methanol)
Intermediate stock stability (days)	5-ASA: 45 days at -20°C (methanol) IS: 98 days at -20°C (methanol)
Processed stability (hrs)	75 hours at room temperature
Freeze-thaw stability (cycles)	4 at -20°C and 4 at -80°C
Long-term storage stability (days)	68 days at -20°C
Dilution integrity	QC3 diluted 2 fold: CV (%) 1.19 % Nominal (%) 91.39 % DQC diluted 20 fold: CV (%) 0.72 % Nominal (%) 94.07 %
Selectivity	Human plasma samples (EDTA K <sub>3</sub> as anti-coagulant) from 10 different individual human blank sources were tested for interfering peaks at the retention time of 5-ASA and the internal standard. None of the sources showed significant interference at the retention time of 5-ASA or the internal standard.

<sup>1</sup>: Table provided by firm

**Table D-3. Fasting Study No. 50256: Additional Table for Bioanalytical Method Validation for Balsalazide and 5-Aminosalicylic Acid (5-ASA, Mesalamine)<sup>1</sup>:**

SOPs submitted	Yes		Yes
20% Chromatograms included (Y/N)	Yes	Serially Selected?	Yes
Is Bioanalytical method acceptable?			NO

<sup>1</sup>: Additional table provided by reviewer.

**Reviewer's Comments:** The bioanalytical method validation is incomplete. The firm does not provide the bioanalytical summary tables for balsalazide and mesalamine for the fasting study, No. 50256. Also, for the re-dosing fasting study No. 60045, the firm does not provide the bioanalytical method validation summary tables for balsalazide and mesalamine.

## E. In Vivo Study

### 1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study			
Study No.	50256		
Study Design	A single center, bioequivalence, open-label, single-dose, randomized, two-way crossover study		
No. of subjects enrolled	77		
No. of subjects completing	72		
No. of subjects analyzed	72		
Subjects (Healthy or Patients?)	Healthy, smoker or non-smoker		
Sex(es) included (how many?)	Male:	72	Female: N/A
Test product	Balsalazide Disodium Capsules		
Reference product	Colazal <sup>®</sup> Capsules		
Strength tested	750 mg		
Dose	3 x 750 mg capsules (single-dose)		

**Table E1-1. Summary of Statistical Analysis, Point Estimates and 90% Confidence Intervals for Balsalazide**

Summary of Statistical Analysis, Fasting Bioequivalence Study		
Additional Information in Appendix, <a href="#">Table A1-9</a> and <a href="#">Table A1-10</a>		
BALSALAZIDE		
Parameter	Point Estimate	90% Confidence Interval
LAUC <sub>T</sub>	1.01	93.60-108.15%
LAUC <sub>∞</sub>	1.00	93.40-107.80%
LC <sub>max</sub>	1.00	91.83-109.69%

**Table E1-2. Summary of Statistical Analysis, Point Estimates and 90% Confidence Intervals for Mesalamine (5-ASA) with and without Subject No. 34 and Subject No. 78 in the Fasting Bioequivalence Study**

<b>Summary of Statistical Analysis, Fasting Bioequivalence Study</b>		
<i>Additional Information in Appendix, <a href="#">Table A1-13</a>, <a href="#">Table A1-14</a>, <a href="#">Table A1-17</a>, <a href="#">Table A1-18</a>, <a href="#">Table A1-20</a>, and <a href="#">Table A1-21</a></i>		
<b>MESALAMINE - All Subjects</b>		
<b>Parameter</b>	<b>Point Estimate</b>	<b>90% Confidence Interval</b>
LAUC <sub>T</sub>	0.88	<b>73.94-105.42%</b>
LAUC <sub>∞</sub>	0.89	<b>79.16-100.23%</b>
LC <sub>max</sub>	0.86	<b>74.25-100.30%</b>
<b>MESALAMINE – EXCLUDING SUBJECT NO. 34</b>		
<b>Parameter</b>	<b>Point Estimate</b>	<b>90% Confidence Interval</b>
LAUC <sub>T</sub>	0.95	82.56-109.24%
LAUC <sub>∞</sub>	0.89	<b>79.16-100.23%</b>
LC <sub>max</sub>	0.91	80.72-103.46%
<b>MESALAMINE – EXCLUDING SUBJECT NO. 78</b>		
<b>Parameter</b>	<b>Point Estimate</b>	<b>90% Confidence Interval</b>
LAUC <sub>T</sub>	0.83	<b>70.96-97.64%</b>
LAUC <sub>∞</sub>	0.89	<b>78.94-100.50%</b>
LC <sub>max</sub>	0.83	<b>72.35-95.24%</b>
<b>MESALAMINE – EXCLUDING SUBJECT NO. 34 AND 78</b>		
<b>Parameter</b>	<b>Point Estimate</b>	<b>90% Confidence Interval</b>
LAUC <sub>T</sub>	0.90	80.20-100.08%
LAUC <sub>∞</sub>	0.89	<b>79.16-100.23%</b>
LC <sub>max</sub>	0.87	<b>78.62-96.85%</b>

**Reviewer's Comments:**

1. Seventy-seven (77) healthy, adult male subjects were enrolled in the study. The subjects were divided and dosed in two separate groups. Treatment Group No. 01 consisted of thirty-six (36) healthy, adult male subjects (Nos. 01 to 20, and 22 to 37) and Treatment Group No. 02 consisted of forty-one (41) healthy, adult male subjects (Nos. 21, 38 to 50, 52 to 67, and 69 to 79). Five of the subjects voluntarily withdrew from the study prior to Period II dosing. For Treatment Group No. 01, thirty-five (35) of the subjects completed the study. For Treatment Group No. 02, thirty-seven (37) of the subjects completed the study. A total of seventy-two (72) subjects completed the study and their data were used for BE statistical evaluations.
2. The firm reported that the subjects enrolled in the study were '*members of the community at large.*' The subjects were all male and have similar demographic

profiles and baseline characteristics, such as age, height, and weight. There were seven (7) days in between dosing of the two groups.

3. The firm and reviewer used the group-by-treatment effect in the statistical model to calculate the pharmacokinetic (PK) parameters. Based on the statistical analysis, the firm and reviewer concluded there is no significant group-by-treatment interaction. Therefore, the data for all seventy-two (72) subjects were combined for pharmacokinetic and statistical analyses.
4. The firm determined that Subject No. 34 had an aberrant response to dosing. Minimal plasma concentration data was obtained for mesalamine (5-ASA). After dosing with Treatment A (test product, Balsalazide Disodium Capsules, 3 x 750 mg) in Period I, detectable concentrations for mesalamine were only obtained for two time points, 16 and 24.0-hours post-dose, 3.14 and 5.13 ng/mL, respectively. The firm stated in their report, '*Subject No. 34 showed only 2 detectable concentrations for 5-ASA and the concentration appeared to be still rising as the second concentration was higher than the first one, demonstrating that something happened regarding the biotransformation of balsalazide to 5-ASA for this subject. Due to this inadequate PK profile, the data from this subject was excluded from pharmacokinetic and statistical analyses only for 5-ASA.*' After dosing in Period II with Treatment B (RLD product, Colazal<sup>®</sup> Capsules, 3 x 750 mg), detectable concentrations for mesalamine were obtained for ten time points, beginning with 5.0- and ending with 32.0-hour post-dose. The concentration of 5-ASA increased and then decreased over this time to 0.0 ng/mL.
5. The reviewer performed the Studentized Residual Outlier test ( $\alpha = 0.05$ , |3.290|) on the data from all the subjects that completed the fasting study **for mesalamine**. Based on the results, both Subject Nos. 34 and 78 had aberrant plasma mesalamine concentrations.

Subject No.	AUC <sub>T</sub>	DAUC <sub>I</sub>	C <sub>max</sub>
34	-5.26895	-	-4.88221
78	4.24489	-	3.96864

Subject No.	Project No. 50256		
	AUC <sub>T</sub> Ratio	AUC <sub>I</sub> Ratio	C <sub>max</sub> Ratio
	A/B	A/B	A/B
34	0.008	--	0.002
78	35.02	--	17.10

These subjects represent two extremes. Subject No. 34 represents the lower extreme and Subject No. 78 represents the higher extreme. This means they would have opposite effects on the results of the fasting study. If Subject No. 34 is dropped the

confidence interval (CI) values will increase; if Subject No. 78 is dropped then the CI values will decrease.

6. The firm conducted a re-dosing fasting BE study consisted of five (5) subjects (Subject Nos. 1, 34, 44, 49 and 61). Subject No. 78 was not included in the re-dosing study.
7. Statistical analyses of plasma concentration data for the parent compound, balsalazide demonstrate bioequivalence. The balsalazide results including all subjects, N =72 (point estimate, 90% CI) are: LAUC<sub>T</sub> of 1.01, 93.60-108.15%, LAUC<sub>∞</sub> of 1.00, 93.40-108.15%, and LC<sub>max</sub> of 1.00, 91.83-109.69%.
8. Statistical analyses of plasma concentration data for the metabolite, mesalamine (5-ASA)] does not demonstrate bioequivalence. The results for mesalamine including all subjects, N =72 (point estimate, 90% CI) are: LAUC<sub>T</sub> of 0.88, **73.94-105.42%**, LAUC<sub>∞</sub> of 0.89, **79.16-100.23%**, and LC<sub>max</sub> of 0.86, **74.25-100.30%**.
9. When Subject No. 34 is dropped from the study analysis, the 90% CIs are within the acceptable range of 80-125% for log-transformed AUC<sub>T</sub>, and C<sub>max</sub> for mesalamine (see Table E1-2).
10. When Subject No. 78 is dropped from study analysis, the 90% CIs are not within the acceptable range of 80-125% for log-transformed AUC<sub>T</sub>, AUC<sub>∞</sub> and C<sub>max</sub> for mesalamine (see TableE1-2).
11. When both Subjects 34 and 78 are dropped, the 90% CIs are not within acceptable range of 80-125% for log-transformed for AUC<sub>∞</sub> and C<sub>max</sub> for mesalamine (see Table E1-2).

**Table E1-3. Reanalysis of Study Samples for Balsalazide\***

Study No. 50256 Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal® Following a 2250 mg dose in Healthy Subjects Under Fasting Conditions								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of Total Assays		Actual number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.0	0.0	0	0	0.0	0.0
Analytical repeat	108	120	3.01	3.34	52	68	1.45	1.89
Unacceptable internal standard response	4	8	0.11	0.22	4	8	0.11	0.22
Incomplete analysis	1	0	0.03	0.0	1	0	0.03	0.0
Sample concentration above upper limit of quantification	36	46	1.00	1.28	36	46	1.00	1.28
Sample reanalyzed to obtain confirming value	66	66	1.84	1.84	11	14	0.31	0.39
Sample repeated or reinjected by error	1	0	0.03	0.0	0	0	0.0	0.0
Total	108	120	3.01	3.34	52	68	1.45	1.89

<sup>1</sup> If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

<sup>T</sup> Balsalazide disodium 750 mg capsule (3 x 750 mg capsules), (Apotex inc., Canada), Lot No: 043-11

<sup>R</sup> Balsalazide disodium (Colazal®) 750 mg capsule (3 x 750 mg capsules), (Salix Pharmaceuticals, Inc., USA), Lot No: 311208

\*: Table provided by firm

**Table E1-4. Reanalysis of Study Samples Mesalamine, 5-ASA\***

Study No. 50256 Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal® Following a 2250 mg dose in Healthy Subjects Under Fasting Conditions								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of Total Assays		Actual number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.0	0.0	0	0	0.0	0.0
Analytical repeat	57	59	1.59	1.64	56	52	1.56	1.45
Poor chromatography	3	4	0.08	0.11	3	4	0.08	0.11
Unacceptable internal standard response	28	19	0.78	0.53	28	19	0.78	0.53
Incomplete analysis	14	8	0.39	0.22	14	8	0.39	0.22
Sample concentration above upper limit of quantification	11	19	0.31	0.53	11	19	0.31	0.53
Sample reanalyzed to obtain confirming value	1	8	0.03	0.22	0	2	0.0	0.06
Sample repeated or reinjected by error	0	1	0.0	0.03	0	0	0.0	0.0
Total	57	59	1.59	1.64	56	52	1.56	1.45

<sup>1</sup> If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

<sup>T</sup> Balsalazide disodium 750 mg capsule (3 x 750 mg capsules), (Apotex inc., Canada), Lot No: 043-11

<sup>R</sup> Balsalazide disodium (Colazal®) 750 mg capsule (3 x 750 mg capsules), (Salix Pharmaceuticals, Inc., USA), Lot No: 311208

\*: Table provided by firm

Did use of recalculated plasma concentration data change study outcome? *Uncertain*

**Reviewer's Comments:** A total of three-hundred and forty-four (344) balsalazide and mesalamine plasma samples were reassayed during this fasting study, 228 and 116 respectively. They were all reassayed for analytical reasons. No samples were reassayed for pharmacokinetic (PK) reasons. One hundred and twenty (120) of the recalculated values for balsalazide were used in pharmacokinetic (PK) and statistical analyses. While, the majority of the balsalazide samples were reassayed for the analytical reason, "to Obtain Confirming Value", only twenty-five (25) of the recalculated values were used in PK and statistical analyses. One-hundred and eight (108) of the recalculated values for mesalamine were used in PK and statistical analyses. In the bioanalytical report of the electronic submission, the tables for balsalazide and mesalamine can not be retrieved. In addition, the links in the bioanalytical report for these tables go to different places in the document and not to the table themselves. Therefore, an accurate assessment of the criteria for reanalysis and the acceptability of the recalculated values for balsalazide and mesalamine, can not be made at this time.

**Reviewer's Comments:** The 90% confidence intervals are within the acceptable range of 80-125% for log transformed  $AUC_T$ ,  $AUC_{\infty}$ , and  $C_{max}$  for balsalazide. The 90% confidence intervals are within the acceptable range of 80-125% for log transformed  $AUC_T$ , and  $C_{max}$  for mesalamine (5-ASA) after excluding Subject No.34 from study analysis. However, after excluding Subject Nos. 34 and 78 from study analysis, the 90% confidence intervals are not within the acceptable range of 80-125% for log transformed  $AUC_{\infty}$ , and  $C_{max}$  for mesalamine. The fasting BE study is incomplete.

## 2. Single-dose Re-dosing Fasting Bioequivalence Study

Study Summary, Re-dosing Fasting Bioequivalence Study			
<b>Study No.</b>	60045		
<b>Study Design</b>	A single-center, randomized, Re-dosing, open-label, two-way crossover study		
<b>No. of subjects enrolled</b>	5		
<b>No. of subjects completing</b>	5		
<b>No. of subjects analyzed</b>	5 (subject Nos. 01, 34, 44, 49 and 61)		
<b>Subjects (Healthy or Patients?)</b>	Healthy		
<b>Sex(es) included (how many?)</b>	Male:	5	Female:
<b>Test product</b>	Balsalazide Disodium Capsules		
<b>Reference product</b>	Colazal <sup>®</sup> Capsules		
<b>Strength tested</b>	750 mg		
<b>Dose</b>	3 x 750 mg capsules (single-dose)		

Table E2-1. Summary of Pharmacokinetic Results, Ratio Test-A/Reference-B for Balsalazide

Subject No.	Project No. 50256 (Original Study)			Project No. 60045 (Re-dosing Study)			
	AUC <sub>T</sub>	AUC <sub>I</sub>	C <sub>max</sub>	Subject No.	AUC <sub>T</sub>	AUC <sub>I</sub>	C <sub>max</sub>
	Ratio A/B	Ratio A/B	Ratio A/B		Ratio A/B	Ratio A/B	Ratio A/B
34	2.74	2.69	2.27	34	0.83	0.83	1.13
61	0.79	0.81	1.36	61	1.06	1.04	0.90
49	1.02	1.07	0.88	49	0.65	0.68	0.96
44	1.16	1.14	1.27	44	0.80	0.83	0.62
01	0.96	0.96	0.90	01	1.88	1.70	1.86

Table E2-2. Summary of Pharmacokinetic Results, Test-A/Reference-B for Mesalamine (5-ASA)

Subject No.	Project No. 50256 (Original Study)			Project No. 60045 (Re-dosing Study)			
	AUC <sub>T</sub>	AUC <sub>I</sub>	C <sub>max</sub>	Subject No.	AUC <sub>T</sub>	AUC <sub>I</sub>	C <sub>max</sub>
	Ratio A/B	Ratio A/B	Ratio A/B		Ratio A/B	Ratio A/B	Ratio A/B
34	0.008	--	0.002	34	0.65	0.72	0.56
61	1.62	--	1.13	61	1.46	1.26	1.50
49	1.65	1.69	1.65	49	0.80	0.81	1.28
44	1.24	1.25	1.30	44	1.05	0.93	0.77
01	0.62	0.58	0.53	01	1.08	1.40	1.52

**Reviewer's Comments:** The firm re-dosed Subject No. 34 along with four (4) additional subjects. Subject Nos. 01, 44, 49 and 61 were included in the re-dosing fasting study. The *redose* data showed that the PK parameter T/R ratio data for all redosed subjects within the range of the data of all subjects of the original fasting study (the original study data excluding Subject No. 34). The *redose* data, therefore confirmed that the original data obtained for Subject No. 34 were aberrant and support the exclusion of this subject from the fasting study analysis for mesalamine.

**Table E2-3. Summary of Statistical Analysis, Point Estimates and 90% Confidence Intervals for Balsalazide and Mesalamine, 5-ASA**

<b>Summary of Statistical Analysis, Re-dosing Fasting Bioequivalence Study</b>		
<i>Additional Information in Appendix, <a href="#">Table A2-9</a>, <a href="#">Table A2-10</a>, <a href="#">Table A2-13</a>, and <a href="#">Table A2-14</a></i>		
<b>BALSALAZIDE</b>		
<b>Parameter</b>	<b>Point Estimate</b>	<b>90% Confidence Interval</b>
LAUC <sub>T</sub>	1.01	66.64-153.68%
LAUC <sub>∞</sub>	1.00	69.13-143.30%
LC <sub>max</sub>	1.09	80.39-147.06%
<b>MESALAMINE</b>		
<b>Parameter</b>	<b>Point Estimate</b>	<b>90% Confidence Interval</b>
LAUC <sub>T</sub>	0.95	67.00-133.68%
LAUC <sub>∞</sub>	1.00	69.97-141.69%
LC <sub>max</sub>	1.03	60.14-174.80%

**Table E2-4. Reanalysis of Study Samples for Balsalazide\***

Study No. 60045 Re-dosing Study From An Open-label, 2-way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal® Following a 2250 mg Dose in Healthy Subjects under Fasting Conditions								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of Total Assays		Actual number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.0	0.0	0	0	0.0	0.0
Analytical repeat	3	2	1.20	0.80	3	2	1.20	0.80
Unacceptable internal standard response	1	0	0.40	0.0	1	0	0.40	0.0
Sample concentration above upper limit of quantification	2	2	0.80	0.80	2	2	0.80	0.80
Total	3	2	1.20	0.80	3	2	1.20	0.80

<sup>1</sup> If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

<sup>T</sup> Balsalazide disodium 750 mg capsule (3 x 750 mg capsules), (Apotex inc., Canada), Lot No: 043-11

<sup>R</sup> Balsalazide disodium (Colazal®) 750 mg capsule (3 x 750 mg capsules), (Salix Pharmaceuticals, Inc., USA), Lot No: 311208

\*: Table provided by firm

**Table E2-5. Reanalysis of Study Samples Mesalamine, 5-ASA\***

Study No. 60045 Re-dosing Study From An Open-label, 2-way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal® Following a 2250 mg Dose in Healthy Subjects under Fasting Conditions								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of Total Assays		Actual number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.0	0.0	0	0	0.0	0.0
Analytical repeat	1	1	0.40	0.40	1	1	0.40	0.40
Unacceptable internal standard response	1	1	0.40	0.40	1	1	0.40	0.40
Total	1	1	0.40	0.40	1	1	0.40	0.40

<sup>1</sup> If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

<sup>T</sup> Balsalazide disodium 750 mg capsule (3 x 750 mg capsules), (Apotex inc., Canada), Lot No: 043-11

<sup>R</sup> Balsalazide disodium (Colazal®) 750 mg capsule (3 x 750 mg capsules), (Salix Pharmaceuticals, Inc., USA), Lot No: 311208

\*: Table provided by firm

**Did use of recalculated plasma concentration data change study outcome? No**

**Reviewer's Comments:** A total of seven (7) balsalazide and mesalamine (5-ASA) plasma samples were reassayed, 5 and 2, respectively. They were all reassayed for analytical reasons. No samples were reassayed for pharmacokinetic reasons. All of the recalculated values were used in pharmacokinetic and statistical analyses. The analytical reasons for repeat analysis are acceptable and in accordance with the firm's SOPs.

**Reviewer's Comments:** The results for the re-dosing fasting study is considered incomplete. Based on the statistical results from Studentized Residual Outlier test ( $\alpha = 0.05$ ); both Subject Nos. 34 and No. 78 had aberrant plasma mesalamine concentrations. However, the firm did not include Subject No.78 in the re-dosing study. These two subjects are on opposite ends of the extremity and they produce opposite effects on the results of the fasting study. When Subject No. 34 was dropped from PK and statistical analyses the 90% confidence intervals are within the acceptable range of 80-125% for log transformed  $AUC_T$ , and  $C_{max}$  for mesalamine (5-ASA). However, after excluding Subject Nos. 34 and 78 from study analysis, the 90% confidence intervals are not within the acceptable range of 80-125% for log transformed  $AUC_{\infty}$ , and  $C_{max}$  for mesalamine. In addition, the firm did not provide a SOP for selecting suspected subjects with anomalous pharmacokinetic parameters for re-dosing study. Therefore, the re-dosing study is incomplete.

**F. Formulation**

<b>Location in appendix</b>	See Appendix, Section B, <a href="#">Table B-1</a>
<b>Are inactive ingredients within IIG limits?</b>	Yes
<b>If yes, list ingredients outside of limits</b>	--
<b>If a tablet, is the product scored?</b>	N/A
<b>If yes, which strengths are scored?</b>	--
<b>Is scoring of RLD the same as test?</b>	--
<b>Is the formulation acceptable?</b>	<b>YES</b>
<b>If not acceptable, why?</b>	--

**Reviewer's Comments:** The formulation for this product is acceptable. The inactive ingredients for Apotex's formulation of Balsalazide Disodium Capsules, 750 mg are within the FDAs IIG limits. The formulation contains a hard gelatin capsule – white/white (b) (4) and red printing ink. The composition of the hard gelatin capsule is located in the chemistry review (V:\FIRMSAM\Apotex\ L TRS&REV\77883R1.doc).

**G. In Vitro Dissolution**

<b>Location in appendix</b>	See Appendix, Section D, <a href="#">Table D-1</a>
<b>Source of Method (USP, FDA or Firm)</b>	FDA
<b>Medium</b>	Phosphate Buffer, pH 6.8
<b>Volume (mL)</b>	900
<b>USP Apparatus type</b>	II (Paddle)
<b>Rotation (rpm)</b>	50
<b>Firm's proposed specifications</b>	None
<b>FDA-recommended specifications</b>	NLT (b) (4) (Q) in 30 minutes
<b>F2 metric calculated?</b>	N/A
<b>If no, reason why F2 not calculated</b>	--
<b>Is method acceptable?</b>	<b>NO</b>
<b>If not then why?</b>	Firm should acknowledge the FDA-recommended specification.

**Reviewer's Comments:** The DBE previously reviewed the dissolution testing and data for Apotex's test product, Balsalazide Disodium Capsules, 750 mg (V:\DIVISION\BIO\Bio Temporary-Ra\77883D1105.doc). The firm had conducted dissolution in four (4) different media: (1) 0.1N HCl, (2) pH 4.5 buffer, (3) pH 6.8 buffer, and (4) pH 7.4 buffer to establish bioequivalency between the test and reference products. The firm also had conducted dissolution testing using a non-FDA recommended method. The firm was informed that they should conduct dissolution testing using the FDA-recommended method. The firm complied with the request. The *in vitro* dissolution testing and data provided by the firm for its Balsalazide Disodium Capsules, 750 mg using the FDA-recommended method was acceptable. The reviewer stated in the dissolution review, 'The firm also submitted additional dissolution testing as recommended in protocol P05-

006. Although this method differs from the current FDA-recommended dissolution method with respect to apparatus and speed, the additional dissolution testing is acceptable and need not be repeated (see comments on page 4).’ It was still suggested to the firm via a deficiency letter to conduct dissolution testing using the current FDA-recommended method. The firm once again complied with the DBE request and amended its ANDA submission on October 16, 2006. The *in vitro* dissolution testing and data provided by the firm for its Balsalazide Disodium Capsules, 750 mg using the current FDA-recommended method is acceptable. However, the firm did not propose a specification, but balsalazide does meet the FDA-recommended specification at the S<sub>1</sub> level. Therefore, the firm should acknowledge the FDA-recommended method and specification. The dissolution testing method and data are incomplete.

## H. Waiver Request(s)

None.

## I. Deficiency Comments

1. The DBE agreed with the firm that Subject No. 34 had aberrant plasma mesalamine concentrations, based on the Studentized Residual Outlier test, and should be redosed for verification of the aberrant response to dosing. The test results also indicated that Subject No. 78 had an aberrant response to dosing and should have been re-dosed as well but was not included in the re-dosing study. Therefore, Subject No. 78 could have been excluded from the re-dosing study with bias toward favorable bioequivalence outcome. The firm is advised to re-dose Subject No.78 with several subjects (control group) chosen at random from the same study (study No. 50256). Alternatively, the firm may conduct a new fasting bioequivalence study. Therefore, the fasting BE study and the re-dosing study are incomplete.
2. The firm does not provide a standard operating procedure (SOP) for selecting suspected subjects with anomalous pharmacokinetic parameters for re-dosing study.
3. In the bioanalytical report for Study No. 50256, the firm does not provide the summary tables for balsalazide and mesalamine (5-ASA).

For balsalazide, the following tables are missing from Section 16.2.51 of the Bioanalytical Report:

- Table 2A. Plasma EDTA K3 Balsalazide Concentrations (ng/mL) in Humans
- Table 2B. Plasma EDTA K3 Balsalazide Concentrations (ng/mL) in Humans
- Table 3. Repeat Analysis Results for Balsalazide in Human Plasma EDTA K3
- Table 4. Summary of Study Sample Reassays
- Table 5A and 5B. Summary of Analytical Runs
- Table 6. Calibration Curve Parameters for Balsalazide Calibration Standards in Human Plasma EDTA K3

- Table 7. Analytical Performance: Back-Calculated Concentration (ng/mL) of Balsalazide Calibration Curve Standard in (Human) (Plasma EDTA K3)
- Table 8. Analytical Performance of Balsalazide Quality Control Samples in Human Plasma EDTA K3

For mesalamine, the following tables are missing from Section 16.2.5.1 of the Bioanalytical Report:

- Table 10A. Plasma EDTA K3 5-ASA Concentrations (ng/mL) in Humans
- Table 10B. Plasma EDTA K3 5-ASA Concentrations (ng/mL) in Humans
- Table 11. Repeat Analysis Results for 5-ASA in Human Plasma EDTA K3
- Table 12. Summary of Study Sample Reassays
- Table 13A and 13B. Summary of Analytical Runs
- Table 14. Calibration Curve Parameters for 5-ASA Calibration Standards in Human Plasma EDTA K3
- Table 15. Analytical Performance: Back-Calculated Concentration (ng/mL) of 5-ASA Calibration Curve Standard in (Human) (Plasma EDTA K3)
- Table 16. Analytical Performance of Balsalazide Quality Control Samples in Human Plasma EDTA K3
3. In the re-dosing fasting study No. 60045, the firm does not provide the bioanalytical method validation summary tables for balsalazide and mesalamine.
  4. The firm conducted its dissolution testing according the FDA-recommended method. However, the firm does not propose a specification. The firm should acknowledge and accept the FDA-recommended method and specification.
  5. On September 21, 2006 the labeling for Colazal® (balsalazide disodium) capsules has been amended to include statements pertaining to a food effect on the drug product in the Clinical Pharmacology and Dosing and Administration sections. As the new labeling now has information about the effect food has on absorption or administration, as per the Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance, the firm should perform a fed study to demonstrate that food has the same effect on its test product.

## A. Recommendations

1. The single-dose *in vivo* fasting bioequivalence (BE) study, No. 50256 conducted by Apotex Inc. comparing its test product, Balsalazide Disodium 750 mg Capsules, Lot/Batch No. 043-11 to the reference-listed (RLD), Colazal<sup>®</sup> 750 mg Capsules, by Salix Pharmaceuticals, Inc., Lot/Batch No. 311208, is **incomplete** for the reasons provided in [deficiency comments Nos. 01 to 03](#).
2. The single-dose *in vivo* Re-dosing fasting BE study, No. 60045 conducted by Apotex Inc. comparing its test product, Balsalazide Disodium 750 mg Capsules, Lot/Batch No. 043-11 to the RLD, Colazal<sup>®</sup> 750 mg Capsules, by Salix Pharmaceuticals, Inc., Lot/Batch No. 311208, is **incomplete** for the reasons provided in [deficiency comment No. 01](#).
3. The firm should conduct a single-dose *in vivo* fed BE study comparing its Balsalazide Disodium 750 mg Capsules to the RLD, Colazal<sup>®</sup> 750 mg Capsules by Salix Pharmaceuticals, Inc.
4. The *in vitro* dissolution testing conducted by Apotex Inc., on its 750 mg strength Balsalazide Disodium Capsules is **incomplete** for the reason given in [deficiency comment No. 04](#).

The dissolution testing should be conducted in Phosphate Buffer, pH 6.8 at 37°C ± 0.5°C using apparatus II (Paddles) at 50 rpm with sinkers. The test product should meet the following specification:

Not less than  $\frac{(b)}{(4)}$  (Q) of the labeled amount of balsalazide in the dosage form is dissolved in 30 minutes

The firm should be informed of the deficiency comments and recommendations.

**IV. Appendix****A. Individual Study Reviews**

## 1. Single-dose Fasting Bioequivalence Study

## a. Study Design

<b>Study Information</b>								
<b>Study Number</b>	50256							
<b>Study Title</b>	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal <sup>®</sup> Following a 2250 mg Dose in Healthy Subjects Under Fasting Conditions							
<b>Clinical Site</b>	SFBC Anapharm, 5160 Boul. Décarie, Suite 800, Montreal (Quebec), Canada H3X 2H9							
<b>Principal Investigator</b>	Richard Larouche, M.D.							
<b>Study/Dosing Dates</b>	Study Dates: June 22, 2005 to July 15, 2005							
	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2" style="text-align: center;">Dosing Dates</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; width: 50%;"><u>Group No. 01</u></td> <td style="text-align: center; width: 50%;"><u>Group No. 02</u></td> </tr> <tr> <td style="text-align: center;">Period I: June 22, 2005</td> <td style="text-align: center;">Period I: June 28, 2005</td> </tr> <tr> <td style="text-align: center;">Period II: July 6, 2005</td> <td style="text-align: center;">Period II: July 12, 2005</td> </tr> </tbody> </table>	Dosing Dates		<u>Group No. 01</u>	<u>Group No. 02</u>	Period I: June 22, 2005	Period I: June 28, 2005	Period II: July 6, 2005
Dosing Dates								
<u>Group No. 01</u>	<u>Group No. 02</u>							
Period I: June 22, 2005	Period I: June 28, 2005							
Period II: July 6, 2005	Period II: July 12, 2005							
<b>Analytical Site</b>	SFBC Anapharm, 2050, Boul. René-Lévesque, Ouest, Sainte-Foy (Québec), Canada G1V 2K8							
<b>Analytical Director</b>	(b) (6) B.Sc.							
<b>Analysis Dates</b>	July 11, 2005 to August 17, 2005							
<b>Storage Period</b>	56 days (June 22, 2005 to August 17, 2005)							

ANDA #: 77-883

Balsalazide Disodium Capsules, 750 mg

Apotex

Review of Bioequivalence Studies and In Vitro Dissolution Testing

Reviewer: April C. Braddy, Ph.D.

<b>Treatment ID</b>	<b>A</b>	<b>B</b>
<b>Test or Reference</b>	Test	Reference
<b>Product Name</b>	Balsalazide Disodium Capsules	Colazal <sup>®</sup> Capsules
<b>Manufacturer</b>	Apotex Inc., Canada	Salix Pharmaceuticals Inc., USA
<b>Batch/Lot No.</b>	043-11	311208
<b>Manufacture Date</b>	Not reported	N/A
<b>Expiration Date</b>	June 2007	June 2006
<b>Strength</b>	750 mg	750 mg
<b>Dosage Form</b>	Capsule	Capsule
<b>Batch Size</b>	(b) (4)	N/A
<b>Production Batch Size</b>	Not reported	N/A
<b>Potency</b>	101.7%	102.1%
<b>Content Uniformity</b>	101.1%	102.1%
<b>Formulation</b>	See Section B, <a href="#">Table B-1</a>	N/A
<b>Dose Administered</b>	3 x 750 mg Capsules	3 x 750 mg Capsules
<b>Route of Administration</b>	Oral	

<b>No. of Sequences</b>	2
<b>No. of Periods</b>	2
<b>No. of Treatments</b>	2
<b>No. of Groups</b>	2
<b>Washout Period</b>	14 days
<b>Randomization Scheme</b>	<p><b>Group No. 01</b>  <u>Sequence AB</u>  Subject Nos. 01, 03, 04, 08, 09, 12, 14, 16, 17, 18, 19, 24, 25, 26, 27, 32, 34, and 35</p> <p><u>Sequence BA</u>  Subject Nos. 02, 05, 06, 07, 10, 11, 13, 15, 20, 22, 23, 28, 29, 30, 31, 33, 36, and 37</p> <p><b>Group No. 02</b>  <u>Sequence AB</u>  Subject Nos. 38, 40, 42, 45, 47, 48, 51, 52, 55, 56, 57, 60, 62, 63, 65, 68, 70, 71, 74, 76, 78, and 80</p> <p><u>Sequence BA</u>  Subject Nos. 21, 39, 41, 43, 44, 46, 49, 50, 53, 54, 58, 59, 61, 64, 66, 67, 69, 72, 73, 75, 77, and 79</p>
<b>Blood Sampling Times</b>	0.0 (pre-dose), 0.167, 0.250, 0.333, 0.500, 0.667, 0.833, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.0, 12.0, 16.0, 24.0, 32.0, 40.0, 48.0, 48.0, and 72.0 hours post-dose in each period.
<b>Blood Volume Collected/Sample</b>	1 x 3mL for balsalazide and 1 x 5 mL for 5-ASA for each sampling time point
<b>Blood Sample Processing/Storage</b>	Blood samples were collected in tubes containing EDTA K3. The blood samples were cooled in an ice bath and were centrifuged at 3,000 rpm for at least 10 minutes at approximately 4°C. Two aliquots of at least 0.5 mL (when possible) of plasma for balsalazide and two aliquots of at least 0.8 mL (when possible) of plasma for 5-ASA, were dispensed into polypropylene tubes (as soon as possible). The aliquots were transferred to a -20°C ± 5°C freezer, pending shipment. No more than 50 minutes passed between the time of each blood draw and the start of centrifugation for balsalazide and 5-ASA. No more than 60 minutes and 181 minutes passed between the start of centrifugation and aliquot storage for balsalazide and 5-ASA, respectively
<b>IRB Approval</b>	Yes
<b>Informed Consent</b>	Yes

<b>Subjects Demographics</b>	See <a href="#">Table A1-1</a>
<b>Length of Fasting</b>	Subjects fasted overnight for at least 10 hours and until at least 4-hours post-dose
<b>Length of Confinement</b>	Subjects were confined to clinical facility from at least 10 hours prior to drug administration until after the 48.0-hour post-dose blood draw, in each period.
<b>Safety Monitoring</b>	Vital signs were not measured during the study. However, throughout the study subjects were monitored for adverse events.

**Is the design of the fasting bioequivalence study acceptable? Yes**

## b. Clinical Results

*Study Demographics***Table A1-1. Demographic Profile of Subjects Completing the Fasting Bioequivalence Study No. 50256<sup>1</sup>**

Category		Randomization		Total
		AB	BA	
Age (years)	Mean ± SD	38 ± 9	39 ± 10	38 ± 9
	Range	23 – 54	18 – 54	18 – 54
	Median	36	38.5	38
	N	37	40	77
Age Groups	< 18	0	0	0
	18-40	24 (64.9%)	22 (55.0%)	46 (59.7%)
	41-64	13 (35.1%)	18 (45.0%)	31 (40.1%)
	65-75	0	0	0
	> 75	0	0	0
Gender	Female	0	0	0
	Male	37 (100.0%)	40 (100.0%)	77 (100.0%)
Race	Black	0	2 (5.0%)	2 (2.6%)
	Caucasian	33 (89.2%)	32 (80.0%)	65 (84.4%)
	American Hispanic	4 (10.8%)	6 (15.0%)	10 (13.0%)
Height (cm)	Mean ± SD	176.4 ± 6.5	175.5 ± 8.5	175.9 ± 7.6
	Range	161.5 – 190.0	155.5 – 194.5	155.5 – 194.5
	Median	177.5	175.75	176.5
	N	37	40	77
Weight (kg)	Mean ± SD	77.9 ± 9.6	78.1 ± 11.5	78.0 ± 10.6
	Range	56.9 – 104.4	48.1 – 98.4	48.1 – 104.4
	Median	76.2	79.15	77.8
	N	37	40	77
BMI (kg/m <sup>2</sup> )	Mean ± SD	25.2 ± 3.0	25.2 ± 3.1	25.2 ± 3.0
	Range	19.8 – 29.8	19.5 – 29.6	19.5 – 29.8
	Median	25.1	25.05	25.1
	N	37	40	77

A= Treatment A, Test product, Balsalazide Disodium Capsules, 750 mg by Apotex, Inc., Canada, Lot/Batch No. 043-11

B = Treatment B, Reference Product, Colazal® Capsules, 750 mg by Salix Pharmaceuticals, Inc., USA, Lot/Batch No. 311208

<sup>1</sup>: Table provided by the firm.

*Study Dropout Information***Table A1-2. Subjects Discontinued from the Fasting Bioequivalence Study, No. 50256**

<b>Subject Number</b>	<b>03</b>
<b>Reason</b>	Voluntarily Withdrew – Personal Reasons
<b>Period</b>	II (Prior to dosing)
<b>Release Date</b>	June 29, 2006
<b>Replacement</b>	None
<b>Subject Number</b>	<b>21</b>
<b>Reason</b>	Voluntarily Withdrew – Personal Reasons
<b>Period</b>	II (Prior to dosing)
<b>Release Date</b>	June 22, 2006
<b>Replacement</b>	None
<b>Subject Number</b>	<b>38</b>
<b>Reason</b>	Voluntarily Withdrew – Personal Reasons
<b>Period</b>	II (Prior to dosing)
<b>Release Date</b>	July 07, 2005
<b>Replacement</b>	None
<b>Subject Number</b>	<b>48</b>
<b>Reason</b>	Voluntarily Withdrew – Personal Reasons
<b>Period</b>	II (Prior to dosing)
<b>Release Date</b>	July 07, 2006
<b>Replacement</b>	None
<b>Subject Number</b>	<b>57</b>
<b>Reason</b>	Voluntarily Withdrew – Personal Reasons
<b>Period</b>	II (Prior to dosing)
<b>Release Date</b>	June 28, 2006
<b>Replacement</b>	None

**Reviewer's Comments:** Five (5) voluntarily withdrew from the fasting study. Subject No. 21 and 57, tested positive for THC and cocaine, respectively. However, the firm reported them as electing to leave the study.

**Was there a difference in side effects for the test versus the reference?** No

**Table A1-3. Incidence of Adverse Events Reported in the Fasting Bioequivalence Study No. 50256<sup>1</sup>**

Additional Information is located in Section 12.2 and 12.3, pp. 39-41 of the Study Report

System Class COSTART	Project No. 50256*	
	A	B
<b>Eye disorders</b>		
Conjunctivitis	1 (2.0%)	
<b>Gastrointestinal disorders</b>		
Constip	1 (2.0%)	1 (2.0%)
Pain abdo		4 (7.8%)
<b>General disorders and administration site conditions</b>		
Asthenia		1 (2.0%)
Pain chest	1 (2.0%)	
<b>Infections and infestations</b>		
Herpes simplex	1 (2.0%)	
<b>Injury, poisoning and procedural complications</b>		
Hem inject site	1 (2.0%)	1 (2.0%)
Pain inject site	1 (2.0%)	4 (7.8%)
<b>Musculoskeletal and connective tissue disorders</b>		
Pain		1 (2.0%)
Pain back		1 (2.0%)
<b>Nervous system disorders</b>		
Dream abnorm		1 (2.0%)
Headache	2 (3.9%)	2 (3.9%)
Somnolence	2 (3.9%)	
<b>Renal and urinary disorders</b>		
Kidney calculus		1 (2.0%)
Urin abnorm	2 (3.9%)	
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough inc	1 (2.0%)	
Dyspnea	1 (2.0%)	
Pharyngitis	1 (2.0%)	
Rhinitis	2 (3.9%)	
<b>Skin and subcutaneous tissue disorders</b>		
Ecchymosis	1 (2.0%)	1 (2.0%)
<b>TOTAL</b>	<b>18</b>	<b>18</b>

\* 15 adverse events in Project No. 50256 could not be assigned to a treatment group.

A= Treatment A, Test product, Balsalazide Disodium Capsules, 750 mg by Apotex, Inc., Canada, Lot/Batch No. 043-11

B = Treatment B, Reference Product, Colazal® Capsules, 750 mg by Salix Pharmaceuticals, Inc., USA, Lot/Batch No. 311208

<sup>1</sup>: Table provided by firm.

**Reviewer's Comments:** Fifty-one (51) adverse events were reported during the fasting study. The firm reported that fourteen (14) of the adverse events were potentially related to Treatment A (test product: Balsalazide Disodium 750 Capsules, 3 x 750 mg); and

eleven (11) of the adverse events were potentially related to Treatment B (reference product: Colazal<sup>®</sup> 750 mg Capsules, 3 x 750 mg). Fifteen (15) of the adverse events reported could not be assigned to a treatment group because they were associated with clinically significant post-laboratory test results. Only one adverse event reported was serious in nature. Subject No. 18 reported experiencing right renal calculus approximately 3 days and 10 minutes after the study drug (Treatment B, reference product: Colazal<sup>®</sup> 750 mg Capsules, 3 x 750 mg) had been administered in Period II. The subject was hospitalized and surgery was performed. The subject underwent ureteroscopy, cystoscopy, and extraction of right nephrolithiasis under regional anesthesia (spinal block). He was discharged approximately 6 hours post-surgery. The firm reported that a continuous follow-up will be performed by a physician if needed. The firm also reported that the subject had no complications after surgery. The firm stated in their report, *'This serious adverse event is still unresolved and was judged to be remotely related to the study medication since this was a pre-existing condition. This subject had history of renal calculus in the past and he is already followed up by his physicians.'* No other serious adverse events were reported. Also, no subjects reported experiencing emesis during the fasting study.

**Was there a difference in protocol deviations for the test versus the reference? No**

*Protocol, Blood Sampling Deviations and Administration of Concomitant Medication during the Fasting Bioequivalence Study, No. 50256*

Additional Information is located in Section 14.3 and 14.4, pp. 320-40

**Table A1-4. Protocol Deviations during the Fasting Bioequivalence Study No. 50256<sup>1</sup>**

Subject Number	Period	Treatment	Protocol Deviation	Excluded from Analysis due to Deviation(s)	
				Safety	PK
01-50, 52-67, 69-79	N/AP	N/AP	A total of 77 subjects were dosed instead of 80 as specified in the protocol.	No	No
			The medication used for this study was received at the SFBC Anapharm Ste-Foy facility before the reception of the "Non-Objection Letter" from the Therapeutic Products Directorate.	No	No
01-30, 38-41, 44-46, 48-50, 52-54	1	A, B	These subjects' 0.167-, 0.250-, 0.333-, 0.667-, 4.00-, 5.00-, 16.0-, and 72.0-hour blood collection tubes (for balsalazide) were stored as much as 88 minutes after sample centrifugation. However, there is no impact since balsalazide is stable in plasma at room temperature for 23 hours with a percentage of change of -1.48% and -1.48%.  Note: this deviation does not apply to all subjects and all sampling times.	No	No
16-17, 20, 45- 49, 52-59 66, 67, 72	1, 2	A, B	These blood collection tubes (for balsalazide and 5-ASA) were centrifuged as much as 61 minutes after blood collection: • Subjects 16-17; 6.00-hour post-dose in Period 1; • Subject 20; 24.0-hour post-dose in Period 2; • Subject 45-49; 6.00-hour post-dose in Period 1; • Subject 52; 8.00-hour post-dose in Period 1; • Subjects 52-54; 5.00-hour post-dose in Period 1; • Subjects 52-55; 6.00-hour post-dose in Period 2; • Subjects 54-59; 12.0-hour post-dose in Period 1; • Subjects 55-57; 16.0-hour post-dose in Period 1; • Subject 66-67; 0.500-hour post-dose in Period 2; • Subject 72; 0.333-hour post-dose in Period 2.  Since all centrifugation start times were not within the tested stability, these samples are rejected.	No	Yes
52-56, 58-67, 69-79	2	A, B	Whether these subjects' 6.00-hour post-dose blood collection tubes (for balsalazide) were stored within 60 minutes after sample centrifugation can not be confirmed (storage time is inconclusive).  These samples can not be used for statistical analysis since no stability data is available for this situation.	No	Yes
03	N/AP	N/AP	No post-study procedures were performed for this subject. The subject could not return to the clinical facility; a letter was sent to the subject.	No	No

<sup>1</sup>: Table provided by firm.

Continued, **Table A1-4. Protocol Deviations during the Fasting Bioequivalence Study No. 50256<sup>1</sup>**

Subject Number	Period	Treatment	Protocol Deviation	Excluded from Analysis due to Deviation(s)	
				Safety	PK
27	N/AP	N/AP	This subject did not sign the new version of the screening ICF dated May 1, 2005, at the moment of the screening procedures.  However, there is no impact since the information written in both Inform Consent Forms was equivalent.	No	No
34	N/AP	N/AP	The investigator delegate did not demonstrated by signing the "ICF Screening Form" that he provided all explanations of the screening informed consent.  However, there is no impact since the volunteer signed all pages of the screening ICF confirming that he received all the information concerning the screening procedures.	No	No
47	1	A	Whether this subject's 1.00-hour post-dose blood collection tube (for balsalazide) was stored within 60 minutes (maximum delay of 214 minutes) after sample centrifugation can not be confirmed (data not recorded)  However, there is no impact since balsalazide is stable in plasma at room temperature for 23 hours with a percentage of change of -1.48% and -1.48%.	No	No
60	1	A	It cannot be confirmed if the alcohol breath test was done on the right subject since it was performed before the verification of the subject identity.  However, all subject's alcohol breath test were negative and the subject confirmed that he did not consumed alcohol-based products 24 hours prior to drug administration.	No	No
66	2	A	Whether this subject's 0.250-hour post-dose blood collection tube (for 5-ASA) was centrifuged within 50 minutes can not be confirmed (due to a conflicting data).  This sample can not be used for statistical analysis.	No	Yes

<sup>1</sup>: Table provided by firm.

**Reviewer's Comments:** The firm reported several protocol deviations. The firm provided a description of the deviation and an explanation as to how it was resolved. Upon review of this information it was determined that these deviations did not have an impact on the outcome of this fasting BE study.

**Table A1-5. Subjects Receiving Non-Scheduled medication Prior to and During the Fasting Bioequivalence Study, No. 50256<sup>1</sup>**

Additional Information Located in Section 14.5, pp. 348

Subject Number	Medication	Dosage	Medication Use	
			Date(s)	Time(s)
57	acyclovir 5% cream	unknown	2005-07-05	09:00
			2005-07-07	09:00
18	Atropine†	1 x 0.4 mg (intra-venous)	2005-07-18	13:09
	Bentylol†	1 x 20 mg (intra-muscular)	2005-07-18	08:15
	Dilaudid†	1 x 1 mg (subcutaneous)	2005-07-16	01:00 and every 3 hours*
			2005-07-17	every 3 hours*
	Gravol† Indocid†	1 x 50 mg (intra-venous) 1 x100 mg (intra-rectal)	2005-07-16 and 2005-07-17	every 6 hours*
			2005-07-18	every 12 hours*
	Morphine†	1 x 5 mg (intra-venous)	2005-07-18	every 4 hours PRN*
	Emtec†	1 or 2 x 30 mg	unknown‡	every 4 hours PRN
Démérol†	1 or 2 x 50 mg	unknown‡	every 4 hours	

\*exact time unknown

† active ingredient unknown

‡ prescription received at the moment of discharge from the hospital on July 17, 2005.

<sup>1</sup>: Table provided by firm.

**Reviewer's Comments:** Two (2) subjects (Nos. 18 and 57) received concomitant medication during this fasting study. Subject No. 57 received medication as treatment for a cold sore prior to Period II dosing. Subject No. 18 underwent surgery and received several medications for the treatment of right renal calculus. This was a pre-existing condition. The firm stated in their report that, '*The subject had a history of renal calculus in the past and he is already followed up by his physicians.*'

**Table A1-6. Blood Sampling Time Deviations during the Fasting Bioequivalence Study No. 50256**

<b>Blood Sampling Time Deviations</b>		
	<b>Period 1</b>	<b>Period 2</b>
<b>Subject Number</b>	01-09, 10, 11, 14, 15, 18, 20-43, 45-48, 50, and 52-79	01, 02, 04-19, 22-47, 49, 50, 52, 56, 58, 60, 61, 64, 66, 67, and 69-79
<b>Time Range</b>	1 minute (late) to 59 minutes (late)	2 minutes (early) to 3 hours and 2 minutes (late)

**Reviewer's Comments:** The firm reported several blood sampling time deviations. The blood sampling deviations were insignificant and did not have an impact on the outcome of the fasting study. In Period I and II, the blood sampling time deviations for balsalazide occurred within 10 minutes of the scheduled time point except for a few samplings at time 1.50-hour post-dose and 10.0-hours post-dose or later. For mesalamine (5-ASA), the blood sampling time deviations all occurred within 10 minutes except for a few samples at 2.0, 3.0- and 10.0-hours post dose or later. The greatest time point deviations of 59 minutes and 3 hours and 2 minutes occurred at the 72-hour post-dose sampling time. The majority of the blood sampling deviations were either due to difficulty drawing blood or for a technical reason.

**Reviewer's Comments:** The reported adverse events, protocol and blood sampling time deviations, along with the administration of concomitant medication to subjects did not have an impact on the outcome nor the integrity of this fasting study.

## c. Bioanalytical Results

**Reviewer's Comments:** The firm does not provide the summary tables for analytical performance: back-calculated concentration (ng/mL) of calibration curve standard in (human) (Plasma EDTA K3), and analytical performance of quality control samples in human plasma EDTA K3 for balsalazide and mesalamine (5-ASA), in the bioanalytical report.

**Table A1-7. Chromatograms Provided in the Bioanalytical Report of the Fasting Study, No. 2005-998**

<b>Any interfering peaks in chromatograms?</b>	No
<b>Were 20% of chromatograms included?</b>	Yes
<b>Were chromatograms serially or randomly selected?</b>	Serially
<b>Chromatograms provided for Subject Nos.</b>	01, 02, 04, 05, 06, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16, and 17

**Are the chromatograms acceptable?** Yes

**Table A1-8. Standard Operation Procedures used for Analysis of Zaleplon Plasma Samples in the Fasting Bioequivalence Study,**

<b>Firm Provided SOPs</b>		<b>Yes</b>
<b>SOP No.</b>	<b>Effective Date of SOP</b>	<b>SOP Title</b>
ANI 8584.01	January 26, 2004	Determination of Balsalazide in Human EDTA K <sub>3</sub> Plasma over a Concentration Range of 1 to 500 ng/mL using High-Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection
ANI 153.07	December 11, 2002	Preparation, Identification and Acceptance Criteria of Stock Solutions, Calibration Standards, Quality Control Samples and Reference Solutions
ANI 156.08	July 01, 2003	Sample Reassays and Reporting of Final Concentrations
ANI 157.04	April 28, 2003	Application of Chromatographic Methods to Routine Drug Analysis
ANI 167.05	June 30, 2005	Chromatographic Acceptance Criteria and Verification of Chromatograms
<b>Were the SOPs appropriate?</b>		Yes
<b>Number of Samples Re-assayed</b>		344
<b>Number of Pharmacokinetic Repeats</b>		0
<b>Were the reassays consistent with objective criteria in SOP?</b>		Uncertain
<b>Impact of Repeat-assays on the study outcome</b>		Uncertain

**Reviewer's Comments:** (on analytical study)

1. The firm provides all the relevant SOPs for performing sample analysis in the fasting study.
2. The firm does not provide summary tables in the bioanalytical report for balsalazide and mesalamine (5-ASA). The summary tables missing include (1) plasma EDTA K3 concentration (ng/mL) in Humans, (2) Repeat analysis results in human plasma EDTA K3, (3) Summary of study sample reassays, (4) Summary of analytical runs, (5) Calibration curve parameters for calibration standards in human plasma EDTA K3, (6) Analytical performance: back-calculated concentration (ng/mL) of calibration curve standard in (human) (Plasma EDTA K3), and (7) Analytical performance of quality control samples in human plasma EDTA K3
3. The reviewer can not make an accurate assessment of the criteria for reanalysis and the acceptability of the recalculated values for balsalazide and mesalamine (5-ASA), because the summary tables with the original and repeat values are not provided.

**Conclusion:** The bioanalytical method is incomplete.

## d. Pharmacokinetic and Statistical Results for Balsalazide

**Table A1-9. Arithmetic Mean of Pharmacokinetic Parameters, N = 72 (SAS Output)**

Mean plasma balsalazide concentrations are presented in [Table A1-12](#) and [Figure A1-1](#)

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC <sub>I</sub>	1415.29	43.24	1434.87	50.12	0.99
AUC <sub>T</sub>	1300.29	44.10	1317.30	52.29	0.99
C <sub>MAX</sub>	358.80	58.48	361.64	62.72	0.99
KE	0.02	18.13	0.02	28.73	0.96
THALF	36.54	17.56	35.99	22.09	1.02
T <sub>MAX</sub>	0.70	85.95	0.65	45.75	1.07

**Table A1-10. Geometric Mean and 90% Confidence Intervals, N = 72 (SAS Output)**

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERC12	UPPERC12
	LAUC <sub>I</sub>	1287.19	1283.56	1.00	93.40
LAUC <sub>T</sub>	1179.59	1172.41	1.01	93.60	108.15
LC <sub>MAX</sub>	312.06	310.93	1.00	91.83	109.69

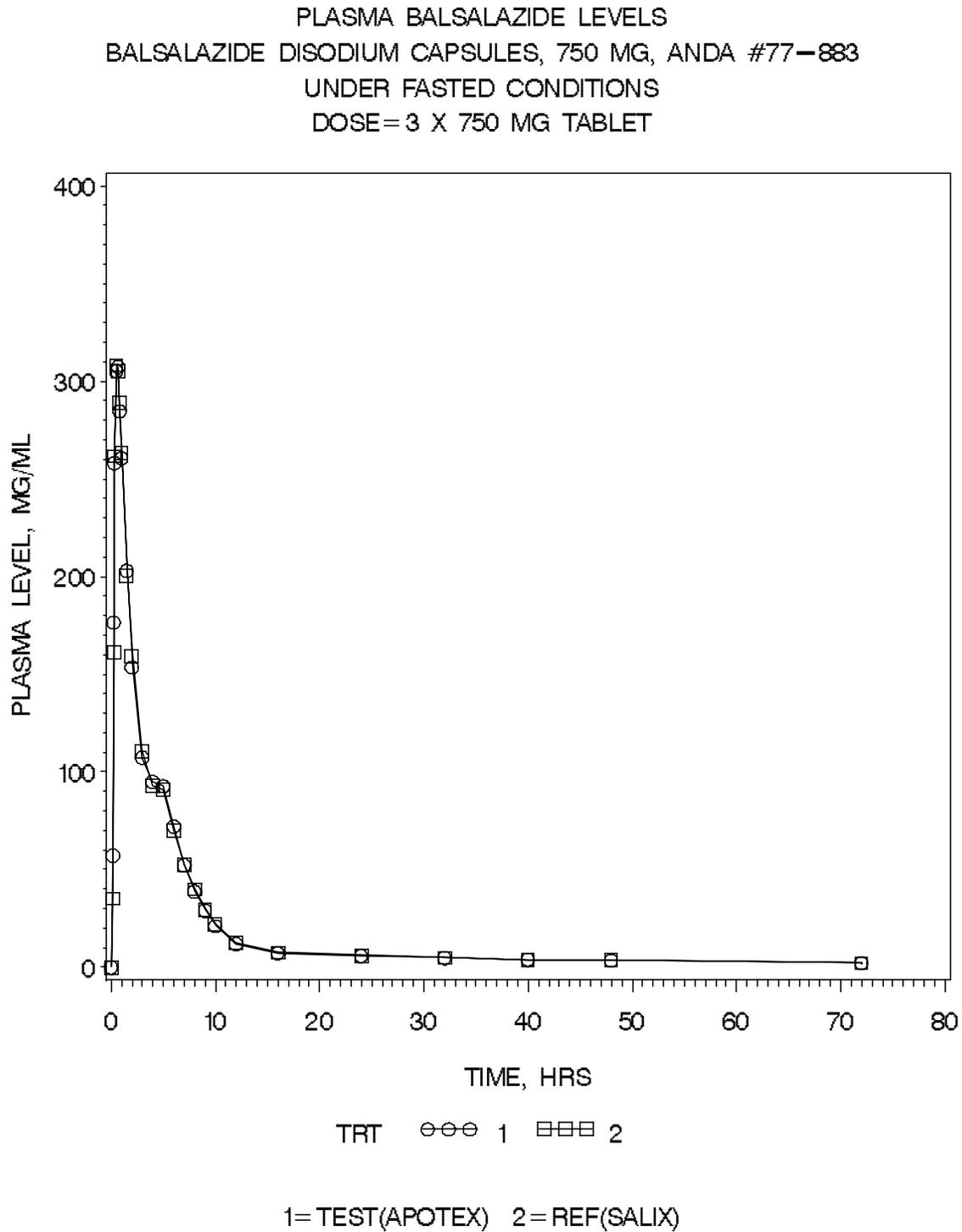
**Table A1-11. Additional Study Information: Total SD and within-subject error (root MSE), N =72: (SAS Output)**

Root mean square error, LAUC <sub>T</sub>	0.259
Root mean square error, LAUC <sub>∞</sub>	0.251
Root mean square error, LC <sub>max</sub>	0.319
Mean ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.91      Reference: = 0.91
Range of values, ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.81 -0.98      Reference: = 0.83 - 0.98

**Table A1-12. Mean Plasma Balsalazide Concentrations for Apotex's Balsalazide Disodium Capsules, 750 mg and Salix's Colazal<sup>®</sup> Capsules, 750 mg - Single-Dose Fasting Study (N =72)**

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0.00	.	0.00	.	.
0.167	57.27	69.84	35.30	101.42	1.62
0.25	176.57	60.35	161.62	70.39	1.09
0.333	258.21	56.02	261.72	67.49	0.99
0.5	305.27	57.68	308.32	63.33	0.99
0.667	307.46	65.84	305.46	61.58	1.01
0.833	284.72	68.08	289.29	72.87	0.98
1	260.60	59.94	263.45	71.53	0.99
1.5	203.06	60.24	200.78	67.90	1.01
2	153.54	54.70	159.56	64.25	0.96
3	107.41	51.37	110.89	60.96	0.97
4	94.88	56.44	93.18	57.76	1.02
5	92.80	63.13	90.77	53.81	1.02
6	72.19	67.75	69.86	102.04	1.03
7	52.28	74.57	52.35	71.54	1.00
8	38.80	79.12	40.01	88.23	0.97
9	29.11	78.74	29.76	81.23	0.98
10	21.12	83.49	21.97	84.48	0.96
12	12.01	69.69	12.52	72.46	0.96
16	7.33	51.58	7.57	51.76	0.97
24	5.81	49.06	6.08	54.32	0.96
32	4.71	48.94	4.84	48.29	0.97
40	4.01	49.29	4.00	48.83	1.00
48	3.53	50.73	3.57	47.44	0.99
72	2.17	68.80	2.15	52.87	1.01

**Figure A1-1. Mean Plasma Balsalazide Concentrations for Apotex's Balsalazide Disodium Capsules, 750 mg and Salix's Colazal<sup>®</sup> Capsules, 750 mg - Single-Dose Fasting Study (N =72)**



## e. Pharmacokinetic and Statistical Results for Mesalamine (5-ASA)

**Table A1-13. Arithmetic Mean of Pharmacokinetic Parameters, N =72 (SAS Output)**

Mean plasma Mesalamine (5-ASA) concentrations are presented in [Table A1-16](#) and [Figure A1-2](#)

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC <sub>I</sub>	3229.29	63.22	3610.85	57.56	0.89
AUC <sub>T</sub>	2907.45	64.44	3208.19	58.61	0.91
C <sub>MAX</sub>	287.19	68.10	322.90	63.41	0.89
KE	0.11	71.94	0.10	66.37	1.04
THALF	10.65	79.43	11.62	92.01	0.92
T <sub>MAX</sub>	9.99	37.88	9.54	22.45	1.05

**Table A1-14. Geometric Mean and 90% Confidence Intervals, N =72 (SAS Output)**

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERC12	UPPERC12
LAUC <sub>I</sub>	2705.15	3036.94	0.89	<b>79.16</b>	100.23
LAUC <sub>T</sub>	2292.40	2596.51	0.88	<b>73.94</b>	105.42
LC <sub>MAX</sub>	221.83	257.06	0.86	<b>74.25</b>	100.30

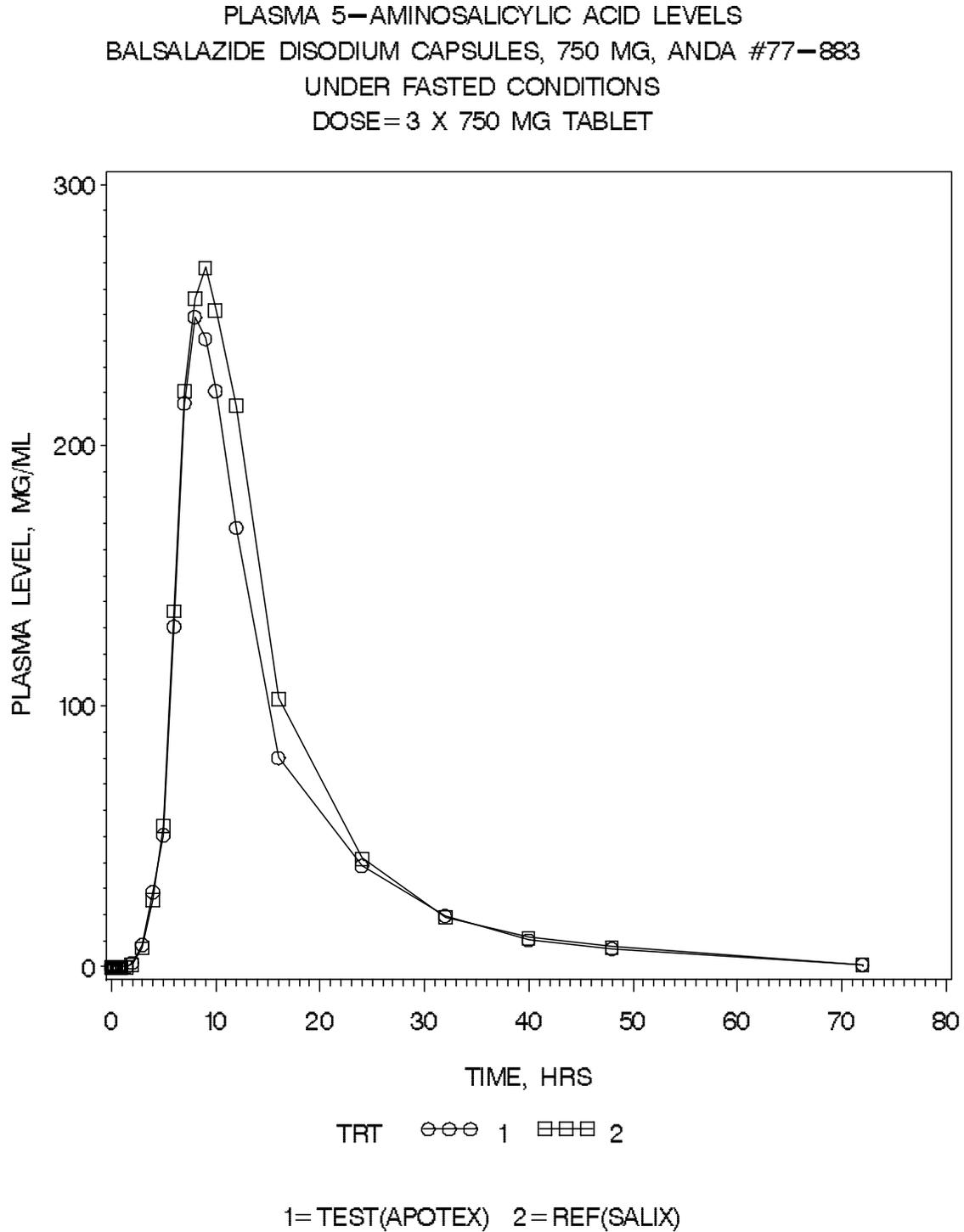
**Table A1-15. Additional Study Information: Total SD and within-subject error (root MSE), N =72: (SAS Output)**

Root mean square error, LAUC <sub>T</sub>	0.636
Root mean square error, LAUC <sub>∞</sub>	0.384
Root mean square error, LC <sub>max</sub>	0.539
Mean ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.94      Reference: = 0.56 - 1.00
Range of values, ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.94      Reference: = 0.68 - 1.00

**Table A1-16. Mean Plasma Mesalamine (5-ASA) Concentrations for Apotex's Balsalazide Disodium Capsules, 750 mg and Salix's Colazal® Capsules, 750 mg - Single-Dose Fasting Study (N =72)**

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0.00	.	0.00	.	.
0.167	0.00	.	0.00	.	.
0.25	0.00	.	0.00	.	.
0.333	0.00	.	0.00	.	.
0.5	0.00	.	0.00	.	.
0.667	0.00	.	0.00	.	.
0.833	0.00	.	0.00	.	.
1	0.00	.	0.00	.	.
1.5	0.10	621.08	0.05	848.53	1.96
2	1.60	391.68	1.04	550.00	1.54
3	8.43	309.58	7.22	293.19	1.17
4	28.78	219.72	25.64	194.22	1.12
5	50.57	162.36	54.14	146.79	0.93
6	130.50	103.33	136.43	88.79	0.96
7	216.12	83.36	221.03	75.51	0.98
8	249.27	73.03	256.17	70.14	0.97
9	240.84	73.00	268.16	68.32	0.90
10	220.86	71.28	251.86	66.59	0.88
12	168.39	76.68	215.17	76.61	0.78
16	80.14	84.28	102.93	81.14	0.78
24	38.72	86.75	41.57	72.88	0.93
32	19.58	130.67	19.14	136.96	1.02
40	10.22	159.35	11.20	187.51	0.91
48	6.88	168.92	7.60	184.88	0.91
72	0.96	345.88	0.88	395.10	1.09

**Figure A1-2. Mean Plasma Mesalamine (5-ASA) Concentrations for Apotex's Balsalazide Disodium Capsules, 750 mg and Salix's Colazal<sup>®</sup> Capsules, 750 mg - Single-Dose Fasting Study (N =72)**



**Table A1-17. Arithmetic Mean of Pharmacokinetic Parameters, N =71-Excluded  
Subject No. 34 (SAS Output)**

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC <sub>I</sub>	3229.29	63.22	3610.85	57.56	0.89
AUC <sub>T</sub>	2948.11	62.91	3215.38	58.86	0.92
C <sub>MAX</sub>	291.16	66.63	324.18	63.52	0.90
KE	0.11	71.94	0.10	66.37	1.04
THALF	10.65	79.43	11.62	92.01	0.92
T <sub>MAX</sub>	9.91	37.78	9.56	22.47	1.04

**Table A1-18. Geometric Mean and 90% Confidence Intervals, N =71-Excluded  
Subject No. 34 (SAS Output)**

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERC12	UPPERC12
LAUC <sub>I</sub>	2705.15	3036.94	0.89	<b>79.16</b>	100.23
LAUC <sub>T</sub>	2462.05	2592.48	0.95	82.56	109.24
LC <sub>MAX</sub>	234.97	257.11	0.91	80.72	103.46

**Table A1-19. Additional Study Information: Total SD and within-subject error  
(root MSE), N =71-Excluded Subject No. 34: (SAS Output)**

Root mean square error, LAUC <sub>T</sub>	0.498
Root mean square error, LAUC <sub>∞</sub>	0.385
Root mean square error, LC <sub>max</sub>	0.441
Mean ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.94      Reference: = 0.94
Range of values, ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.56 – 1.00      Reference: = 0.68 – 1.00

**Table A1-20. Arithmetic Mean of Pharmacokinetic Parameters, N =70-Excluded Subject No. 34 and 78 (SAS Output)**

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC <sub>I</sub>	3229.29	63.22	3610.85	57.56	0.89
AUC <sub>T</sub>	2966.92	62.74	3260.65	57.26	0.91
C <sub>MAX</sub>	291.67	66.98	328.60	62.08	0.89
KE	0.11	71.94	0.10	66.37	1.04
THALF	10.65	79.43	11.62	92.01	0.92
T <sub>MAX</sub>	9.95	37.73	9.61	22.08	1.04

**Table A1-21. Geometric Mean and 90% Confidence Intervals, N =70-Excluded Subject No. 34 and 78 (SAS Output)**

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERC12	UPPERC12
LAUC <sub>I</sub>	2705.15	3036.94	0.89	<b>79.16</b>	100.23
LAUC <sub>T</sub>	2475.62	2763.30	0.90	80.20	100.08
LC <sub>MAX</sub>	234.53	268.78	0.87	<b>78.62</b>	96.85

**Table A1-22. Additional Study Information: Total SD and within-subject error (root MSE), N =70-Excluded Subject No. 34 and 78: (SAS Output)**

Root mean square error, LAUC <sub>T</sub>	0.390
Root mean square error, LAUC <sub>∞</sub>	0.385
Root mean square error, LC <sub>max</sub>	0.368
Mean ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.94      Reference: = 0.94
Range of values, ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.56 – 1.00      Reference: = 0.68 – 1.00

**Reviewer's Comments:** (on pharmacokinetic analysis)

1. The firm assayed the plasma concentration for the parent compound, balsalazide and its active metabolite, mesalamine (5-ASA). The firm provided the plasma profiles for balsalazide and 5-ASA.
2. Seventy-seven (77) healthy, adult male subjects were enrolled into the study and divided into two (2) groups. Treatment Group No. 01 consisted of thirty-six (36) healthy, adult male subjects and Treatment Group No. 02 consisted of forty-one (41) healthy, adult male subjects.
3. The seventy-seven (77) healthy, adult male subjects were not enrolled in the study at the same time. The subjects were screened on different dates. All subjects enrolled in Treatment Group No. 01 were screened prior to Period I dosing. For Treatment Group No. 02, Subject Nos. 38, 40, 42, 45, 47, 48, 52, 57, 58, 60, 59, 61, 63, 74, 75, 76, 78, and 79 were screened prior to the start of Period I for Treatment Group No. 01. All other subjects enrolled in Treatment Group No. 02 were screened after the start of the fasting study for Treatment Group No. 01. There is seven (7) days in between the dosing of the two groups. Five (5) subjects voluntarily withdrew.
4. The firm and the reviewer analyzed the data using the group-by-treatment effect in the statistical model. Statistical analysis was performed on the pharmacokinetic (PK) parameters ( $AUC_{\infty}$ ,  $AUC_T$ ,  $C_{max}$ ,  $T_{max}$ , and  $K_{el}$ ) using the GLM procedure of SAS with a 90% confidence interval (CI). Based on the results from the statistical analysis, the firm and the reviewer concluded there is no significant group-by-treatment interaction. Therefore, the data for all seventy-two (72) subjects were combined for pharmacokinetic and statistical analyses.
5. The firm reported Subject No. 34 had aberrant plasma mesalamine concentrations. The firm stated in their report, '*Subject No. 34 showed only 2 detectable concentrations for 5-ASA and the concentration appeared to be still rising as the second concentration was higher than the first one, demonstrating that something happened regarding the biotransformation of balsalazide to 5-ASA for this subject. Due to this inadequate PK profile, the data from this subject was excluded from pharmacokinetic and statistical analyses only for 5-ASA.*'
6. For mesalamine, the reviewer performed the Studentized Residual Outlier test ( $\alpha = 0.05$ , |3.290|) on the data from all the subjects that completed the fasting study. The results confirmed that subject Nos. 34 and 78 had aberrant plasma mesalamine concentrations. These two subjects represent two opposing extremes and had opposite effects on the results of the fasting study. If Subject No. 34 was dropped the 90% CI values for the log-transformed PK parameters increased; if Subject No. 78 was dropped then the 90% CI values decreased for the log transformed PK parameters. However, the firm only conducted a re-dosing fasting study for Subject No. 34.

7. Statistical analyses of plasma concentration data for the parent compound, balsalazide demonstrate bioequivalence. The balsalazide results including all subjects, N=72 (point estimate, 90% CI) are: LAUC<sub>T</sub> of 1.01, 93.60-108.15%, LAUC<sub>∞</sub> of 1.00, 93.40-108.15%, and LC<sub>max</sub> of 1.00, 91.83-109.69%.
8. Statistical analyses of plasma concentration data for the metabolite, mesalamine (5-ASA)] does not demonstrate bioequivalence. The results for mesalamine including all subjects, N=72 (point estimate, 90% CI) are: LAUC<sub>T</sub> of 0.88, **73.94-105.42%**, LAUC<sub>∞</sub> of 0.89, **79.16-100.23%**, and LC<sub>max</sub> of 0.86, **74.25-100.30%**.
9. When Subject No. 34 is dropped, the 90% CIs are not within the acceptable range of 80-125% for log-transformed AUC<sub>∞</sub> for 5-ASA. Yet, the 90% CIs did increase within acceptable range for log-transformed AUC<sub>T</sub>, and C<sub>max</sub> as compared to 90% CI intervals for the log-transformed PK parameters using the data from all the subjects that completed the study.
10. When Subject No. 78 is dropped, the 90% CIs are not within the acceptable range of 80-125% for log-transformed AUC<sub>T</sub>, AUC<sub>∞</sub> and C<sub>max</sub> for mesalamine (5-ASA).
11. When both Subjects 34 and 78 are dropped, the 90% CIs are not within acceptable range of 80-125% for log-transformed for AUC<sub>∞</sub> and C<sub>max</sub> for mesalamine (5-ASA).

**Conclusion:** The single-dose fasting bioequivalence study is incomplete.

## 2. Single-dose Re-dosing Fasting Bioequivalence Study

## a. Study Design

Study Information	
Study Number	60045
Study Title	Re-dosing Study From an Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal <sup>®</sup> Following a 2250 mg Dose in Healthy Subjects Under Fasting Conditions
Clinical Site	SFBC Anapharm, 5160 Boul. Décarie, Suite 800, Montreal (Quebec), Canada H3X 2H9
Principal Investigator	Richard Larouche, M.D.
Study/Dosing Dates	<u>Study Dates</u> Start Date: March 12, 2006 End Date: March 30, 2006  <u>Dosing Dates</u> Period I: March 13, 2006 Period II: March 27, 2006
Analytical Site	SFBC Anapharm, 2050, Boul. René-Lévesque, Ouest, Sainte-Foy (Québec), Canada G1V 2K8
Analytical Director	(b) (6) B.Sc.
Analysis Dates	April 09, 2006 to April 12, 2006
Storage Period	30 days (March 13, 2006 to April 12, 2006)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Balsalazide Disodium Capsules	Colazal <sup>®</sup> Capsules
Manufacturer	Apotex Inc., Canada	Salix Pharmaceuticals Inc., USA
Batch/Lot No.	043-11	311208
Manufacture Date	Not reported	N/A
Expiration Date	June 2007	June 2006
Strength	750 mg	750 mg
Dosage Form	Capsule	Capsule
Batch Size	(b) (4)	N/A
Production Batch Size	Not reported	N/A
Potency	101.7%	102.1%
Content Uniformity	101.1%	102.1%
Formulation	See Section B, <a href="#">Table B-1</a>	N/A
Dose Administered	3 x 750 mg Capsules	3 x 750 mg Capsules
Route of Administration	Oral	

<b>No. of Sequences</b>	2
<b>No. of Periods</b>	2
<b>No. of Treatments</b>	2
<b>No. of Groups</b>	1
<b>Washout Period</b>	14 days
<b>Randomization Scheme</b>	<p><u>Sequence AB</u> Subject Nos. 01, and 34</p> <p><u>Subject BA</u> Subject Nos. 44, 49, and 61</p>
<b>Blood Sampling Times</b>	0.0 (pre-dose), 0.167, 0.250, 0.333, 0.500, 0.667, 0.833, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.0, 12.0, 16.0, 24.0, 32.0, 40.0, 48.0, 48.0, and 72.0 hours post-dose in each period.
<b>Blood Volume Collected/Sample</b>	1 x 4 mL for balsalazide and 1 x 4 mL for 5-ASA for each sampling time point
<b>Blood Sample Processing/Storage</b>	Blood samples were collected in tubes containing EDTA K2. The blood samples were cooled in an ice bath and were centrifuged at 3,000 rpm for at least 10 minutes at approximately 4°C. Two aliquots of at least 0.5 mL (when possible) of plasma for balsalazide and two aliquots of at least 0.8 mL (when possible) of plasma for 5-ASA, were dispensed into polypropylene tubes (as soon as possible). The aliquots were transferred to a -20°C ± 5°C freezer, pending shipment. No more than 50 minutes passed between the time of each blood draw and the start of centrifugation for balsalazide and 5-ASA. No more than 70 minutes and 191 minutes passed between the start of centrifugation and aliquot storage for balsalazide and 5-ASA, respectively
<b>IRB Approval</b>	Yes
<b>Informed Consent</b>	Yes
<b>Subjects Demographics</b>	See <a href="#">Table A2-1</a>
<b>Length of Fasting</b>	Subjects fasted overnight for at least 10 hours and until at least 4-hours post-dose
<b>Length of Confinement</b>	Subjects were confined to clinical facility from at least 10 hours prior to drug administration until after the 48.0-hour post-dose blood draw, in each period.
<b>Safety Monitoring</b>	Vital signs were not measured during the study. However, throughout the study subjects were monitored for adverse events.

**Is the design of the re-dosing fasting bioequivalence study acceptable? No**

**Reviewer's Comments:** The firm does not provide a standard operation procedure (SOP) for selecting suspected subjects with anomalous pharmacokinetic parameters for re-dosing study.

b. Clinical Results

*Study Demographics*

**Table A2-1. Demographic Profile of Subjects Completing the Fasting Bioequivalence Study No. 60045<sup>1</sup>**

Category		Safety / PK population		
		Randomization		Total
		AB	BA	
Age (years)	Mean ± SD	38 ± 11	50 ± 4	45 ± 9
	Range	30 - 46	47 - 55	30 - 55
	Median	38	49	47
	N	2	3	5
Age Groups	< 18	0	0	0
	18-40	1 (50.0 %)	0	1 (20.0 %)
	41-64	1 (50.0 %)	3 (100.0%)	4 (80.0 %)
	65-75	0	0	0
	> 75	0	0	0
Gender	Female	0	0	0
	Male	2 (100.0 %)	3 (100.0 %)	5 (100.0 %)
Race	Asian	0	0	0
	Black	0	0	0
	Caucasian	2 (100.0 %)	1 (33.3 %)	3 (60.0 %)
	American Hispanic	0	2 (66.7 %)	2 (40.0 %)
Height (cm)	Mean ± SD	175.5 ± 4.9	169.5 ± 12.4	171.9 ± 9.7
	Range	172.0 - 179.0	155.5 - 179.0	155.5 - 179.0
	Median	175.5	174.0	174.0
	N	2	3	5
Weight (kg)	Mean ± SD	86.8 ± 3.3	75.2 ± 8.6	79.8 ± 8.9
	Range	84.4 - 89.1	68.3 - 84.9	68.3 - 89.1
	Median	86.8	72.5	84.4
	N	2	3	5
BMI (kg/m <sup>2</sup> )	Mean ± SD	28.2 ± 0.5	26.3 ± 3.2	27.0 ± 2.5
	Range	27.8 - 28.5	22.6 - 28.2	22.6 - 28.5
	Median	28.2	28.0	28.0
	N	2	3	5

A= Treatment A, Test product, Balsalazide Disodium Capsules, 750 mg by Apotex, Inc., Canada, Lot/Batch No. 043-

ANDA #: 77-883                      Balsalazide Disodium Capsules, 750 mg                      Apotex  
 Review of Bioequivalence Studies and In Vitro Dissolution Testing                      Reviewer: April C. Braddy, Ph.D.

B = Treatment B, Reference Product, Colazal® Capsules, 750 mg by Salix Pharmaceuticals, Inc., USA, Lot/Batch No. 311208

<sup>1</sup>: Table provided by firm.

*Study Dropout Information*

**Reviewer's Comments:** No subjects withdrew and/or were dropped out of this Re-dosing fasting study.

**Was there a difference in side effects for the test versus the reference?** No

**Table A2-2. Incidence of Adverse Events Reported in the Fasting Bioequivalence Study No. 60045<sup>1</sup>**

System Class COSTART	Project No. 60045	
	A	B
<b>Eye disorders</b>		
Eye dis	1 (12.5%)	
<b>Gastrointestinal disorders</b>		
Constip	1 (12.5%)	1 (12.5%)
Dry mouth		1 (12.5%)
<b>Nervous system disorders</b>		
Headache	2 (25.0%)	1 (12.5%)
Taste pervers	1 (12.5%)	
<b>TOTAL</b>	<b>5</b>	<b>3</b>

A= Treatment A, Test product, Balsalazide Disodium Capsules, 750 mg by Apotex, Inc., Canada, Lot/Batch No. 043-11

B = Treatment B, Reference Product, Colazal® Capsules, 750 mg by Salix Pharmaceuticals, Inc., USA, Lot/Batch No. 311208

<sup>1</sup>: Table provided by the firm.

**Reviewer's Comments:** A total of eight (8) adverse events were reported during the re-dosing fasting study. All of the adverse events reported are potentially related to Treatment A (test product: Balsalazide Disodium 750 mg Capsules, 3 x 750 mg) and Treatment B, reference product: Colazal® 750 mg Capsules, 3 x 750 mg), 5 and 3 respectively. They were all mild in severity. No serious adverse events were reported nor did any of the subjects report experiencing emesis during the study.

**Was there a difference in protocol deviations for the test versus the reference?** No

*Protocol and Blood Sampling Deviations during the Re-dosing Fasting Bioequivalence Study, No. 60045*

Additional Information is located in Section 14.3 and 14.4, pp. 63-65

**Table A2-3. Protocol Deviations during the Re-dosing Fasting Bioequivalence Study No. 60045<sup>1</sup>**

Subject Number	Period	Treatment	Protocol Deviation	Excluded from Analysis due to Deviation(s)	
				Safety	PK
01-05	N/AP	N/AP	The medication used for the main study No. 50256 was received at the SFBC Anapharm Ste-Foy facility before the reception of the “Non-Objection Letter” from the Therapeutic Products Directorate. However, the “Non-Objection Letter” for study No. 60045 was received prior to Period 1 study drug administration.	No	No
	1, 2	A, B	During medication storage, the humidity of the storage facility rose above the range specified in the Anapharm Inc. Standard Operating Procedures, to as high as 69.93 % RH, on ten occasions (durations: less than one minute and one minute).	No	No
			During medication storage, the humidity of the storage facility fell beneath the accepted range, to as low as 27.49 %RH between October 10, 2005 and March 1, 2006.	No	No
			During medication storage, the temperature of the storage facility fell beneath the accepted range, to as low as 14.8°C on September 15, 2005.	No	No

<sup>1</sup>: Table provided by firm.

**Reviewer’s Comments:** The firm reported several protocol deviations. The deviations all dealt with the study drugs. The firm provided a description of the deviation, and how it would impact the study. Upon review of this information it was determined that these deviations should not have an impact on the outcome of this re-dosing fasting BE study.

**Table A2-4. Blood Sampling Time Deviations during the Re-dosing Fasting Bioequivalence Study No. 60045**

<b>Blood Sampling Time Deviations</b>		
	<b>Period 1</b>	<b>Period 2</b>
<b>Subject Number</b>	02, 04, and 05	01 to 05
<b>Time Range</b>	1 minute (late) to 15 minutes (late)	1 minute (late) to 12 minutes (late)

**Reviewer's Comments:** The blood sampling time deviations which occurred during the Re-dosing fasting study are insignificant. All deviations were within 10 minutes, except for two (2), at the 32-hour time point in Period I and at the 16-hour time point in Period II. The blood sampling time deviations were mainly due to difficulty drawing the blood samples.

**Reviewer's Comments:** The firm reported several protocol and blood sampling time deviations. No non-scheduled medication was given prior or during this study. All of these deviations were insignificant and did not impact the outcome or the integrity of the fasting study.

## c. Bioanalytical Results

**Table A2-5. Assay Quality Control – Within Study for Balsalazide**

<b>Accuracy and Precision Summary: Quality Control Sample Analysis</b>								
<b>QC Conc. (ng/mL)</b>	<b>3.00</b>			<b>150.12</b>			<b>350.28</b>	
<b>Interday Accuracy (%)</b>	<b>105.00</b>			<b>99.25</b>			<b>96.62</b>	
<b>Interday Precision (%CV)</b>	<b>13.97</b>			<b>2.60</b>			<b>2.27</b>	
<b>Accuracy and Precision Summary: Calibration Curve</b>								
<b>Cal. Standards Conc. (ng/mL)</b>	<b>1.00</b>	<b>2.00</b>	<b>20.03</b>	<b>100.16</b>	<b>200.32</b>	<b>300.48</b>	<b>400.64</b>	<b>500.80</b>
<b>Interday Accuracy (%)</b>	<b>100.00</b>	<b>99.00</b>	<b>101.45</b>	<b>102.20</b>	<b>101.17</b>	<b>98.71</b>	<b>98.87</b>	<b>98.15</b>
<b>Interday Precision (%CV)</b>	<b>3.00</b>	<b>4.55</b>	<b>2.12</b>	<b>1.91</b>	<b>2.36</b>	<b>1.93</b>	<b>0.96</b>	<b>2.11</b>
<b>Linearity Range (range of R<sup>2</sup> values) :</b>				<b>0.9989</b>				

**Table A2-6. Assay Quality Control – Within Study for 5-ASA**

<b>Accuracy and Precision Summary: Quality Control Sample Analysis</b>								
<b>QC Conc. (ng/mL)</b>	<b>6.04</b>			<b>181.30</b>			<b>423.02</b>	
<b>Interday Accuracy (%)</b>	<b>95.36</b>			<b>100.17</b>			<b>101.16</b>	
<b>Interday Precision (%CV)</b>	<b>3.99</b>			<b>3.72</b>			<b>3.86</b>	
<b>Accuracy and Precision Summary: Calibration Curve</b>								
<b>Cal. Standards Conc. (ng/mL)</b>	<b>2.02</b>	<b>4.04</b>	<b>20.19</b>	<b>121.15</b>	<b>242.30</b>	<b>363.40</b>	<b>484.61</b>	<b>605.76</b>
<b>Interday Accuracy (%)</b>	<b>102.97</b>	<b>96.04</b>	<b>92.92</b>	<b>100.69</b>	<b>100.46</b>	<b>101.92</b>	<b>103.75</b>	<b>101.66</b>
<b>Interday Precision (%CV)</b>	<b>4.81</b>	<b>6.44</b>	<b>3.04</b>	<b>4.49</b>	<b>2.64</b>	<b>2.78</b>	<b>2.69</b>	<b>2.63</b>
<b>Linearity Range (range of R<sup>2</sup> values) :</b>				<b>0.9966</b>				

Is the study assay quality control acceptable: Yes

**Table A2-7. Chromatograms Provided in the Bioanalytical Report of the Re-dosing Fasting Bioequivalence Study No. 60045**

<b>Any interfering peaks in chromatograms?</b>	None
<b>Were 20% of chromatograms included?</b>	Yes
<b>Were chromatograms serially or randomly selected?</b>	Serially
<b>Chromatograms provided for Subject Nos.</b>	01, and 02

**Are the chromatograms acceptable?** Yes

**Table A2-8. Standard Operation Procedures used for Analysis of Zaleplon Plasma Samples in the Fasting Bioequivalence Study No. 60045**

<b>Firm Provided SOPs</b>		<b>Yes</b>
<b>SOP No.</b>	<b>Effective Date of SOP</b>	<b>SOP Title</b>
ANI 153.09	November 02, 2005	Preparation, Identification, Acceptance Criteria of Stock, Calibration Standards, Quality Controls, Reference Solutions
ANI 156.09	September 23, 2005	Sample Reassays and Reporting Final Concentrations
ANI 157.06	January 09, 2006	Application of Chromatographic Methods to Routine Drug Analysis
ANI 167.05	June 30, 2005	Chromatographic Acceptance Criteria and Verification of Chromatograms
<b>Were the SOPs appropriate?</b>		Yes
<b>Number of Samples Re-assayed</b>		7
<b>Number of Pharmacokinetic Repeats</b>		0
<b>Were the reassays consistent with objective criteria in SOP?</b>		Yes
<b>Impact of Repeat-assays on the study outcome</b>		None

**Reviewer's Comments:** (on analytical study)

1. The firm provides all the relevant SOPs for performing sample analysis in the fasting study.
2. The firm does not provide the bioanalytical method validation summary table for balsalazide and mesalamine (5-ASA).
3. All plasma samples were reassayed for acceptable analytical reasons.
4. The use of the all the recalculated values in the pharmacokinetic and statistical analyses do not have an impact on the outcome of the study.

**Conclusion:** The bioanalytical method is incomplete for the reasons given in deficiency section.

## d. Pharmacokinetic and Statistical Results for Balsalazide

**Table A2-9. Arithmetic Mean of Pharmacokinetic Parameters, N = 5 (SAS Output)**

Mean plasma balsalazide concentrations are presented in [Table A2-12](#) and [Figure A2-1](#)

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC <sub>I</sub>	1518.58	31.17	1589.72	35.54	0.96
AUC <sub>T</sub>	1395.67	30.62	1459.85	38.10	0.96
C <sub>MAX</sub>	371.81	39.14	360.45	37.82	1.03
KE	0.02	18.89	0.02	12.05	0.97
THALF	37.01	23.75	35.20	11.86	1.05
T <sub>MAX</sub>	0.60	50.49	0.90	42.63	0.67

**Table A2-10. Geometric Mean and 90% Confidence Intervals, N = 5 (SAS Output)**

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERC12	UPPERC12
	LAUC <sub>I</sub>	1408.58	1415.22	1.00	69.13
LAUC <sub>T</sub>	1300.82	1285.40	1.01	66.64	153.68
LC <sub>MAX</sub>	351.02	322.85	1.09	80.39	147.06

**Table A2-11. Additional Study Information: Total SD and within-subject error (root MSE), N =5: (SAS Output)**

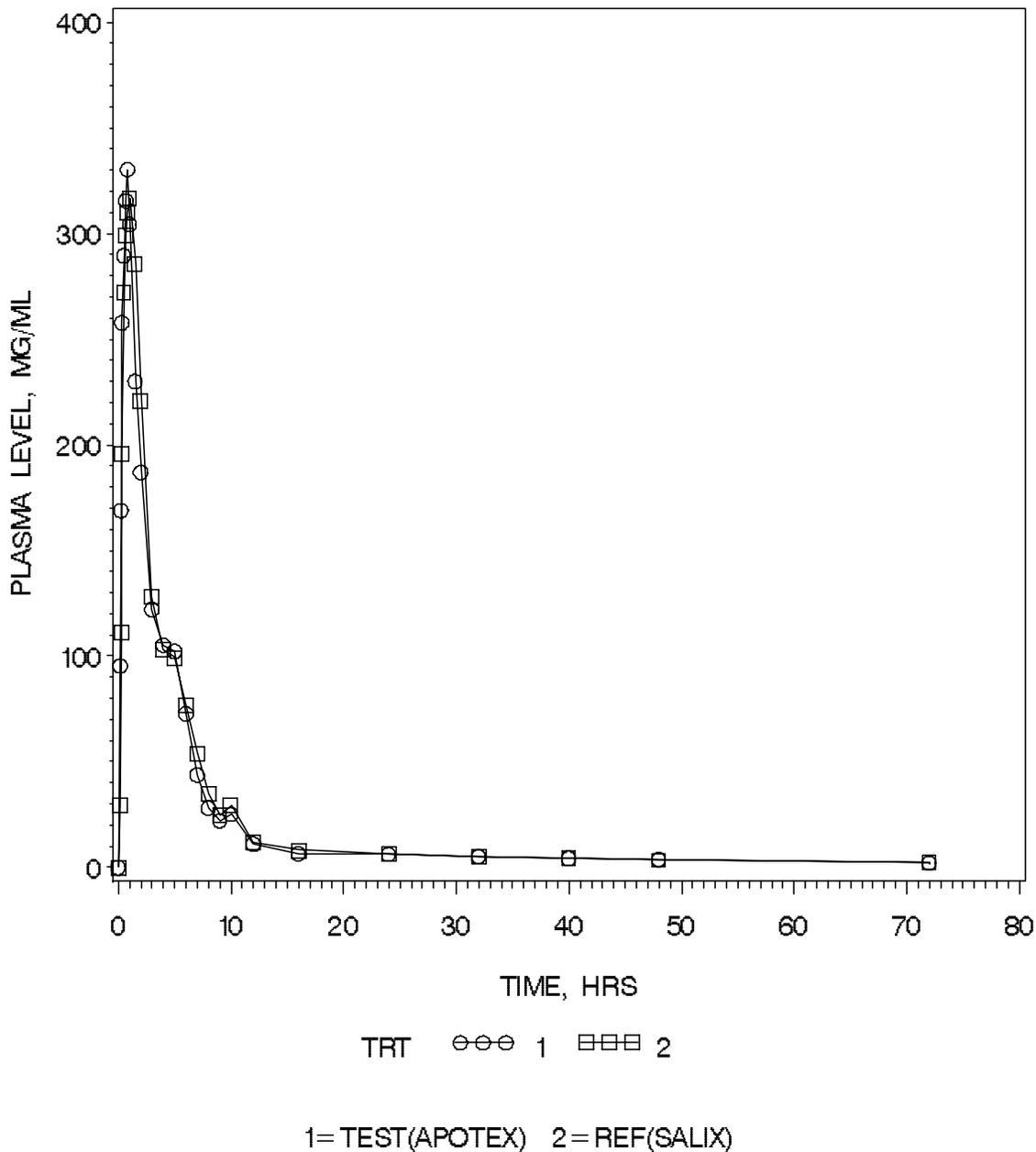
Root mean square error, LAUC <sub>T</sub>	0.275
Root mean square error, LAUC <sub>∞</sub>	0.239
Root mean square error, LC <sub>max</sub>	0.199
Mean ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.92      Reference: = 0.91
Range of values, ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.89 – 0.94      Reference: = 0.84 – 0.96

**Table A2-12. Mean Plasma Balsalazide Concentrations for Apotex's Balsalazide Disodium Capsules, 750 mg and Salix's Colazal® Capsules, 750 mg - Single-Dose Re-Dosing Fasting Study (N =5)**

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0.00	.	0.00	.	.
0.167	95.49	114.19	29.36	44.10	3.25
0.25	168.96	97.55	111.23	33.24	1.52
0.333	257.85	68.87	196.07	27.45	1.32
0.5	289.62	35.98	272.44	16.60	1.06
0.667	315.62	41.10	299.21	23.15	1.05
0.833	330.41	42.62	309.99	37.72	1.07
1	304.38	41.11	316.95	51.64	0.96
1.5	230.06	55.79	285.41	60.00	0.81
2	187.10	62.62	220.84	52.48	0.85
3	122.09	42.19	128.08	73.20	0.95
4	105.35	36.53	103.25	65.46	1.02
5	102.30	40.14	99.39	57.07	1.03
6	72.74	43.10	76.74	59.69	0.95
7	43.84	46.76	54.10	59.23	0.81
8	28.10	63.65	34.97	57.57	0.80
9	22.22	86.48	24.53	60.65	0.91
10	25.21	124.12	29.42	122.30	0.86
12	11.08	62.40	12.02	65.37	0.92
16	6.53	61.97	8.17	47.25	0.80
24	6.28	57.08	6.26	48.31	1.00
32	5.25	56.84	5.03	44.91	1.04
40	4.34	52.69	4.28	46.03	1.01
48	3.78	55.10	3.53	55.85	1.07
72	2.13	71.67	2.51	43.30	0.85

**Figure A2-1. Mean Plasma Balsalazide Concentrations for Apotex's Balsalazide Disodium Capsules, 750 mg and Salix's Colazal® Capsules, 750 mg - Single-Dose Re-Dosing Fasting Study (N =5)**

PLASMA BALSALAZIDE LEVELS  
BALSALAZIDE DISODIUM CAPSULES, 750 MG, ANDA #77-883  
UNDER FASTED CONDITIONS (RE-DOSING)  
DOSE = 3 X 750 MG TABLET



## e. Pharmacokinetic and Statistical Results for Mesalamine

**Table A2-13. Arithmetic Mean of Pharmacokinetic Parameters, N = 5 (SAS Output)**

Mean plasma Mesalamine (5-ASA) concentrations are presented in [Table A2-16](#) and [Figure A2-2](#)

PARAMETER	TEST		REFERENCE		RATIO T/R
	MEAN1	%CV	MEAN2	%CV	
AUC <sub>I</sub>	2353.45	23.40	2513.94	46.60	0.94
AUC <sub>T</sub>	2067.42	25.48	2250.59	47.00	0.92
C <sub>MAX</sub>	246.50	32.82	281.27	72.32	0.88
KE	0.06	81.33	0.06	59.88	0.99
THALF	18.69	84.50	16.79	84.83	1.11
T <sub>MAX</sub>	8.80	20.33	8.40	24.69	1.05

**Table A2-14. Geometric Mean and 90% Confidence Intervals, N = 5 (SAS Output)**

PARAMETER	TEST	REFERENCE	RATIO T/R	90% CI	
	LSM1	LSM2	RLSM12	LOWERC12	UPPERC12
LAUC <sub>I</sub>	2331.95	2342.07	1.00	69.97	141.69
LAUC <sub>T</sub>	1976.59	2088.50	0.95	67.00	133.68
LC <sub>MAX</sub>	236.64	230.79	1.03	60.14	174.80

**Table A2-15. Additional Study Information: Total SD and within-subject error (root MSE), N =5: (SAS Output)**

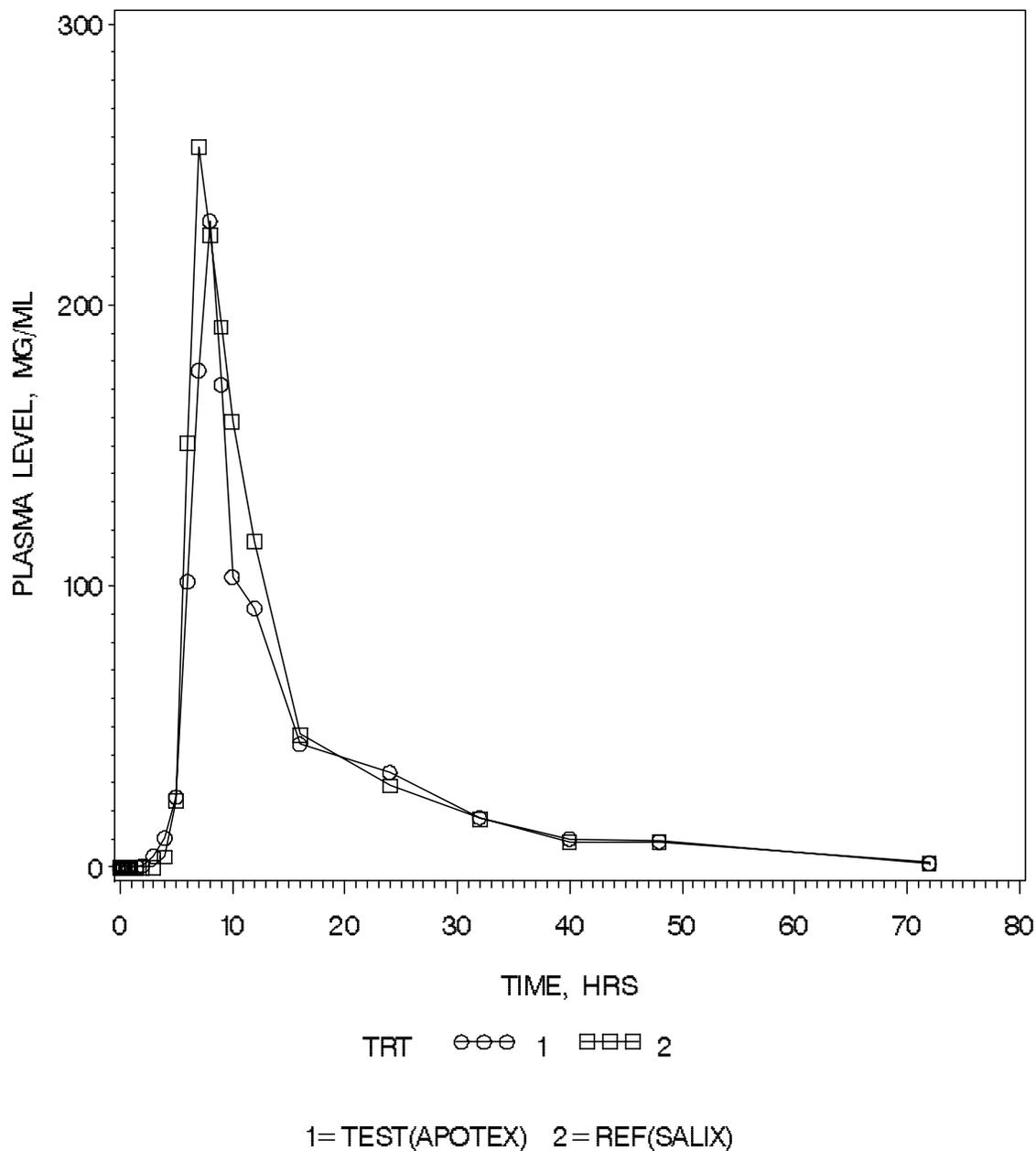
Root mean square error, LAUC <sub>T</sub>	0.227
Root mean square error, LAUC <sub>∞</sub>	0.232
Root mean square error, LC <sub>max</sub>	0.351
Mean ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.88      Reference: = 0.89
Range of values, ratio AUC <sub>T</sub> /AUC <sub>∞</sub>	Test = 0.68 – 0.99      Reference: = 0.82 – 0.98

**Table A2-16. Mean Plasma Mesalamine (5-ASA) Concentrations for Apotex's Balsalazide Disodium Capsules, 750 mg and Salix's Colazal® Capsules, 750 mg - Single-Dose Re-Dosing Fasting Study (N =5)**

Time (hr)	Test Product		Reference Product		Ratio T/R
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0.00	.	0.00	.	.
0.167	0.00	.	0.00	.	.
0.25	0.00	.	0.00	.	.
0.333	0.00	.	0.00	.	.
0.5	0.00	.	0.00	.	.
0.667	0.00	.	0.00	.	.
0.833	0.00	.	0.00	.	.
1	0.00	.	0.00	.	.
1.5	0.00	.	0.00	.	.
2	0.57	223.61	0.00	.	.
3	3.88	223.61	0.00	.	.
4	10.37	146.49	3.64	108.55	2.85
5	24.99	59.35	23.73	106.13	1.05
6	101.61	58.30	150.98	104.92	0.67
7	176.71	44.27	256.36	89.97	0.69
8	229.92	45.00	224.84	72.04	1.02
9	171.70	38.87	192.22	74.82	0.89
10	103.28	33.75	158.59	74.13	0.65
12	92.09	62.74	115.87	56.46	0.79
16	43.77	72.22	47.20	35.93	0.93
24	33.72	73.36	29.02	58.10	1.16
32	17.69	64.29	17.24	89.91	1.03
40	10.09	101.51	8.80	110.64	1.15
48	9.15	102.01	9.02	132.59	1.01
72	1.40	146.78	1.56	158.64	0.90

**Figure A2-2. Mean Plasma Mesalamine, 5-ASA Concentrations for Apotex's Balsalazide Disodium Capsules, 750 mg and Salix's Colazal<sup>®</sup> Capsules, 750 mg - Single-Dose Re-Dosing Fasting Study (N =5)**

PLASMA 5-AMINOSALICYCLIC ACID LEVELS  
 BALSALAZIDE DISODIUM CAPSULES, 750 MG, ANDA #77-883  
 UNDER FASTED CONDITIONS (RE-DOSING)  
 DOSE = 3 X 750 MG TABLET



**Reviewer's Comments:** (on pharmacokinetic analysis)

1. The firm assayed the plasma concentration for the parent compound, balsalazide and its active metabolite, mesalamine (5-ASA). The firm provided the plasma profiles for balsalazide and mesalamine.
2. The firm enrolled four (4) additional subjects along with Subject No. 34 in the re-dosing fasting study.
3. The *redose* data confirmed that the original data obtained for Subject No. 34 was aberrant and supported the exclusion of this subject from the fasting study analysis. The reviewer also identified Subject No. 78 as having aberrant plasma mesalamine concentrations. However, the firm did not identify this particular subject as having aberrant plasma mesalamine concentrations and was not included in the re-dosing study.
4. The firm did not provide a standard operation procedure (SOP) for selecting suspected subjects with anomalous pharmacokinetic parameters for re-dosing study.

**Conclusion:** The single-dose, re-dosing fasting bioequivalence study is incomplete.

**B. Formulation****Table B-1. Formulation for Balsalazide Disodium Capsules, 750 mg manufactured by Apotex Inc.****Table 5. Formulation Data**

Ingredient	Amount (mg)/Capsule 750 mg	Amount (%) 750 mg Capsule
<b>Core</b>		
Balsalazide Disodium Dihydrate	750	99.3
Colloidal Silicon Dioxide	(b) (4)	(b) (4)
Magnesium Stearate	(b) (4)	-
Hard Gelatin Capsule - white/white opaque	(b) (4)	-
<b>Coating</b>		
None	N/A	-
Total	755	100
(b) (4)		

\*Detailed composition of Capsules and Printing Ink can be found in module section 3.2.P.4 (Control of Excipients).

<sup>1</sup>: Table is provided by the firm.

**C. Product Description****Table C-1. Product Description of Balsalazide Disodium Capsules, 750 mg manufactured by Apotex Inc., Canada**

<b>Capsule</b>	<b>Color:</b>	White
<b>Imprint/Emboss/ Engraving:</b>	The cap is imprinted with "APO" in red ink. The body is imprinted with "8750" in red ink.	
<b>Other pertinent details:</b>	Hard-gelatin	

**Table C-2. Product Description of Colazal<sup>®</sup> Capsules, 750 mg manufactured by Salix Pharmaceuticals, Inc., USA**

<b>Capsule</b>	<b>Color:</b>	Beige
<b>Imprint/Emboss/Engraving:</b>	The cap is imprinted with “CZ” in black ink. The body has no inscription.	
<b>Other pertinent details:</b>	Hard-gelatin	

## D. In Vitro Dissolution

**Table D-1. Summary of *In Vitro* Dissolution Testing Studies for Apotex's Balsalazide Disodium 750 mg Capsules and Salix's Colazal® 750 mg Capsules**

Study Reference No.	Product ID (Batch)	Dosage Form	Conditions	No. of Dosage Units	Collection Times									Study Report Location
					5	10	15	20	30	45	60*	80*	120*	
50256	Balsalazide Disodium Capsules (043-11)	750mg	<b>Medium:</b> Potassium Phosphate Buffer <b>Apparatus:</b> USP Apparatus 2 (Paddles) <b>Speed:</b> 50 rpm	12	23	62	85	95	99	100	100	100	100	In this Amendment
50256	Colazal® Tablets (311208)	750mg	<b>Wavelength:</b> 357nm (background correction at 590nm) <b>Temperature:</b> 37±0.5°C	12	21	24	81	93	102	103	103	103		

†: Table provided by the firm.

\*: Values added to the table by reviewer.

**Table D-2. Summary of *In Vitro* Dissolution Testing Data for Apotex’s Balsalazide Disodium 750 mg Capsules<sup>1</sup>**

**APOTEX INC.**

**INVESTIGATION OF THE RATE OF DRUG RELEASE  
BALSALAZIDE DISODIUM CAPSULES 750 MG**

**Table 1: Balsalazide Disodium Capsules Apotex (L) 043-11**

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												14-32	23	26
10	(b) (4)												53-71	62	10
15	(b) (4)												75-97	85	8
20	(b) (4)												88-101	95	4
30	(b) (4)												96-102	99	2
45	(b) (4)												96-104	100	2
60	(b) (4)												96-104	100	2
80	(b) (4)												96-104	100	2
120	(b) (4)												96-104	100	3

<sup>1</sup>: Table provided by firm in comparative dissolution study report.

**Table D-3. Summary of *In Vitro* Dissolution Testing Data for Salix's Colazal<sup>®</sup> 750 mg Capsules<sup>1</sup>**

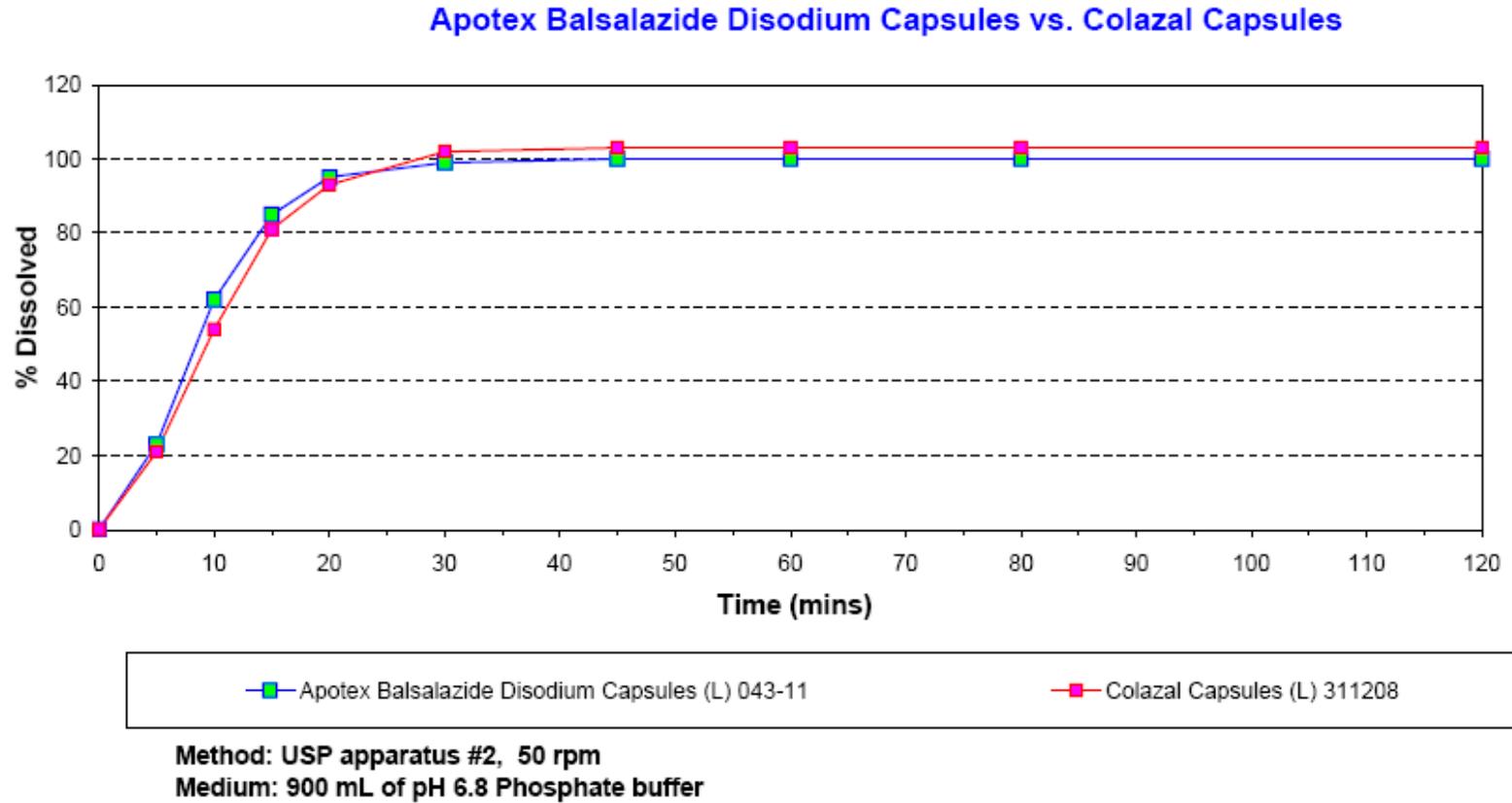
**APOTEX INC.**

**INVESTIGATION OF THE RATE OF DRUG RELEASE  
 BALSALAZIDE DISODIUM CAPSULES 750 MG**

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												16-24	21	12
10	(b) (4)												47-60	54	8
15	(b) (4)												65-89	81	10
20	(b) (4)												81-103	93	7
30	(b) (4)												96-109	102	3
45	(b) (4)												97-109	103	3
60	(b) (4)												97-109	103	3
80	(b) (4)												97-109	103	3
120	(b) (4)												97-109	103	3

<sup>1</sup>: Table provided by firm in comparative dissolution study report.

**Figure D-1. *In Vitro* Dissolution Comparative Rate of Drug Release for Apotex’s Balsalazide Disodium 750 mg Capsules and Salix’s Colazal® 750 mg Capsules<sup>1</sup>**



<sup>1</sup>: Figure provided by firm in comparative dissolution study report.

**E. Consult Reviews**

None.

**F. Attachments**

None.

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-883

APPLICANT: Apotex Inc.

DRUG PRODUCT: Balsalazide Disodium Capsules, 750 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The DBE agrees with your decision to conduct a re-dosing study based on a hypothesis that Subject No. 34 showed aberrant mesalamine plasma concentrations during study #50256. However, the DBE noted that, based on the test/reference {AUC, or Cmax} ratios, Subject No. 78 may have also had an aberrant response. Thus, Subject no. 78 should have been re-dosed as well but was not included in the re-dosing study. Therefore, Subject No. 78 could have been excluded from the re-dosing study with bias toward favorable bioequivalence outcome. You are advised to re-dose Subject No.78 with several subjects (control group) chosen at random from the same study (study #50256). Alternatively, you may conduct a new fasting bioequivalence study. Therefore, the fasting BE study and the re-dosing study are incomplete.
2. Please provide a SOP for selecting suspected subjects with anomalous/outlying pharmacokinetic parameters for re-dosing study.
3. Please provide the bioanalytical summary tables for balsalazide and mesalamine for fasting BE Study No. 50256.

For balsalazide, the following tables are missing from Section 16.2.51 of the Bioanalytical Report:

Table 2A. Plasma EDTA K3 Balsalazide Concentrations (ng/mL) in Humans

Table 2B. Plasma EDTA K3 Balsalazide Concentrations (ng/mL) in Humans

Table 3. Repeat Analysis Results for Balsalazide in Human Plasma EDTA K3

Table 4. Summary of Study Sample Reassays

Table 5A and 5B. Summary of Analytical Runs  
Table 6. Calibration Curve Parameters for Balsalazide  
Calibration Standards in Human Plasma EDTA K3  
Table 7. Analytical Performance: Back-Calculated  
Concentration (ng/mL) of Balsalazide Calibration Curve  
Standard in (Human) (Plasma EDTA K3)  
Table 8. Analytical Performance of Balsalazide  
Quality Control Samples in Human Plasma EDTA K3

For mesalamine, the following tables are missing from  
Section 16.2.5.1 of the Bioanalytical Report:

Table 10A. Plasma EDTA K3 5-ASA Concentrations  
(ng/mL) in Humans  
Table 10B. Plasma EDTA K3 5-ASA Concentrations  
(ng/mL) in Humans  
Table 11. Repeat Analysis Results for 5-ASA in  
Human Plasma EDTA K3  
Table 12. Summary of Study Sample Reassays  
Table 13A and 13B. Summary of Analytical Runs  
Table 14. Calibration Curve Parameters for 5-ASA  
Calibration Standards in Human Plasma EDTA K3  
Table 15. Analytical Performance: Back-Calculated  
Concentration (ng/mL) of 5-ASA Calibration Curve Standard  
in (Human) (Plasma EDTA K3)  
Table 16. Analytical Performance of Balsalazide  
Quality Control Samples in Human Plasma EDTA K3

4. For the re-dosing fasting study No. 60045, please provide the bioanalytical method validation summary tables for balsalazide and mesalamine.
5. Please acknowledge the following dissolution method and specification.

The dissolution testing should be conducted in phosphate buffer, pH 6.8 at 37°C ± 0.5°C using apparatus II (Paddles) at 50 rpm with sinkers. The test product should meet the following specification:

Not less than  $\frac{(b)}{(4)}\%$  (Q) of the labeled amount of balsalazide in the dosage form is dissolved in 30 minutes

6. The labeling for the reference listed drug (RLD), Colazal<sup>®</sup> (balsalazide disodium) capsules, 750 mg has been changed to include statements about the effect of food on

absorption or administration of the capsule product. As per the CDER Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance for Industry (posted January 31, 2003) the FDA recommends a bioequivalence study under fed conditions for all orally administered immediate-release drug products if the RLD label makes statements about the effect of food on absorption or administration.

Therefore, please perform a single dose, two-way crossover fed in-vivo bioequivalence study comparing Balsalazide Disodium Capsules, 750mg to the reference listed drug, Colazal ® Capsules 750mg.

Please measure plasma concentrations of both balsalazide (parent) and mesalamine (metabolite) using an appropriate assay. For an acceptable fed bioequivalence study, the 90% confidence intervals of the test/reference geometric mean ratios for AUC and Cmax of both balsalazide and mesalamine should fall within the range of 0.8 to 1.25.

Sincerely yours,

*(See appended electronic signature page)*

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

CC: 77-883

BIOEQUIVALENCY – IC

Submission date: October 15, 2005

1. **FASTING STUDY (STF)**

Strength: 750 mg

**Outcome: IC**

Clinical Site: SFBC Anapharm  
5160 Boul. Décarie, Suite 800  
Montreal (Quebec), Canada H3X 2H9

Analytical Site: SFBC Anapharm 2050  
Boul. René-Lévesque  
Ouest, Sainte-Foy (Québec), Canada G1V 2K8

2. **RE-DOSING FASTING STUDY (STP)**

Strength: 750 mg

**Outcome: IC**

Clinical and Analytical Sites: Same as the fasting study

3. **STUDY AMENDMENT (STA)**

October 16, 2006

Strength: 750 mg

**Outcome: IC**

Dissolution Amendment – Dissolution testing method and data

Outcome Decisions: **IC**

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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April Braddy  
12/8/2006 02:40:55 PM  
BIOPHARMACEUTICS

Moheb H. Makary  
12/8/2006 02:47:29 PM  
BIOPHARMACEUTICS

Barbara Davit  
12/8/2006 02:56:44 PM  
BIOPHARMACEUTICS

## DIVISION OF BIOEQUIVALENCE REVIEW

<b>ANDA No.</b>	77-883
<b>Drug Product Name</b>	Balsalazide Disodium Capsules
<b>Strength(s)</b>	750 mg
<b>Applicant Name</b>	Apotex, Inc.
<b>Address</b>	150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
<b>Applicant's Point of Contact</b>	Kiran Krishan, Manager, Regulatory Affairs, Apotex Corp., 2400 N. Commerce Parkway Suite 400, Weston, FL 33326
<b>Contact's Telephone Number</b>	954-349-4217
<b>Contact's Fax Number</b>	954-349-4233
<b>Original Submission Date(s)</b>	June 15, 2006 (Refuse to File: November 03, 2005)
<b>Submission Date(s) of Amendment(s) Under Review</b>	August 22, 2007 (Fasting and fed BE studies) September 21, 2007 (Telephone amendment)
<b>Reviewer</b>	April C. Braddy, Ph.D.
<b>Study Number (s)</b>	Fasting (STF)
<b>Study Type (s)</b>	70038
<b>Strength (s)</b>	3 x 750 mg Capsules
<b>Clinical Site</b>	Anapharm
<b>Clinical Site Address</b>	2050, boul. René-Lévesque Ouest, Québec (Québec), Canada G1V 2K8
<b>Analytical Site</b>	Anapharm
<b>Analytical Site Address</b>	2500, rue Einstein, Québec (Québec), Canada, G1P 0A2
<b>Study Number (s)</b>	Fed (STP)
<b>Study Type (s)</b>	60652
<b>Strength (s)</b>	3 x 750 mg Capsules
<b>Clinical Site</b>	Anapharm
<b>Clinical Site Address</b>	2050, boul. René-Lévesque Ouest, Québec (Québec), Canada G1V 2K8
<b>Analytical Site</b>	Anapharm
<b>Analytical Site Address</b>	2050, boul. René-Lévesque Ouest, Québec (Québec), Canada G1V 2K8

## Review of an Amendment

### 1 EXECUTIVE SUMMARY

On August 22, 2007, the firm submitted an amendment to its application for Balsalazide Disodium Capsules, 750 mg. The amendment was in response to the deficiency letter sent to the firm on December 12, 2006 from the Division of Bioequivalence (DBE). The firm's original application was incomplete due to several significant clinical and bioanalytical deficiencies in its fasting BE study No. 50256 and redosing study No. 60045, along with incomplete dissolution testing because the firm had not acknowledged and accepted the FDA-recommended dissolution method for its test product (see [Section 4.4. Detailed Regulatory History](#)). In addition, the labeling for the reference product, Colazal<sup>®</sup> (balsalazide disodium) Capsules, by Salix Pharmaceuticals, was amended to include statements pertaining to food effect on absorption. Therefore, the DBE requested the firm perform a fed BE study as well. The firm addresses all of the deficiencies in this amendment. The firm responses are acceptable and provided below.

This amendment contains the results of the new fasting and fed bioequivalence (BE) studies comparing the firm's test product, Balsalazide Disodium Capsules to the corresponding reference product, Colazal<sup>®</sup> (balsalazide disodium) Capsules, 750 mg. The study design for each of the BE studies was a two-way, crossover study in healthy male and female subjects. Statistical analyses of the plasma concentration data for balsalazide and mesalamine demonstrate bioequivalence in both studies. The firm's fasting and fed BE studies are acceptable. The results are summarized in the tables below.

Balsalazide					Mesalamine				
3 x 750 mg Capsules Fasting Bioequivalence Study No. 70038 N=99 (Male=43 and Female=56) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					3 x 750 mg Capsules Fasting Bioequivalence Study No. 70038 N=98 (Male=42 and Female=56) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	Test	Reference	Ratio	90% C.I.	Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC <sub>0-t</sub> (ng·hr/mL)	1466.49	1461.85	1.00	94.21- 106.82	AUC <sub>0-t</sub> (ng·hr/mL)	2653.49	2604.21	1.02	93.27- 111.31
AUC <sub>∞</sub> (ng·hr/mL)	1568.65	1560.56	1.01	94.64- 106.76	AUC <sub>∞</sub> (ng·hr/mL)	3085.74	3145.77	0.98	88.28- 108.99
C <sub>max</sub> (ng/mL)	449.96	501.40	0.90	83.63- 96.29	C <sub>max</sub> (ng/mL)	240.35	224.21	1.07	97.33- 118.07

Balsalazide					Mesalamine				
3 x 750 mg Capsules Fed Bioequivalence Study No. 60652 N=160 (Male=98 and Female=62) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					3 x 750 mg Capsules Fasting Bioequivalence Study No. 60652 N=157 (Male=96 and Female=61) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	Test	Reference	Ratio	90% C.I.	Parameter (units)	Test	Reference	Ratio	90% C.I.
<b>AUC<sub>0-t</sub></b> (ng·hr/mL)	1586.55	1595.01	0.99	95.71- 103.38	<b>AUC<sub>0-t</sub></b> (ng·hr/mL)	1292.99	1306.58	0.99	91.61- 106.90
<b>AUC<sub>∞</sub></b> (ng·hr/mL)	1758.42	1761.23	1.00	96.13- 103.69	<b>AUC<sub>∞</sub></b> (ng·hr/mL)	1421.52	1439.91	0.99	91.27- 106.78
<b>C<sub>max</sub></b> (ng/mL)	366.27	386.61	0.95	87.15- 102.99	<b>C<sub>max</sub></b> (ng/mL)	71.47	73.74	0.97	89.45- 105.02

The firm has conducted acceptable comparative dissolution testing on its test product using the FDA-recommended dissolution method. Also, as previously stated in the original submission and DBE dissolution review, the firm conducted dissolution testing using 900 mL in four (4) different medias: (1) 0.1N HCl, (2) pH 4.5 buffer, (3) pH 6.8 buffer, and (4) pH 7.4 buffer with Apparatus I (Basket) at 100 rpm (V:\DIVISION\BIO\Bio Temporary-Ra\77883D0805.doc and Division of System Files v 2.0. ANDA #77-883. Bioequivalence Review. N 077883 N 000 AB 16-Oct-2006 (03-Nov-2005).

On August 22, 2007, the firm acknowledged the FDA-recommended dissolution method and specification.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is acceptable with no deficiencies.

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### 3 SUBMISSION SUMMARY

#### 3.1 Drug Product Information

<b>Test Product</b>	Balsalazide Disodium Capsules, 750 mg
<b>Reference Product</b>	Colazal <sup>®</sup> (balsalazide disodium) Capsules, 750 mg
<b>RLD Manufacturer</b>	Salix Pharmaceuticals
<b>NDA No.</b>	20-610
<b>RLD Approval Date</b>	July 18, 2000
<b>Indication</b>	It is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

#### 3.2 PK/PD Information<sup>1</sup>

<b>Bioavailability</b>	Systemic absorption of balsalazide is minimal and variable in healthy subjects.	
<b>Food Effect</b>	Under fed (high-fat meal) conditions, the C <sub>max</sub> and AUC for balsalazide and its metabolites decrease, whereas the T <sub>max</sub> is prolonged compared to fasted conditions in healthy subjects.	
<b>Tmax</b>	<b>Fasted Conditions</b> Balsalazide: 0.8 ± 0.85 5-ASA: 8.2 ± 1.98	<b>Fed Conditions</b> Balsalazide: 1.2 ± 1.11 5-ASA: 22.0 ± 8.23
<b>Metabolism</b>	Balsalazide undergoes extensive colorectal metabolism, the bacterial azoreductases cleave the compound to release mesalamine (5-aminosalicylic acid, 5-ASA), the therapeutically active portion, and 4-amino-beta-alanine. The compounds 5-ASA and 4-amino-beta-alanine are further metabolized to N-acetylated metabolites.	
<b>Excretion</b>	<p>The major route of elimination is via the feces. Balsalazide and its metabolites have been identified in plasma, urine and feces.</p> <ul style="list-style-type: none"> <li>Following single-dose administration of 2.25 g COLAZAL (three 750 mg capsules) under fasting conditions in healthy subjects, mean urinary recovery of balsalazide, 5-ASA, and N-Ac-5-ASA was 0.20%, 0.22% and 10.2%, respectively.</li> <li>In a multiple-dose study in healthy subjects receiving a COLAZAL dose of two 750 mg capsules twice daily (3 g/day) for 10 days, mean urinary recovery of balsalazide, 5-ASA, and N-Ac-5-ASA was 0.1%, 0%, and 11.3%, respectively. During this study, subjects received their morning dose 0.5 hours after being fed a standard meal, and subjects received their evening dose 2 hours after being fed a standard meal.</li> <li>In a study with 10 healthy volunteers, 65% of a single 2.25-g dose of COLAZAL was recovered as 5-ASA, 4-aminobenzoyl-β-alanine, and the N-acetylated metabolites in feces, while &lt;1% of the dose was recovered as parent compound.</li> </ul>	

<sup>1</sup> 1. External Database: Online-Drugs@FDA database. (2007). [Drugs@FDA](#). Search: Colazal . Label Information. Label approved on 12/20/2006. Last accessed: 09/24/2007.

2. Online-Clinical Pharmacology (2007). <http://cpip.gsm.com> . World-Class Drug Information: Monographs: Colazal. Last updated: 02/13/2007. Last accessed: 09/24/2007

	<ul style="list-style-type: none"> <li>In a study that examined the disposition of balsalazide in patients who were taking 3-6 g of COLAZAL daily for more than 1 year and who were in remission from ulcerative colitis, less than 1% of an oral dose was recovered as intact balsalazide in the urine. Less than 4% of the dose was recovered as 5-ASA, while virtually no 4-aminobenzoyl-β-alanine was detected in urine. The mean urinary recovery of N-Ac-5-ASA and N-acetyl-4-aminobenzoyl-β-alanine comprised &lt;16% and &lt;12% of the balsalazide dose, respectively. No fecal recovery studies were performed in this population.</li> </ul>
<b>Half-life</b>	Cannot be determined because of large intersubject variability
<b>Drug Specific Issues (if any)</b>	<ul style="list-style-type: none"> <li>Exacerbation of the symptoms of ulcerative colitis was reported in both adult and pediatric patients. Observe patients closely for worsening of these symptoms while on treatment.</li> <li>Prolonged gastric retention of COLAZAL may occur in patients with pyloric stenosis.</li> </ul>

### 3.3 OGD Recommendations for Drug Product

<b>Number of studies recommended:</b>	2, fasting and fed
---------------------------------------	--------------------

<b>1.</b>	<b>Type of study:</b>	Fasting
	<b>Design:</b>	Single-dose, two-treatment, two-period crossover in-vivo
	<b>Strength:</b>	750 mg
	<b>Subjects:</b>	Normal healthy males and females, general population
	<b>Additional Comments:</b>	Dose: 3 x 750 mg Capsules

<b>2.</b>	<b>Type of study:</b>	Fed
	<b>Design:</b>	Single-dose, two-treatment, two-period crossover in-vivo
	<b>Strength:</b>	750 mg
	<b>Subjects:</b>	Normal healthy males and females, general population
	<b>Additional Comments:</b>	Dose: 3 x 750 mg Capsules

<b>Analytes to measure (in plasma/serum/blood):</b>	Balsalazide and Mesalamine (in plasma)
<b>Bioequivalence based on:</b>	90% CI: LAUC <sub>T</sub> , LAUC <sub>I</sub> , and LC <sub>max</sub>
<b>Waiver request of in-vivo testing:</b>	None
<b>Source of most recent recommendations:</b>	Controlled Correspondence No. 07-0592. Submission date: April 13, 2007. <a href="\\cdsnas\OGDS6\CONTROLS\2007-docs\07-0592.pdf">\\cdsnas\OGDS6\CONTROLS\2007-docs\07-0592.pdf</a>
<b>Summary of OGD or DBE History (for details, see Appendix 4.4):</b>	According to the <a href="#">Electronic Orange Book</a> (current through August 2007), <sup>2</sup> there are currently no approved generic products on the market for Balsalazide Disodium Capsules, 750 mg.

<sup>2</sup> Last accessed: 09/24/2007.

### 3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	--
In vitro dissolution	Yes	1
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments*	Yes	2

\* This submission is an amendment and contains an amendment as well.

### 3.5 Pre-Study Bioanalytical Method Validation

#### A. Balsalazide<sup>3</sup>

Information Requested	Data
70038 Fast 60652 Fed	
Bioanalytical method validation report location	Annex of bioanalytical report section 16.2.5.3
Analyte	Balsalazide
Internal standard (IS)	(b) (4)
Method description	This method involves the extraction of Balsalazide and the internal standard from human EDTA plasma by a (b) (4) solid phase extraction cartridges. Samples are kept frozen at -20°C prior to analysis and 100µL of human EDTA plasma was used for analysis.
Limit of quantitation (ng/mL)	1.00
Average recovery of drug (%)	80.59 to 84.83
Average recovery of IS (%)	78.83
Standard curve concentrations (ng/mL)	1.00 to 500.40
QC concentrations (ng/mL)	QC1: 3.02 QC2: 150.84 QC3: 351.96
QC Intraday precision range (%)	3.04 to 7.61
QC Intraday accuracy range (%)	98.92 to 105.78
QC Interday precision range (%)	3.22 to 5.47
QC Interday accuracy range (%)	98.53 to 100.85
Bench-top stability (hrs)	23 hours at room temperature
Stock stability (days)	Analyte: 430 days at -20°C IS: 196 days at -20°C
Processed stability (hrs)	96 hours at room temperature
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	195 days at -20°C (EDTA K <sub>3</sub> ), 76 days at -20°C (EDTA K <sub>2</sub> ) 5 days at -80°C
Dilution integrity	QC3 diluted 1/2: CV (%) 3.10 Nominal (%) 100.56 DQC diluted 1/20: CV (%) 2.48 Nominal (%) 99.23
Selectivity	No interfering peaks noted in blank plasma samples

<sup>3</sup> The tables are provided by the firm.

## B. Mesalamine (5-aminosalicylic acid, 5-ASA)

Information Requested 70038 Fast	Data
Bioanalytical method validation report location	Annex 1 of bioanalytical report section 16.2.5.3
Analyte	5-ASA
Internal standard (IS)	(b) (4)
Method description	This method involves the extraction of 5-ASA and the internal standard from human EDTA plasma by a (b) (4) solid phase extraction cartridges. Samples are kept frozen at -80°C prior to analysis and 0.400 mL of human EDTA plasma was used for analysis.
Limit of quantitation (ng/mL)	1.01 2.00
Average recovery of drug (%)	73.40 to 81.32 70.04 to 71.92
Average recovery of IS (%)	72.71 72.12
Standard curve concentrations (ng/mL)	1.00 to 607.18
QC concentrations (ng/mL)	QC1: 3.01 QC2: 180.58 QC3: 421.34
QC Intraday precision range (%)	0.80 to 2.12
QC Intraday accuracy range (%)	95.99 to 109.17
QC Interday precision range (%)	2.06 to 2.94
QC Interday accuracy range (%)	99.49 to 107.68
Bench-top stability (hrs)	15 hours at room temperature
Stock stability (days)	Analyte: 167 days at -20°C (acidified methanol) at -80°C: to be determine IS: 167 days at -20°C (acidified methanol) at -80°C: to be determine
Processed stability (hrs)	75 hours at room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	186 days at -80°C
Dilution integrity	QC2 diluted 1/2: CV (%) 1.19 Nominal (%) 91.39 DQC diluted 1/20: CV (%) 0.72 Nominal (%) 94.07
Selectivity	No interfering peaks noted in blank plasma samples

Information Requested 60652 Fed	Data
Bioanalytical method validation report location	Annex 1 of bioanalytical report section 16.2.5.3
Analyte	5-ASA
Internal standard (IS)	(b) (4)
Method description	This method involves the extraction of 5-ASA and the internal standard from human EDTA plasma by a (b) (4) solid phase extraction cartridges. Samples are kept frozen at -80°C prior to analysis and 0.400 mL of human EDTA plasma was used for analysis.
Limit of quantitation (ng/mL)	1.01
Average recovery of drug (%)	73.40 to 81.32
Average recovery of IS (%)	72.71
Standard curve concentrations (ng/mL)	1.00 to 607.18
QC concentrations (ng/mL)	QC1: 3.01 QC2: 180.58 QC3: 421.34
QC Intraday precision range (%)	0.80 to 2.12
QC Intraday accuracy range (%)	95.99 to 109.17
QC Interday precision range (%)	2.06 to 2.94
QC Interday accuracy range (%)	99.49 to 107.68
Bench-top stability (hrs)	15 hours at room temperature
Stock stability (days)	Analyte: 167 days at -20°C (acidified methanol) at -80°C: to be determine IS: 167 days at -20°C (acidified methanol) at -80°C: to be determine
Processed stability (hrs)	75 hours at room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	186 days at -80°C
Dilution integrity	QC2 diluted 1/2: CV (%) 1.19 Nominal (%) 91.39 DQC diluted 1/20: CV (%) 0.72 Nominal (%) 94.07
Selectivity	No interfering peaks noted in blank plasma samples

Analytes	Balsalazide	5-ASA
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes

**Comments on the Pre-Study Method Validation:**

Acceptable.

### 3.6 In Vivo Studies

**Table 1. Summary of all in vivo Bioequivalence Studies<sup>3</sup>**

#### A. Balsalazide

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/mL)	Tmax* (hr)	AUC0-t (ng-h/mL)	AUC∞ (ng-h/mL)	T½ (hr)	Kel (hr-1)	
70038	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal® (Reference) Following a 2250 mg Dose in Healthy Subjects Under Fasting Conditions	Randomized single-dose crossover	Balsalazide Disodium (3 x 750 mg capsules p.o.) [Lot/Batch No: 043-11]  Colazal® (3 x 750 mg capsules p.o.) [Lot/Batch No.: 320195]	99 completing (43 M/56 F) Healthy subjects Age (years) = 36 (18-55) Data set for statistical analysis = 99	498.34 (259.16)  551.99 (267.41)	0.500 (0.333-6.10)  0.333 (0.333-1.50)	1605.32 (709.86)  1590.10 (722.41)	1712.56 (747.59)  1693.58 (764.06)	30.28 (7.57)  29.62 (6.61)	0.0249 (0.0124)  0.0250 (0.0082)	5.3.1.2
60652	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal (Reference) Following a 2250 mg Dose in Healthy Subjects Under Fed Conditions	Randomized single-dose crossover	Balsalazide Disodium (3 x 750 mg capsules p.o.) [Lot/Batch No: 043-11]  Colazal® (3 x 750 mg capsules p.o.) [Lot/Batch No.: 6E0002]	160 completing (98 M/62 F) Healthy subjects Age (years) = 37 (18-55) Data set for statistical analysis = 160	524.75 (555.52)  538.64 (497.31)	0.500 (0.250-6.00)  0.500 (0.250-6.00)	1812.26 (1122.66)  1796.61 (907.88)	1983.75 (1145.35)  1961.40 (928.73)	22.60 (6.84)  21.52 (7.13)	0.0343 (0.0134)  0.0364 (0.0141)	5.3.1.2

\* Tmax is presented as median (range)

## B. Mesalamine (5-aminosalicylic acid, 5-ASA)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/mL)	Tmax* (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
70038	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal® (Reference) Following a 2250 mg Dose in Healthy Subjects Under Fasting Conditions	Randomized single-dose crossover	Balsalazide Disodium (3 x 750 mg capsules p.o.) [Lot/Batch No: 043-11] Colazal® (3 x 750 mg capsules p.o.) [Lot/Batch No.: 320195]	99 completing (42 M/56 F) Healthy subjects Age (years) = 36 (18-55) Data set for statistical analysis = 98	293.60 (193.90) 277.45 (193.04)	10.0 (6.00-36.0) 9.03 (6.00-48.0)	3220.46 (2074.62) 3227.64 (2032.89)	3657.12 (2185.00) 3743.87 (2190.18)	12.17 (7.63) 12.83 (15.68)	0.0839 (0.0545) 0.0901 (0.0800)	5.3.1.2
60652	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal (Reference) Following a 2250 mg Dose in Healthy Subjects Under Fed Conditions	Randomized single-dose crossover	Balsalazide Disodium (3 x 750 mg capsules p.o.) [Lot/Batch No: 043-11] Colazal® (3 x 750 mg capsules p.o.) [Lot/Batch No.: 6E0002]	160 completing (96 M/61 F) Healthy subjects Age (years) = 37 (18-55) Data set for statistical analysis = 157	93.44 (76.05) 94.85 (80.41)	19.0 (8.00-60.0) 23.0 (6.00-60.0)	1636.18 (1102.48) 1669.46 (1204.65)	1805.15 (1256.39) 1840.90 (1320.01)	11.07 (8.37) 10.37 (8.32)	0.1225 (0.1470) 0.1219 (0.1271)	5.3.1.2

\* Tmax is presented as median (range)

**Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer**

**A. Balsalazide**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Balsalazide					
Fasting Bioequivalence Study No. 700038 (N=99)					
Parameter	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (ng·h/mL)	1466.49	1461.85	1.00	94.21	106.82
AUC <sub>∞</sub> (ng·h/mL)	1568.65	1560.56	1.01	94.64	106.76
C <sub>max</sub> (ng/mL)	449.96	501.40	0.90	83.63	96.29
Fed Bioequivalence Study No. 60652 (N=160)					
Parameter	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (ng·h/mL)	1586.55	1595.01	0.99	95.71	103.38
AUC <sub>∞</sub> (ng·h/mL)	1758.42	1761.23	1.00	96.13	103.69
C <sub>max</sub> (ng/mL)	366.27	386.61	0.95	87.15	102.99

**B. Mesalamine (5-aminosalicylic acid, 5-ASA)**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals 5-ASA					
Fasting Bioequivalence Study No. 700038 (N=98)					
Parameter	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (ng·h/mL)	2653.49	2604.21	1.02	93.27	111.31
AUC <sub>∞</sub> (ng·h/mL)	3085.74	3145.77	0.98	88.28	108.99
C <sub>max</sub> (ng/mL)	240.35	224.21	1.07	97.33	118.07
Fed Bioequivalence Study No. 60652 (N=157)					
Parameter	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (ng·h/mL)	1292.99	1306.58	0.99	91.61	106.90
AUC <sub>∞</sub> (ng·h/mL)	1421.52	1439.91	0.99	91.27	106.78
C <sub>max</sub> (ng/mL)	71.47	73.74	0.97	89.45	105.02

**Table 3. Reanalysis of Study Samples<sup>3</sup>**

**A. Balsalazide**

*Fasting BE study No. 70038*

Study No. 70038OKC Randomized, Open-Label, 2 Way-Crossover, Bioequivalence Study Of Balsalazide 750 mg Capsule And Colazal (Reference) Following A 2250 mg Dose In Healthy Subjects Under Fasting Conditions Additional information in tables 3 and 4 of bioanalytical report								
Balsalazide								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	7	10	0.17	0.24	7	10	0.17	0.24
Incomplete analysis	6	4	0.14	0.10	6	4	0.14	0.10
Sample concentration above upper limit of quantification	80	116	1.92	2.78	80	116	1.92	2.78
Sample reanalyzed to obtain confirming value	6	8	0.14	0.19	6	8	0.14	0.19
Rejected sample dilution	6	1	0.14	0.02	6	1	0.14	0.02
Total	105	139	2.52	3.34	105	139	2.52	3.34

1 - If no repeats were performed for pharmacokinetic reasons, insert “0.0.”

<sup>T</sup> Balsalazide disodium 750 mg capsule (3 x 750 mg capsules per period), Apotex Inc., (Canada) Lot: 043-11

<sup>R</sup> Balsalazide disodium 750 mg capsule (Colazal®), (3 x 750 mg capsules per period), Salix Pharmaceuticals, Inc., (USA) Lot: 320195

Fed BE study No. 60652

<b>Study No. 60652NYV</b> <b>Randomized, Open-Label, 2 Way-Crossover, Bioequivalence Study Of Balsalazide 750 mg Capsule And Colazal (Reference)</b> <b>Following A 2250 mg Dose In Healthy Subjects Under Fed Conditions</b> <b>Additional information in tables 3 and 4 of bioanalytical report</b>								
<b>Balsalazide</b>								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	8	9	0.13	0.14	8	9	0.13	0.14
Incomplete analysis	3	11	0.05	0.17	3	11	0.05	0.17
Sample concentration above upper limit of quantification	177	197	2.77	3.08	177	197	2.77	3.08
Sample reanalyzed to obtain confirming value	1	4	0.02	0.06	1	3	0.02	0.05
Sample repeated or reinjected by error	4	0	0.06	0.00	0	0	0.00	0.00
Total	193	221	3.02	3.46	189	220	2.97	3.44

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

<sup>T</sup> Balsalazide disodium 750 mg capsule (3 x 750 mg capsules per period), Apotex Inc., (Canada) Lot: 043-11

<sup>R</sup> Balsalazide disodium 750 mg capsule (Colazal), (3 x 750 mg capsules per period), Salix Pharmaceuticals, Inc., (USA) Lot: 6E0002

**B. Mesalamine (5-aminosalicylic acid, 5-ASA)**

*Fasting BE study No. 70038*

Study No. 70038OKD Randomized, Open-Label, 2 Way-Crossover, Bioequivalence Study Of Balsalazide 750 mg Capsule And Colazal (Reference) Following A 2250 mg Dose In Healthy Subjects Under Fasting Conditions Additional information in tables 10 and 11 of bioanalytical report 5-ASA								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.00	0.00	0	0	0.00	0.00
Poor Chromatography	4	3	0.12	0.09	4	3	0.12	0.09
Unacceptable internal standard response	7	6	0.21	0.18	7	6	0.21	0.18
Incomplete analysis	3	6	0.09	0.18	3	6	0.09	0.18
Sample concentration above upper limit of quantification	38	26	1.13	0.77	38	26	1.13	0.77
Sample concentration above or below modified calibration curve range	63	60	1.87	1.79	63	60	1.87	1.79
Sample repeated or reinjected by error	7	4	0.21	0.12	0	0	0.00	0.00
Total	122	105	3.63	3.12	115	101	3.42	3.01

<sup>1</sup> - If no repeats were performed for pharmacokinetic reasons, insert “0.0.”

<sup>T</sup> Balsalazide disodium 750 mg capsule (3 x 750 mg capsules per period), Apotex Inc., (Canada) Lot: 043-11

<sup>R</sup> Balsalazide disodium 750 mg capsule (Colazal®), (3 x 750 mg capsules per period), Salix Pharmaceuticals, Inc., (USA) Lot: 320195

Study No. 60652OSA Randomized, Open-Label, 2 Way-Crossover, Bioequivalence Study Of Balsalazide 750 mg Capsule And Colazal (Reference) Following A 2250 mg Dose In Healthy Subjects Under Fed Conditions Additional information in tables 10 and 11 of bioanalytical report								
5-ASA								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.00	0.00	0	0	0.00	0.00
Poor Chromatography	78	83	0.87	0.93	78	83	0.87	0.93
Unacceptable internal standard response	61	82	0.68	0.92	61	82	0.68	0.92
Incomplete analysis	20	24	0.22	0.27	20	24	0.22	0.27
Sample concentration above upper limit of quantification	195	184	2.18	2.06	195	184	2.18	2.06
Sample concentration above or below modified calibration curve range	7	8	0.08	0.09	7	8	0.08	0.09
Sample reanalyzed to obtain confirming value	7	8	0.08	0.09	1	4	0.01	0.04
Rejected sample dilution	12	22	0.13	0.25	12	22	0.13	0.25
Sample repeated or reinjected by error	1	2	0.01	0.02	0	0	0.00	0.00
Sample stability exceeding validation data	56	60	0.63	0.67	0	0	0.00	0.00
Total	437	473	4.88	5.28	374	407	4.18	4.55

<sup>1</sup> - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

<sup>T</sup> Balsalazide disodium 750 mg capsule (3 x 750 mg capsules per period), Apotex Inc., (Canada) Lot: 043-11

<sup>R</sup> Balsalazide disodium 750 mg capsule (Colazal), (3 x 750 mg capsules per period), Salix Pharmaceuticals, Inc., (USA) Lot: 6E0002

**Did use of recalculated plasma concentration data change study outcome? No**

## Comments from the Reviewer:

### Fasting BE Study No. 70038

1. Ninety-nine (99) healthy, adult male and female subjects completed the fasting BE study. Initially, one-hundred and six (106) subjects were enrolled in the study; however, seven (7) subjects did not complete the study ([Table 8](#)).
2. The one-hundred and six (106) subjects were dosed in three (3) groups. Treatment Group No. 01 consisted of thirty-six (36) subjects (Nos. 01 to 36). Treatment Group No. 02 consisted of thirty-six (36) subjects (Nos. 37 to 72) and Treatment Group No. 03 consisted of thirty-four (34) subjects (Nos. 73 to 106).
3. The firm stated in its clinical report that the study was composed of the three (3) groups due to logistical reasons. **The subjects were dosed at the same clinical site.**
4. Each of the one-hundred and six (106) subjects was recruited from the community at large (Quebec, Canada) and consisted of both male and female subjects. According to their respective genders, the subjects had similar demographic profiles. Also, **all of the subjects were screened prior to the initiation and dosing of Treatment Group No. 01 in Period I of the fasting BE study.** The screening and dosing dates for the subjects enrolled in each group are as follows:

Treatment Group	Screening Dates	Dosing Dates	
		Period I	Period 2
01	03/16/2007 – 03/21/2007	04/01/2007	04/15/2007
02	03/09/2007 – 03/27/2007	04/06/2007	04/20/2007
03	03/12/2007 – 03/28/2007	04/07/2007	04/21/2007

There was six (6) days in between the dosing of Treatment Group No. 01 and 03.

Initially, the firm used a group-by-treatment effect in its statistical model. Based on their statistical results and the high variability of balsalazide and 5-ASA, the firm combined the three (3) groups to compare the test and reference product. The reviewer agrees with the firm in the combining of the data for the three (3) groups to establish bioequivalence between the test and RLD product, based on the following reasons:

- a. According to the FDA's Guidance to Industry, Statistical Approaches to Establishing Bioequivalence issued in 2001, when combining groups for a single analysis, questions should arise (1) when the subjects are studied at different clinical sites, or (2) at the same site but are greatly separated in time (i.e., months). None of the issues are a concern for this study.
- b. Dividing the subjects into three (3) separate groups resulted in three groups which may have been underpowered to demonstrate bioequivalence.

5. Three (3) subjects (Nos. 47, 84 and 92) experienced emesis during the fasting BE study. The time of dosing and onset of the reported adverse event (AE) is provided in the table below:

Subject	Period	Treatment	Dosing Date and Time*	Onset of Emesis Date and Time*	Time Elapsed Between Dosing
47	II	A	04/20/2007 @ 07:20	04/21/2007 @ 02:25	~ 19 hrs
84	I	B	04/07/2007 @ 07:22	04/10/2007 @ 06:15	~ 3 days and 7 min
92	I	B	04/07/2007 @ 07:38	04/08/2007 @ 04:01	~ 21 hrs and 37 min
92	II	A	04/21/2007 @ 07:38	04/21/2007 @ 12:07	~ 4 hrs and 29 min

\* Military Time (HH:MM)

Treatment A – test product, Balsalazide Disodium Capsules, 750 mg (3 x 750 mg Capsules) – Apotex

Treatment B – RLD product, Colazal® (balsalazide disodium) Capsules, 750 mg (3 x 750 mg Capsules) - Salix

For the test product, the median  $T_{max}$  for balsalazide and 5-ASA were 0.50 and 10.0 hrs, respectively, and for the reference product were 0.33 and 9.0 hrs, respectively.

Subject No. 47 experienced emesis within 2x the median  $T_{max}$  for 5-ASA after receiving a single-oral dose of the reference product. Therefore, the firm decided to exclude the data for this subject in BE statistical evaluations for 5-ASA but not balsalazide. Subject No. 92 experienced emesis after receiving the test and reference product. The subject was subsequently withdrawn from the study. Whereas, in Period I subject No. 84 experienced emesis well after 2x the median  $T_{max}$  for balsalazide and 5-ASA after receiving a single-oral dose of the reference product and therefore the data for this subject was included in BE statistical evaluations. The reviewer agrees with the firm's decision concerning all three (3) subjects.

- The 90% confidence intervals for log-transformed  $AUC_T$ ,  $AUC_I$ ,  $C_{max}$  are within the acceptable range of 80-125% for balsalazide (N=99) and 5-ASA (N=98).
- Two-hundred and forty-four (244) balsalazide plasma samples were reanalyzed for analytical reasons during the fasting BE study. The recalculated values for these samples were used in PK and statistical analyses.
- Two-hundred and twenty-seven (227) 5-ASA plasma samples were reanalyzed for analytical reasons during the fasting BE study. The recalculated values for two-hundred and sixteen (216) were used in PK statistical analysis.
- The analytical reasons provided by the firm for reanalysis of balsalazide and 5-ASA plasma samples are acceptable and in accordance with its bioanalytical SOPs.
- The fasting BE study is acceptable.

**Fed BE Study No. 60652**

1. One-hundred and sixty (160) healthy, adult male and female subjects completed the fed BE study. Initially, one-hundred and seventy (170) subjects were enrolled in the study; however, ten (10) of the subjects did not the complete the study ([Table 28](#)).
2. The one-hundred and seventy (170) subjects were dosed in four (4) groups. Treatment Group No. 01 (subject Nos. 01 to 40) and Treatment Group No. 02 (subject Nos. 41 to 80) consisted of 40 subjects each. Treatment Group No. 03 consisted of forty-four (44) subjects (Nos. 81 to 124) and Treatment Group No. 04 consisted of forty-six (46) subjects (Nos. 125 to 172).
3. As in the fasting BE study, the subjects were dosed in the four (4) groups due to logistical reasons. **The subjects were dosed at the same clinical site.**
4. Each of the one-hundred and seventy (170) subjects were recruited from the community at large (Quebec, Canada) and consisted of both male and female subjects. According to their respective genders, the subjects had similar demographic profiles. Also, **all of the subjects were screened prior to the initiation and dosing of Treatment Group No. 01 in Period I of the fed BE study.** The screening and dosing dates for the subjects enrolled in each group are as follows:

Treatment Group	Screening Dates	Dosing Dates	
		Period I	Period 2
01	12/19/2006 – 12/22/2006	01/16/2007	01/30/2007
02	01/03/2007-01/05/2007	01/18/2007	02/01/2007
03	01/04/2007-01/09/2007	01/25/2007	02/08/2007
04	01/05/2007-01/11/2007	01/28/2007	02/11/2007

There was twelve (12) days in between the dosing of Treatment Group No. 01 and 04.

5. For balsalazide and 5-ASA, the firm and reviewer pooled the data from the four (4) groups in BE statistical evaluations. Again, it is possible that by dividing the study into four (4) groups for statistical analysis may result in four (4) groups which have not been adequately powered to demonstrate bioequivalence.
6. During Period I, subject No. 122 reported experiencing emesis approximately 1.75 days (41 hrs) after receiving a single-oral dose of the reference product. Emesis occurred well after 2x the median  $T_{max}$  for balsalazide and 5-ASA. Therefore, the subject was not withdrawn from the study and their data was used in BE statistical evaluations. The firm’s decision is in accordance with the FDA Guidance to Industry, *2003 Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Consideration*, in which the data for the subject who vomits within 2x median  $T_{max}$  should not be included in statistical analysis.

7. The 90% confidence intervals for log-transformed  $AUC_T$ ,  $AUC_1$ ,  $C_{max}$  are within the acceptable range of 80-125% for balsalazide (N=160) and 5-ASA (N=157).
8. Four hundred and fourteen (414) balsalazide plasma samples were reanalyzed for analytical reasons. The recalculated values for four hundred and nine (409) samples were used in PK and statistical analysis.
9. Nine hundred and ten (910) 5-ASA plasma samples were reanalyzed for analytical reasons. The recalculated values for seven hundred and eighty-one (781) samples were used in PK and statistical analysis.
10. The analytical reasons provided by the firm for reanalysis of balsalazide and 5-ASA plasma samples are acceptable and in accordance with its bioanalytical SOPs.
11. The fed BE study is acceptable.

### 3.7 Formulation

Location in appendix	Section 4.2, Page 73
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	<b>FORMULATION ACCEPTABLE</b>
If not acceptable, why?	N/A

### 3.8 In Vitro Dissolution

Location of DBE Dissolution Review	1. V:\DIVISION\BIO\Bio Temporary-Ra\77883D0805.doc 2. Division of System Files v 2.0. ANDA #77-883. Bioequivalence Review. N 077883 N 000 AB 16-Oct-2006 (03-Nov-2005)
Source of Method (USP, FDA or Firm)	FDA
Medium	Phosphate Buffer, pH 6.8
Volume (mL)	900
USP Apparatus type	II (Paddle)
Rotation (rpm)	50
DBE-recommended specifications	NLT <sup>(b)</sup> <sub>(4)</sub> % (Q) in 30 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	N/A
If no, reason why F2 not calculated	
Is method acceptable?	<b>METHOD ACCEPTABLE</b>
If not then why?	--

#### Reviewer's Comments:

1. In the firm's original submission, the firm used its Balsalazide Disodium Capsules Lot No. 043-11(exp. date 06/2007) to conduct its fasting BE study. The bio-lot of the firm's test product had not expired and was therefore used once again to conduct its fasting and fed BE studies. The dissolution testing has previously been determined to be acceptable.
2. In the firm's original submission, reference-listed drug (RLD) product, Colazal<sup>®</sup> (balsalazide disodium) Capsules, Lot No. 311208 was used to conduct its fasting BE study. This lot expired in June 2006. Therefore, the firm conducted its fasting and fed BE studies using Colazal<sup>®</sup> (balsalazide disodium) Capsules, Lot No. 320195 (exp. date 03/2009) and Lot No. 6E0002 (exp. date: 03/2009), respectively. The firm provided the dissolution testing data for both lots of the RLD product.
3. As requested, in the deficiency letter sent to the firm from the Division of Bioequivalence on December 12, 2006, the firm has acknowledged and accepted the

FDA-recommended dissolution method and specification of NLT <sup>(b)</sup><sub>(4)</sub>% (Q) in 30 minutes. Also, as previously stated in the original ANDA and DBE dissolution review, the firm conducted additional dissolution testing using 900 mL in four (4) different medias: (1) 0.1N HCl, (2) pH 4.5 buffer, (3) pH 6.8 buffer, and (4) pH 7.4 buffer with Apparatus I (Basket) at 100 rpm.

4. The firm's dissolution testing is acceptable.

### **3.9 Waiver Request(s)**

None.

### 3.10 Deficiency Comments

None.

### 3.11 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study No. 70038 conducted by the Apotex, Inc. on its Balsalazide Disodium Capsules, 750 mg, Lot No. 043-11 comparing it to Salix Pharmaceuticals' Colazal<sup>®</sup> (balsalazide disodium, USP) Capsules, 750 mg, Lot No. 320195.
2. The Division of Bioequivalence accepts the fed BE study No. 60652 conducted by the Apotex, Inc. on its Balsalazide Disodium Capsules, 750 mg, Lot No. 043-11 comparing it to Salix Pharmaceuticals' Colazal<sup>®</sup> (balsalazide disodium, USP) Capsules, 750 mg, Lot No. 6E0002.
3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of Potassium Phosphate Buffer, pH 6.8 at temp, 37°C ± 0.5°C using USP apparatus II(Paddle) at 50 rpm. The test product should meet the following specification(s):

NLT <sup>(b)</sup><sub>(4)</sub>% (Q) of balsalazide dissolved in 30 min

4. The Division of Bioequivalence deems the test product, Balsalazide Disodium Capsules, manufactured by Apotex, Inc., to be bioequivalent to the reference product, Colazal<sup>®</sup> (balsalazide disodium, USP) Capsules, manufactured by Salix Pharmaceuticals.

The firm should be informed of the above recommendations.

### 3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	None

## 4 APPENDIX

### 4.1 Individual Study Reviews

#### 4.1.1 Single-dose Fasting Bioequivalence Study

##### 4.1.1.1 Study Design

**Table 4 Study Information<sup>3</sup>**

<b>Study Number</b>	70038
<b>Study Title</b>	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal® (Reference) Following a 2250 mg Dose in Healthy Subjects Under Fasting Conditions
<b>Clinical Site (Name, Address, Phone #)</b>	Anapharm 2050, boul. René-Lévesque Ouest Québec (Québec), Canada G1V 2K8 Tel.: (418) 527-4000 Fax: (418) 527-3456
<b>Principal Investigator</b>	Denis Audet, M.D.
<b>Dosing Dates</b>	April 1, 2007, and April 15, 2007 (Subjects No. 001 to 036) April 6, 2007, and April 20, 2007 (Subjects No. 037 to 072) April 7, 2007, and April 21, 2007 (Subjects No. 073 to 106)
<b>Analytical Site (Name, Address, Phone #)</b>	Anapharm 2500, rue Einstein Québec (Québec) Canada, G1P 0A2 Tél. : (418) 527-4000 Fax.: (418) 527-3456
<b>Analysis Dates</b>	2007-04-22 to 2007-06-05 (Balsalazide) 2007-04-29 to 2007-06-07 (5-ASA)
<b>Analytical Director</b>	(b) (6) Ph.D.
<b>Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)</b>	65 days (2007-04-01 to 2007-06-05) (Balsalazide) 67 days (2007-04-01 to 2007-06-07) (5-ASA)

**Table 5. Product information**

Product	Test	Reference
Treatment ID	A	B
Product Name	balsalazide disodium	Colazal® (balsalazide disodium)
Manufacturer	Apotex Inc., Canada	Salix Pharmaceuticals Inc., U.S.A.
Batch/Lot No.	043-11	320195
Manufacture Date	June 2005	N/AV
Expiration Date	June 2007	07/09
Strength	750 mg	750 mg
Dosage Form	capsule	capsule
Bio-batch Size		N/AV
Production Batch Size		N/AV
Potency	101.7%	101.4%
Content Uniformity (mean, %CV)	101.1%, 1.2%	100.5%, 1.2%
Dose Administered	3 x 750 mg capsules (2250 mg)	3 x 750 mg capsules (2250 mg)
Route of Administration	oral	oral

**Table 6. Study Design, Single-Dose Fasting Bioequivalence Study**

Number of Subjects	Enrolled: 106 Dosed: 106 Completed: 99 Analyzed: Balsalazide – 100 (1 for safety reasons) 5-ASA – 100 (2 for safety reasons)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	3
Washout Period	14 days
Randomization Scheme	<b>Group No. 01 (subject Nos. 01-36)</b>  AB: 01, 02, 04, 07, 10, 11, 14, 15, 17, 18, 21, 23, 25, 27, 29, 31, 35, and 36  BA: 03, 05, 06, 08, 09, 12, 13, 16, 19, 20, 22, 24, 26, 28, 30, 32, 33, and 34
	<b>Group No. 02 (subject Nos. 37-72)</b>  AB: 37, 40, 42, 43, 44, 48, 49, 54, 56, 57, 58, 60, 62, 63, 64, 65, and 69  BA: 38, 39, 41, 45, 46, 47, 50, 51, 52, 53, 55, 59, 61, 66, 67, 68, 70, 71 and 72

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	<p><b>Group No. 02 (subject Nos. 73-106)</b></p> <p>AB: 73, 74, 76, 78, 80, 81, 82, 85, 88, 90, 93, 94, 95, 99, 100, 102, 103, and 106</p> <p>BA: 75, 77, 79, 83, 84, 86, 87, 89, 91, 92, 96, 97, 98, 101, 104, and 105</p>
<b>Blood Sampling Times</b>	<p><u>Balsalazide</u> 0.00 hrs (pre-dose), 0.083, 0.167, 0.333, 0.750, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0 36.0, 48.0, and 72.0 hours (post-dose)</p> <p><u>5-ASA</u> 0.00 hrs (pre-dose), 2.00, 4.00, 6.00, 7.00, 8.00, 9.00, 10.00, 11.0, 12.0, 14.0, 16.0, 20.0, 24.0, 36.0, 48.0, and 72.0 hrs (pos-dose)</p>
<b>Blood Volume Collected/Sample</b>	<p>Balsalazide: 1 x 3 mL each (21 samples per period) 5-ASA: 1 x 6 mL each (17 samples per period)</p>
<b>Blood Sample Processing/Storage</b>	<p><u>Balsalazide</u> Blood samples were cooled in an ice bath and were centrifuged at 3,000 rpm for at least 10 minutes at approximately 4°C. Two aliquots of at least 0.5 mL (when possible) of plasma were dispensed into polypropylene tubes (as soon as possible). The aliquots were transferred to a -20°C±5°C freezer, pending shipment to the analytical facility. No more than 50 minutes passed between the time of each blood draw and the start of centrifugation and no more than 70 minutes passed between the start of centrifugation and aliquot storage.</p> <p><u>5-ASA</u> Blood samples were cooled in an ice bath and were centrifuged at 3,000 rpm for at least 10 minutes at approximately 4°C. Two aliquots of at least 1.0 mL (when possible) of plasma were dispensed into polypropylene tubes (as soon as possible). The aliquots were flash-frozen at approximately -80°C and subsequently transferred to a -80°C (-65°C to -85°C) freezer, pending shipment to the analytical facility. No more than 50 minutes passed between the time of each blood draw and the start of centrifugation and no more than 191 minutes passed between the start of centrifugation and aliquot storage.</p>
<b>IRB Approval</b>	Yes
<b>Informed Consent</b>	Yes
<b>Length of Fasting</b>	Subjects fasted overnight for at least 10 hours, until 4 hours post-dose.
<b>Length of Confinement</b>	Subjects were confined to the Anapharm Clinical Research Facility from at least 10 hours prior to drug administration until after the 24.0-hour post-dose blood draw, in each period.
<b>Safety Monitoring</b>	Throughout the study, subjects were monitored for adverse events. At the times of admission and departure, subjects were asked a standard probe question concerning the onset of any new health problems. All adverse events including those reported within 14 days following last drug administration were recorded onto appropriate data sheets.

**Comments on Study Design:**

The study design is acceptable.

**4.1.1.2 Clinical Results**

**Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study<sup>3</sup>**

Study No. 70038					
		Treatment Groups			
		Balsalazide Analysis		5-Aminosalicylic Acid Analysis	
		Test Product N = 99	Reference Product N = 99	Test Product N = 98	Reference Product N = 98
<b>Age (years)</b>	<b>Mean ± SD</b>	36 ± 10	36 ± 10	36 ± 10	36 ± 10
	<b>Range</b>	18 - 55	18 - 55	18 - 55	18 - 55
<b>Age Groups</b>	<b>&lt; 18</b>	0	0	0	0
	<b>18 – 40</b>	64 (64.6 %)	64 (64.6 %)	63 (64.3 %)	63 (64.3 %)
	<b>41 – 64</b>	35 (35.4 %)	35 (35.4 %)	35 (35.7 %)	35 (35.7 %)
	<b>65 – 75</b>	0	0	0	0
	<b>&gt; 75</b>	0	0	0	0
<b>Sex</b>	<b>Male</b>	43 (43.4 %)	43 (43.4 %)	42 (42.9 %)	42 (42.9 %)
	<b>Female</b>	56 (56.6 %)	56 (56.6 %)	56 (57.1 %)	56 (57.1 %)
<b>Race</b>	<b>Asian</b>	0	0	0	0
	<b>Black</b>	0	0	0	0
	<b>Caucasian</b>	97 (98.0 %)	97 (98.0 %)	96 (98.0 %)	96 (98.0 %)
	<b>Hispanic</b>	1 (1.0 %)	1 (1.0 %)	1 (1.0 %)	1 (1.0 %)
	<b>Other</b>	1 (1.0 %)	1 (1.0 %)	1 (1.0 %)	1 (1.0 %)
<b>BMI</b>	<b>Mean ± SD</b>	24.7 ± 2.9	24.7 ± 2.9	24.7 ± 2.9	24.7 ± 2.9
	<b>Range</b>	19.6 - 29.8	19.6 - 29.8	19.6 - 29.8	19.6 - 29.8
<b>Height</b>	<b>Mean ± SD</b>	167.0 ± 8.9	167.0 ± 8.9	166.8 ± 8.7	166.8 ± 8.7
	<b>Range</b>	148.0 - 191.5	148.0 - 191.5	148.0 - 191.5	148.0 - 191.5
<b>Weight</b>	<b>Mean ± SD</b>	68.9 ± 10.5	68.9 ± 10.5	68.8 ± 10.5	68.8 ± 10.5
	<b>Range</b>	47.2 - 101.0	47.2 - 101.0	47.2 - 101.0	47.2 - 101.0

**Table 8. Dropout Information, Fasting Bioequivalence Study<sup>3</sup>**

Study No. 70038				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
036	2007-04-13 11:43 / test / was withdraw due to adverse event (Skin reaction at different parts of the body)	1	No	N/AP
079	2007-04-08 07:08 / reference / was withdrawn due to adverse event (Red pimples on all body)	1	No	N/AP
092	2007-04-21 12:31 / test / was withdrawn due to vomiting	2	No	N/AP
100	2007-04-17 15:50 / test / was withdrawn due to adverse event (Loose stools)	1	No	N/AP
102	2007-04-18 09:30 / test / elected to withdraw due to adverse event (Flu syndrome)	1	No	N/AP
103	2007-04-20 15:45 / test / elected to withdraw for personal reason	1	No	N/AP
104	2007-04-17 16:13 / reference / was withdrawn due to adverse event (Loose stools)	1	No	N/AP

**Table 9. Study Adverse Events, Fasting Bioequivalence Study<sup>3</sup>**

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 70038	
	Test N = 104	Reference N = 102
<b>Body as a Whole</b>		
Asthenia		2 (2.0%)
Chills	1 (1.0%)	
Edema face		1 (1.0%)
Fever	1 (1.0%)	
Flu synd	3 (2.9%)	2 (2.0%)
Headache	10 (9.6%)	20 (19.6%)
Hem inject site	1 (1.0%)	4 (3.9%)
Hysn inject site	6 (5.8%)	4 (3.9%)
Inject site react	1 (1.0%)	1 (1.0%)
Injury accid		1 (1.0%)
Mass inject site	2 (1.9%)	
Neck rigid	1 (1.0%)	
Pain	2 (1.9%)	
Pain abdo	3 (2.9%)	2 (2.0%)
Pain back		1 (1.0%)
Pain inject site	5 (4.8%)	6 (5.9%)
Pain neck	1 (1.0%)	
<b>Cardiovascular System</b>		
Vasc dis	1 (1.0%)	
Vasodilat	3 (2.9%)	3 (2.9%)
<b>Digestive System</b>		
Constip	1 (1.0%)	
Diarrhea	2 (1.9%)	1 (1.0%)
Dry mouth	1 (1.0%)	
Dyspepsia	1 (1.0%)	1 (1.0%)
Flatul	2 (1.9%)	
Nausea	5 (4.8%)	5 (4.9%)
Vomit	2 (1.9%)	2 (2.0%)
<b>Hemic and Lymphatic System</b>		
Ecchymosis		1 (1.0%)

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Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. 70038	
	Test N = 104	Reference N = 102
<b>Metabolic and Nutritional Disorders</b>		
Creatinine inc	1 (1.0%)	
<b>Musculoskeletal System</b>		
Myalgia	1 (1.0%)	
Myasthenia		1 (1.0%)
<b>Nervous System</b>		
Dizziness	3 (2.9%)	3 (2.9%)
Hypesthesia	1 (1.0%)	3 (2.9%)
Insomnia	1 (1.0%)	1 (1.0%)
Paresthesia		1 (1.0%)
Sleep dis		1 (1.0%)
Somnolence	10 (9.6%)	6 (5.9%)
Tremor	1 (1.0%)	
<b>Respiratory System</b>		
Hiccup		1 (1.0%)
Pharyngitis	2 (1.9%)	
Rhinitis		2 (2.0%)
Voice alterat	1 (1.0%)	
<b>Skin and Appendages</b>		
Nodule skin	1 (1.0%)	
Pruritus	1 (1.0%)	
Rash	2 (1.9%)	2 (2.0%)
Skin dis	1 (1.0%)	
<b>Special Senses</b>		
Amblyopia	1 (1.0%)	1 (1.0%)
<b>Urogenital System</b>		
Albuminuria	1 (1.0%)	1 (1.0%)
Dysuria	1 (1.0%)	1 (1.0%)
Hematuria	1 (1.0%)	2 (2.0%)
Pyuria	1 (1.0%)	
Urin abnorm	1 (1.0%)	
<b>Total</b>	<b>46 (44.2%)</b>	<b>44 (43.1%)</b>

**Table 10. Protocol Deviations, Fasting Bioequivalence Study<sup>3</sup>**

Study No. 70038		
Type	Subject #s (Test)	Subject #s (Ref.)
During the medication storage, the humidity of the storage facility fell beneath the accepted range, to as low as 28.14%RH, between April 6, 2007 to April 19, 2007.	001-078, 080-103, 105, 106*	001-035, 037-099, 101, 104-106*
These subjects' 0.333-hour post-dose Period 1 plasma aliquots for balsalazide analysis were stored 73 minutes after the start of centrifugation. However, There is no impact since balsalazide was found to be stable in human EDTA K2 whole blood for 107 minutes at 4°C and in human EDTA K2 plasma partitioned over erythrocytes for an additional 174 minutes at 4°C.	001, 002, 004, 007, 010, 011	003, 005, 006, 008, 009
These subjects' 0.500-hour post-dose Period 1 plasma aliquots for balsalazide analysis were stored 72 minutes after the start of centrifugation. However, There is no impact since balsalazide was found to be stable in human EDTA K2 whole blood for 107 minutes at 4°C and in human EDTA K2 plasma partitioned over erythrocytes for an additional 174 minutes at 4°C.	001, 002, 004	003, 005, 006
These subjects' 48.0-hour post-dose Period 1 plasma aliquots for 5-ASA analysis were stored at -20°C instead of -80°C for 1 day 19 minutes and were not flash frozen prior to storage, in error. There is no impact since 5-ASA was found to be stable in human EDTA K3 plasma for 68 days at -20°C.	001, 002, 004, 007, 010, 011, 014, 015, 017, 018, 021, 035	003, 005, 006, 008, 009, 012, 013, 016, 019, 020, 022
This subject consumed 2 sips of cola beverage 2 days 11 hours 58 minutes after study drug administration in Period 2.		002
For the 48.0-hour post-dose return visit in Period 2, the answers to the questions concerning restriction between the 36.0-hour and the 48.0-hour post-dose return visit were not recorded for these subjects. However, subjects were called back and confirmed they answered no to all questions.	016	011
This subject's 24.0-hour post-dose Period 2 blood samples for balsalazide and 5-ASA analysis were centrifuged 52 minutes after blood collection. However, there is no impact since balsalazide was found to be stable in human EDTA K2 whole blood for 107 minutes at 4 °C and in human EDTA K2 plasma partitioned over erythrocytes for an additional 174 minutes at 4 °C, and since 5-ASA was found to be stable in human EDTA K2 whole blood for 109 minutes at 4°C and in human EDTA K2 plasma partitioned over erythrocytes for an additional 182 minutes at 4°C.	013	
This subject's post-study hematology test was performed 21 days after the last participation of the subject in the study. However, all results were within normal ranges or judged not clinically significant by the Qualified Investigator.	055 (post-study)	

<b>Study No. 70038</b>		
<b>Type</b>	<b>Subject #s (Test)</b>	<b>Subject #s (Ref.)</b>
These subjects' Period 1 pre-dose blood samples for balsalazide and 5-ASA analysis were centrifuged for 3 minutes at 22°C instead of 4°C, in error, and were then centrifuged at 3000rpm for 10 minutes at 4°C. There is no impact for balsalazide since it was found to be stable in human EDTA K2 whole blood for 30 minutes at room temperature. There is an impact for 5-ASA, since it was not found to be stable in human EDTA K2 whole blood for 10 minutes. In period 1, pre-dose blood samples of subjects 073 to 086 and 088 to 091 were inconclusive for 5-ASA.	073, 074, 076, 078, 080-082, 085, 088, 090	075, 077, 079, 083, 084, 086, 089, 091
This subject's post-study procedures were performed 16 days after the last participation of the subject in the study. However, all results were within normal ranges or judged not clinically significant by the Qualified Investigator.		079 (post-study)
This subject consumed 350 mL of diet cola beverage 2 days 6 hours 32 minutes after study drug administration in Period 1.		087
This subject consumed approximately 50 mL of coffee 1 day 3 hours 14 minutes after study drug administration in Period 2.	096	
This subject's post-study procedures were performed 28 days after the last participation of the subject in the study. However, all results were within normal ranges or judged not clinically significant by the Qualified Investigator.	097 (post-study)	

\*This deviation does not apply to all subjects.

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

1. Seven (7) of the healthy male and female subjects did not complete the fasting BE study ([Table 8](#)). Five (5) subjects (Nos. 036, 079, 092, 100, and 104) were withdrawn from the study due to adverse events (AEs). While two (2) subjects (Nos. 102 and 103) elected to withdraw from the study. All of the subjects were discontinued in the study according to the firm's protocol (Section 8.12).
2. One-hundred and eighty-four (184) AEs were reported during the fasting BE study ([Table 9](#)). The data in Table 9 represented the number of AEs reported at least one time by a subject. Ninety-five (95) AEs were reported after subjects received a single oral dose of the test product, while eighty-nine (89) AEs were reported after subjects received a single-oral dose of the reference product.
3. No serious adverse events (SAEs) were reported during the study.
4. The firm reported in its protocol deviations that there is an impact on the analysis of samples for subject Nos. 73-86, and 88-91 because their blood samples were centrifuged for 3 minutes at 22°C instead of 4°C, in error, and were then centrifuged

at 3000 rpm for 10 minutes at 4°C ([Table 10](#)). Therefore in Period I the pre-dose blood samples of subjects 073 to 086 and 088 to 091 were reported as inconclusive.

5. The reported discontinued subjects, AEs and protocol deviations do not have an impact on the outcome or the integrity of the study.

#### 4.1.1.3 Bioanalytical Results

**Table 11. Assay Validation – Within the Fasting Bioequivalence Study<sup>3</sup>**

##### A. Balsalazide

Bioequivalence Study No. 70038OKC								
Balsalazide								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	1.00	2.01	20.07	100.33	200.65	300.98	401.30	501.63
Inter day Precision (%CV)	4.00	3.48	2.45	2.05	2.02	1.96	2.23	2.48
Inter day Accuracy (%)	100.00	100.00	99.70	102.47	100.70	99.57	98.76	98.82
Linearity	0.9971 to 0.9998							
Linearity Range (ng/mL)	1.00 to 501.63							
Sensitivity/LOQ (ng/mL)	1.00							

Bioequivalence Study No. 70038OKC				
Balsalazide				
Parameter	Quality Control Samples			
Concentration (ng/mL)	3.01	150.49	351.14	75.25
Inter day Precision (%CV)	3.56	2.71	2.83	4.55
Inter day Accuracy (%)	102.666	101.16	99.47	102.83

\* Accuracy (%) was converted by the review from  $\pm$  value to actual number, i.e.  $-0.53$  to  $99.47$ .

##### B. Mesalamine (5-aminosalicylic acid, 5-ASA)

Bioequivalence Study No. 70038OKD								
5-ASA								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	1.01	2.01	16.10	80.51	161.02	241.54	322.05	402.56
Inter day Precision (%CV)	9.90	4.48	1.47	1.13	2.12	1.17	1.78	1.49
Inter day Accuracy (%)	100.00	100.00	101.24	101.54	97.12	100.24	100.27	99.60
Linearity	0.9952 to 0.9997							
Linearity Range (ng/mL)	1.01 to 402.56							
Sensitivity/LOQ (ng/mL)	1.01							

Bioequivalence Study No. 70038OKD				
5-ASA				
Parameter	Quality Control Samples			
Concentration (ng/mL)	3.02	100.56	301.68	20.11
Inter day Precision (%CV)	5.90	1.32	1.53	2.19
Inter day Accuracy (%)	95.36	97.24	96.18	86.47

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Bioequivalence Study No. 70038OKD								
5-ASA								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	2.00	4.00	19.98	119.90	239.81	359.71	479.62	599.52
Inter day Precision (%CV)	4.64	5.24	2.12	2.44	2.06	1.91	2.11	2.94
Inter day Accuracy (%)	97.00	105.00	101.35	100.43	102.17	99.48	97.23	97.05
Linearity	0.9930 to 0.9996							
Linearity Range (ng/mL)	2.00 to 599.52							
Sensitivity/LOQ (ng/mL)	2.00							

Bioequivalence Study No. 70038OKD				
5-ASA				
Parameter	Quality Control Samples			
Concentration (ng/mL)	6.00	59.95	179.86	419.66
Inter day Precision (%CV)	6.34	2.55	2.59	3.31
Inter day Accuracy (%)	97.33	94.30	93.49	93.38

**Comments on Study Assay Validation:**

Acceptable.

Any interfering peaks in chromatograms?	No significant interfering peaks
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

**Comments on Chromatograms:**

Acceptable.

**Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples<sup>3</sup>**

SOP No.	Effective Date of SOP	SOP Title
ANI 156.09	2005-09-23	Sample Reassays and Reporting of Final Concentrations

**Table 13. Additional Comments on Repeat Assays**

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	--

**Summary/Conclusions, Study Assays:**

1. According to the firm's bioanalytical report, following the results of the first runs for 5-ASA plasma samples, it was observed that the several sample concentrations were above the upper limit of quantitation (402.56 ng/mL). Therefore, another range was used for the rest of analysis. Based on these results the plasma samples for subjects 01 to 20 were analyzed with a calibration standard range from 1.00 to 400.00 ng/mL (SOP ANI 8780.02) and the 5-ASA plasma samples for subjects 021 to 101 were analyzed with a calibration standard range of 2.00 to 600.0 ng/mL (SOP ANI 8733.05). The reviewer accepts the firm's analytical decision.
2. The study assay is acceptable.

#### 4.1.1.4 Pharmacokinetic Results

##### A. Balsalazide

**Table 14. Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in [Table 22](#) and [Figure 1](#)

Fasting Bioequivalence Study No. 70038									
Balsalazide									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC <sub>0-t</sub> (hr *ng/ml)	1605.32	44.22	466.81	3391.52	1590.10	45.43	554.08	5490.23	1.01
AUC <sub>∞</sub> (hr *ng/ml)	1712.56	43.65	510.49	3744.77	1693.58	45.11	630.87	5751.73	1.01
C <sub>max</sub> (ng/ml)	498.34	52.01	175.56	1563.12	551.99	48.44	152.76	1586.27	0.90
T <sub>max</sub> * (hr)	0.50	.	0.33	6.10	0.33	.	0.33	1.50	1.50
Kel (hr <sup>-1</sup> )	0.02	49.96	0.01	0.14	0.02	32.89	0.01	0.08	1.00
T <sub>1/2</sub> (hr)	30.28	25.01	5.07	74.27	29.62	22.33	8.63	48.26	1.02

\* T<sub>max</sub> values are presented as median, range

**Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Balsalazide				
Fasting Bioequivalence Study No. 70038				
Parameter (units)	Test	Reference	% Ratio	90% C.I.
AUC <sub>0-t</sub> (hr *ng/ml)	1466.49	1461.85	100.32	94.23-106.80
AUC <sub>∞</sub> (hr *ng/ml)	1568.65	1560.56	100.52	94.66-106.74
C <sub>max</sub> (ng/ml)	449.96	501.40	89.74	83.65-96.27

**Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Balsalazide					
Fasting Bioequivalence Study No. 70038					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (hr *ng/ml)	1466.49	1461.85	1.00	94.21	106.82
AUC <sub>∞</sub> (hr *ng/ml)	1568.65	1560.56	1.01	94.64	106.76
C <sub>max</sub> (ng/ml)	449.96	501.40	0.90	83.63	96.29

**Table 17. Additional Study Information, Fasting Study No. 70038**

Root mean square error, AUC <sub>0-t</sub>	0.2648	
Root mean square error, AUC <sub>∞</sub>	0.2541	
Root mean square error, C <sub>max</sub>	0.2971	
	Test	Reference
Kel and AUC <sub>∞</sub> determined for how many subjects?	99	99
Do you agree or disagree with firm's decision?	--	--
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C <sub>max</sub>	0	0
Were the subjects dosed as more than one group?	Yes	Yes

Ratio of AUC <sub>0-t</sub> /AUC <sub>∞</sub>				
Treatment	n	Mean	Minimum	Maximum
Test	99	0.94	0.79	0.99
Reference	99	0.94	0.81	0.99

**B. Mesalamine (5-aminosalicylic acid, 5-ASA)**

**Table 18. Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in [Table 23](#) and [Figure 2](#)

Fasting Bioequivalence Study No. 70038									
5-ASA									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC <sub>0-t</sub> (hr *ng/ml)	3220.46	64.42	515.21	10789.89	3227.64	62.98	172.31	9015.12	1.00
AUC <sub>∞</sub> (hr *ng/ml)	3657.12	59.75	802.62	10812.66	3743.87	58.50	188.41	9163.62	0.98
C <sub>max</sub> (ng/ml)	293.60	66.04	34.87	981.53	277.45	69.58	39.25	1145.51	1.06
T <sub>max</sub> * (hr)	10.00	.	6.00	36.00	9.03	.	6.00	48.02	1.11
Kel (hr <sup>-1</sup> )	0.08	64.96	0.02	0.24	0.09	88.71	0.01	0.57	0.93
T <sub>1/2</sub> (hr)	12.17	62.72	2.83	36.22	12.83	122.20	1.23	137.63	0.95

\* T<sub>max</sub> values are presented as median, range

**Table 19. Geometric Means and 90% Confidence Intervals - Firm Calculated**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
5-ASA				
Fasting Bioequivalence Study No. 70038				
Parameter (units)	Test	Reference	% Ratio	90% C.I.
AUC <sub>0-t</sub> (hr *ng/ml)	2653.49	2604.21	101.89	93.29-111.29
AUC <sub>∞</sub> (hr *ng/ml)	3085.74	3145.77	98.09	88.32-108.94
C <sub>max</sub> (ng/ml)	224.82	236.59	106.33	96.81-116.78

**Table 20. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
5-ASA					
Fasting Bioequivalence Study No. 70038					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (hr *ng/ml)	2653.49	2604.21	1.02	93.27	111.31
AUC <sub>∞</sub> (hr *ng/ml)	3085.74	3145.77	0.98	88.28	108.99
C <sub>max</sub> (ng/ml)	240.35	224.21	1.07	97.33	118.07

**Table 21. Additional Study Information, Fasting Study No. 70038**

Root mean square error, AUC <sub>0-t</sub>	0.3712	
Root mean square error, AUC <sub>∞</sub>	0.3845	
Root mean square error, C <sub>max</sub>	0.4053	
	Test	Reference
Kel and AUC <sub>∞</sub> determined for how many subjects?	75	75
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C <sub>max</sub>	0	0
Were the subjects dosed as more than one group?	Yes	Yes

Ratio of AUC <sub>0-t</sub> /AUC <sub>∞</sub>				
Treatment	n	Mean	Minimum	Maximum
Test	75	0.91	0.41	1.00
Reference	75	0.90	0.46	1.00

**Comments on Pharmacokinetic and Statistical Analysis:**

1. The firm assayed the plasma concentrations and provided the plasma profiles for balsalazide and 5-ASA.
2. 5-ASA is a highly variable drug. The root-mean square error for LAUC<sub>T</sub>, LAUC<sub>I</sub> and LC<sub>max</sub> are 37%, 38% and 40%, respectively.
3. The ninety-nine (99) healthy, adult male and female subjects that completed the study were dosed in three (3) groups.

4. For balsalazide and 5-ASA, the firm and reviewer pooled the data for the three (3) groups to conduct BE statistical evaluations.
5. For balsalazide, the data for ninety-nine (99) subjects were used in BE statistical evaluations. Whereas, for 5-ASA, the data for ninety-eight (98) subjects were used in BE statistical evaluations due to subject No. 47 vomiting within 2x the median  $T_{max}$ .
6. The firm and reviewer calculated the PK parameters ( $AUC_{\infty}$ ,  $AUC_T$ ,  $C_{max}$ ,  $T_{max}$ , and  $K_{el}$ ) for balsalazide and 5-ASA. Statistical analysis was performed on the PK parameters using the GLM procedure of SAS with a 90% confidence interval. The reviewer agrees with the firm's results for balsalazide and 5-ASA.
7. For 5-ASA, the firm did not calculate the elimination rate constant,  $K_{el}$  and  $AUC_1$  for twenty-three (23) subjects (Nos. 09, 11, 19, 20, 24, 34, 39, 40, 42, 45, 48, 56, 66, 67, 71, 72, 76, 86, 90, 93, 94, 105, and 106) due to either low correlation coefficients of ln-linear portion of the terminal elimination phase or an insufficient number of concentrations in the terminal phase. The reviewer accepts with the firm's decision.

**Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:**

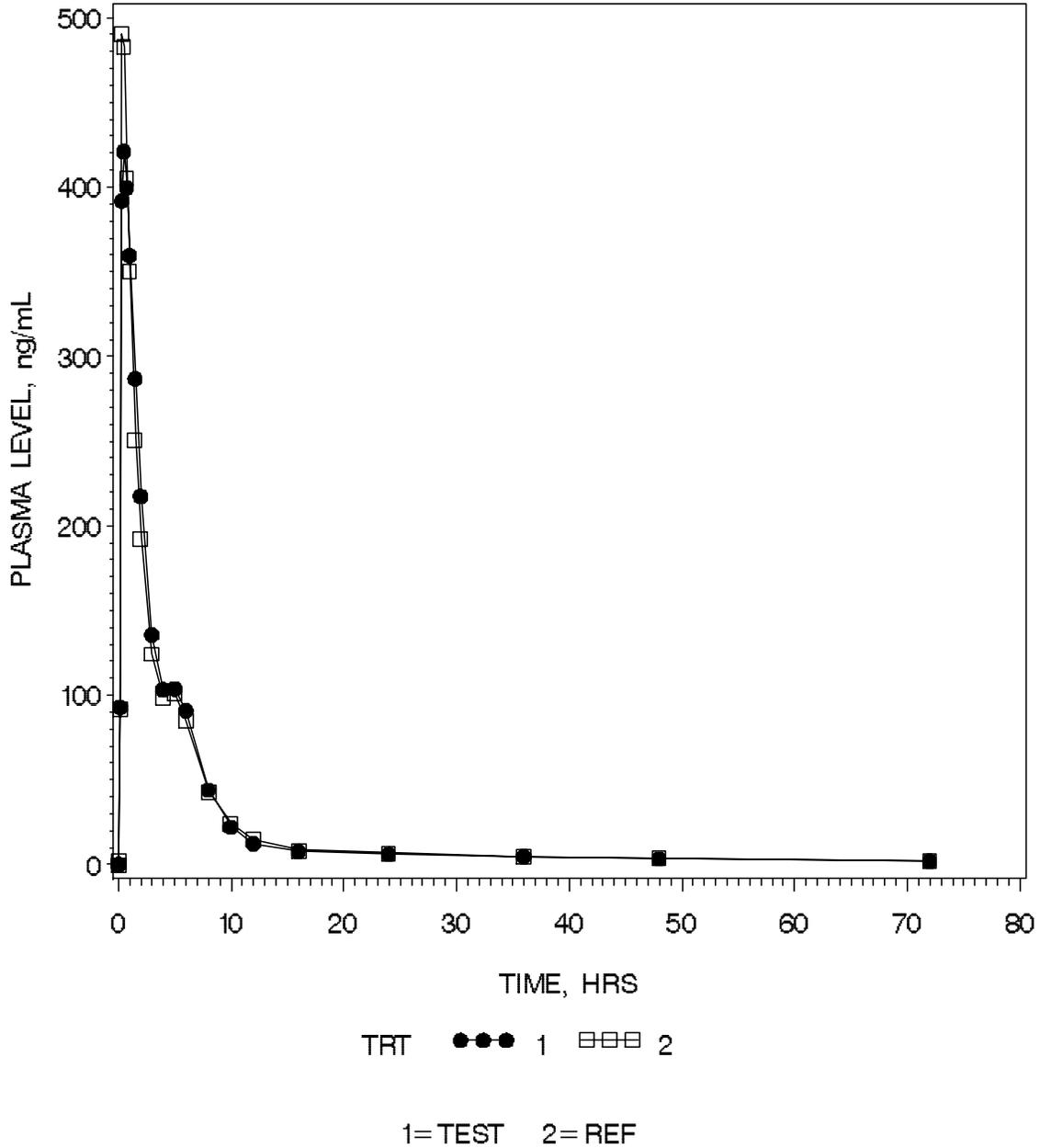
The single-dose fasting bioequivalence study is acceptable.

**Table 22. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

Balsalazide					
Time (hr)	Test (n=99)		Reference (n=99)		Ratio Mean (ng/mL)
	Mean (ng/mL)	CV%	Mean (ng/mL)	Time (hr)	
0.00	0.00	.	0.00	.	.
0.08	0.33	413.10	2.20	542.08	0.15
0.17	92.88	76.78	91.85	82.21	1.01
0.33	391.90	55.48	490.72	53.09	0.80
0.50	421.05	53.07	482.97	51.83	0.87
0.75	399.55	60.04	405.53	51.15	0.99
1.00	359.73	56.67	350.58	51.44	1.03
1.50	286.88	62.29	250.93	50.50	1.14
2.00	217.45	66.27	192.63	53.52	1.13
3.00	135.67	64.80	124.41	54.17	1.09
4.00	103.40	53.62	98.93	53.13	1.05
5.00	103.94	54.72	101.43	54.42	1.02
6.00	91.00	95.57	85.00	59.76	1.07
8.00	44.09	71.31	43.14	69.04	1.02
10.00	22.10	71.59	24.42	92.26	0.90
12.00	12.30	56.72	14.70	115.70	0.84
16.00	7.85	51.21	8.47	86.82	0.93
24.00	6.18	53.27	6.83	127.40	0.90
36.00	4.80	56.22	4.86	67.65	0.99
48.00	3.57	62.18	3.65	69.84	0.98
72.00	2.01	76.37	2.04	85.29	0.99

**Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

PLASMA BALASALAZIDE LEVELS  
BALSALAZIDE DISODIUM CAPSULES, 750 MG, ANDA 77-883  
UNDER FASTED CONDITIONS  
DOSE= 3 x 750 MG

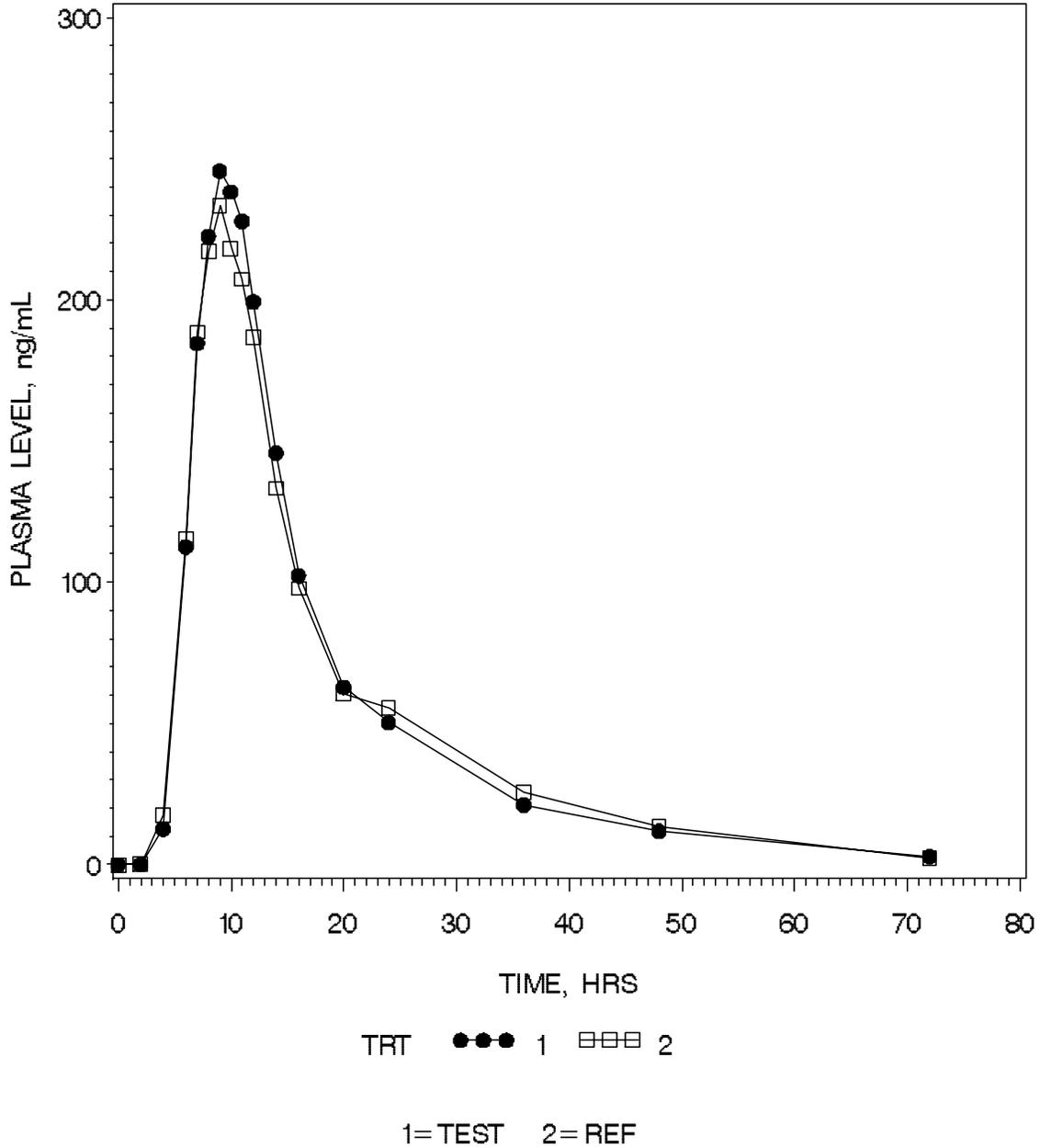


**Table 23. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

5-ASA					
Time (hr)	Test (n=98)		Reference (n=98)		Ratio Mean (ng/mL)
	Mean (ng/mL)	CV%	Mean (ng/mL)	Time (hr)	
0.00	0.00	.	0.00	0.00	0.00
2.00	0.08	759.64	0.34	2.00	0.08
4.00	12.67	309.95	17.41	4.00	12.67
6.00	112.56	111.09	115.47	6.00	112.56
7.00	184.68	88.70	188.69	7.00	184.68
8.00	222.51	77.93	217.26	8.00	222.51
9.00	245.67	70.01	233.39	9.00	245.67
10.00	238.34	67.43	218.12	10.00	238.34
11.00	227.92	68.61	207.42	11.00	227.92
12.00	199.46	73.01	186.71	12.00	199.46
14.00	145.81	83.27	133.41	14.00	145.81
16.00	102.39	96.28	97.93	16.00	102.39
20.00	62.90	83.91	60.68	20.00	62.90
24.00	50.34	89.98	55.64	24.00	50.34
36.00	21.16	147.24	25.73	36.00	21.16
48.00	11.84	189.99	13.39	48.00	11.84
72.00	2.89	255.26	2.50	72.00	2.89

**Figure 2. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

PLASMA MESALAMINE (5-ASA) LEVELS  
BALSALAZIDE DISODIUM CAPSULES, 750 MG, ANDA 77-883  
UNDER FASTED CONDITIONS  
DOSE= 3 x 750 MG



## 4.1.2 Single-dose Fed Bioequivalence Study

### 4.1.2.1 Study Design

**Table 24. Study Information<sup>3</sup>**

<b>Study Number</b>	60652
<b>Study Title</b>	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Balsalazide 750 mg Capsule and Colazal (Reference) Following a 2250 mg Dose in Healthy Subjects Under Fed Conditions
<b>Clinical Site (Name, Address, Phone #)</b>	Anapharm 2050, boul. René-Lévesque Ouest Québec (Québec), Canada G1V 2K8 Tel.: (418) 527-4000 Fax: (418) 527-3456
<b>Principal Investigator</b>	Denis Audet, M.D.
<b>Dosing Dates</b>	January 16, 2007, and January 30, 2007 (Subject No. 001 to 040) January 18, 2007, and February 01, 2007 (Subject No. 041 to 080) January 25, 2007, and February 8, 2007 (Subject No. 081 to 124) January 28, 2007, and February 11, 2007 (Subject No. 125 to 170)
<b>Analytical Site (Name, Address, Phone #)</b>	Anapharm 2050, Boul. René-Lévesque Ouest Québec (Québec) Canada, G1V 2K8 Tel.: (418) 527-4000 Fax: (418) 527-3456
<b>Analysis Dates</b>	2007-02-09 to 2007-03-22 (Balsalazide) 2007-02-26 to 2007-05-02 (5-ASA)
<b>Analytical Director</b>	(b) (6) Ph.D.
<b>Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)</b>	65 days (2007-01-16 to 2007-03-22) (Balsalazide) 106 days (2007-01-16 to 2007-05-02) (5-ASA)

**Table 25. Product Information<sup>3</sup>**

Product	Test	Reference
Treatment ID	A	B
Product Name	balsalazide disodium	Colazal® (balsalazide disodium)
Manufacturer	Apotex Inc., Canada	Salix Pharmaceuticals Inc., U.S.A.
Batch/Lot No.	043-11	6E0002
Manufacture Date	June 2005	N/AV
Expiration Date	June 2007	03/09
Strength	750 mg	750 mg
Dosage Form	capsule	capsule
Bio-batch Size		N/AV
Production Batch Size		N/AV
Potency	101.7%	102.8%
Content Uniformity (mean, %CV)	101.1%, 1.2%	102.3%, 3.8%
Dose Administered	3 x 750 mg capsules (2250 mg)	3 x 750 mg capsules (2250 mg)
Route of Administration	oral	oral

**Table 26. Study Design, Single-Dose Fed Bioequivalence Study**

No. of Subjects	Enrolled: 170 Dosed: 170 Completed: 160 Analyzed: Balsalazide – 160 5-ASA – 157
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	4
Washout Period	14 days
Randomization Scheme	<b>Group No. 01 (subject Nos. 01-40)</b>  AB: 01, 02, 03, 05, 06, 14, 15, 18, 19, 20, 23, 24, 25, 27, 29, 32, 33, 34, 38, and 40  BA: 04, 07, 08, 09, 10, 11, 12, 13, 16, 17, 21, 22, 26, 28, 30, 31, 35, 36, 37, and 39
	<b>Group No. 02 (subject Nos. 41-80)</b>  AB: 41, 42, 43, 45, 50, 53, 54, 55, 57, 59, 61, 63, 67, 68, 70, 74, 76, 77, 78, and 80  BA: 44, 46, 47, 48, 49, 51, 52, 56, 58, 60, 62, 64, 65, 66, 69, 71, 72, 73, 75, and 79

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	<p><b>Group No. 03 (subject Nos. 81-124)</b></p> <p>AB: 82, 86, 88, 89, 90, 91, 96, 97, 98, 99, 102, 103, 104, 109, 110, 112, 113, 116, 118, 120, 121, 123, and 124</p> <p>BA: 81, 83, 84, 85, 87, 92, 93, 94, 95, 100, 101, 105, 106, 107, 108, 111, 114, 115, 117, 119, and 122</p>
	<p><b>Group No. 04 (subject Nos. 125-170)</b></p> <p>AB: 127, 130, 131, 133, 135, 136, 138, 141, 143, 144, 147, 149, 152, 153, 156, 159, 160, 162, 164, 165, 166, and 169</p> <p>BA: 125, 126, 128, 129, 132, 134, 137, 139, 140, 142, 145, 146, 148, 150, 151, 154, 155, 157, 158, 161, 163, 167, 168, and 170</p>
<b>Blood Sampling Times</b>	<p><u>Balsalazide</u> 0.0 hrs (pre-dose), 0.250, 0.500, 0.750, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hours post-dose</p> <p><u>5-ASA</u> 0.0 hrs (pre-dose), 4.00, 6.00, 8.00, 10.0, 12.0, 14.0, 16.0, 17.0, 18.0, 19.0, 20.0, 21.0, 22.0, 23.0, 24.0, 25.0, 26.0, 27.0, 28.0, 30.0, 32.0, 36.0, 40.0, 44.0, 48.0, 60.0, and 72.0 hours post-dose</p>
<b>Blood Volume Collected/Sample</b>	<p>Balsalazide: 1 x 3 mL each (20 samples per period) 5-ASA: 1 x 6mL each (28 samples per period)</p>
<b>Blood Sample Processing/Storage</b>	<p><u>Balsalazide</u> Blood samples were cooled in an ice bath and were centrifuged at 3,000 rpm for at least 10 minutes at approximately 4°C. Two aliquots of at least 0.5 mL (when possible) of plasma were dispensed into polypropylene tubes (as soon as possible). The aliquots were transferred to a -20°C±5°C freezer, pending analysis. No more than 50 minutes passed between the time of each blood draw and the start of centrifugation and no more than 70 minutes passed between the start of centrifugation and aliquot storage.</p> <p><u>5-ASA</u> Blood samples were cooled in an ice bath and were centrifuged at 3,000 rpm for at least 10 minutes at approximately 4°C. Two aliquots of at least 1.0 mL (when possible) of plasma were dispensed into polypropylene tubes (as soon as possible). The aliquots were flash-frozen at approximately -80°C and subsequently transferred to a -80°C (-65°C to -85°C) freezer, pending analysis. No more than 50 minutes passed between the time of each blood draw and the start of centrifugation and no more than 191 minutes passed between the start of centrifugation and aliquot storage.</p>
<b>IRB Approval</b>	Yes
<b>Informed Consent</b>	Yes
<b>Length of Fasting Before Meal</b>	Subjects fasted overnight for at least 10 hours and 30 minutes before drug administration
<b>Length of Confinement</b>	Subjects were confined from at least 11 hours before dosing until after the 48.0-hour post-dose blood draw.

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<b>Safety Monitoring</b>	Throughout the study, subjects were monitored for adverse events. At the times of admission and departure, subjects were asked a standard probe question concerning the onset of any new health problems. All adverse events including those reported within 14 days following last drug administration were recorded onto appropriate data sheets.
<b>Standard FDA Meal Used?</b>	Yes

**Comments on Study Design:**

The study design is acceptable.

**4.1.2.2 Clinical Results**

**Table 27. Demographics Profile of Subjects Completing the Bioequivalence Study<sup>3</sup>**

Study No. 60652					
		Treatment Groups			
		Balsalazide Analysis		5-Aminosalicylic Acid Analysis	
		Test Product N = 160	Reference Product N = 160	Test Product N = 157	Reference Product N = 157
<b>Age (years)</b>	<b>Mean ± SD</b>	37± 10	37± 10	37± 10	37± 10
	<b>Range</b>	18 - 55	18 - 55	18 - 55	18 - 55
<b>Age Groups</b>	<b>&lt; 18</b>	0	0	0	0
	<b>18 – 40</b>	97 (60.6%)	97 (60.6%)	94 (59.9%)	94 (59.9%)
	<b>41 – 64</b>	63 (39.4%)	63 (39.4%)	63 (40.1%)	63 (40.1%)
	<b>65 – 75</b>	0	0	0	0
	<b>&gt; 75</b>	0	0	0	0
<b>Sex</b>	<b>Male</b>	98 (61.3%)	98 (61.3%)	96 (61.1%)	96 (61.1%)
	<b>Female</b>	62 (38.8%)	62 (38.8%)	61 (38.9%)	61 (38.9%)
<b>Race</b>	<b>Asian</b>	0	0	0	0
	<b>Black</b>	0	0	0	0
	<b>Caucasian</b>	158 (98.8%)	158 (98.8%)	155 (98.7%)	155 (98.7%)
	<b>Hispanic</b>	2 (1.3%)	2 (1.3%)	2 (1.3%)	2 (1.3%)
	<b>Other</b>	0	0	0	0
<b>BMI</b>	<b>Mean ± SD</b>	25.0 ± 2.7	25.0 ± 2.7	25.0 ± 2.7	25.0 ± 2.7
	<b>Range</b>	19.6 – 29.9	19.6 – 29.9	19.6 – 29.9	19.6 – 29.9
<b>Height</b>	<b>Mean ± SD</b>	170.4 ± 8.1	170.4 ± 8.1	170.4 ± 8.2	170.4 ± 8.2
	<b>Range</b>	152.0 – 193.0	152.0 – 193.0	152.0 – 193.0	152.0 – 193.0
<b>Weight</b>	<b>Mean ± SD</b>	73.0 ± 11.2	73.0 ± 11.2	72.9 ± 11.3	72.9 ± 11.3
	<b>Range</b>	50.3 – 104.8	50.3 – 104.8	50.3 – 104.8	50.3 – 104.8

**Table 28. Dropout Information, Fed Bioequivalence Study<sup>3</sup>**

Study No. 60652				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
001	2007-01-29 20:28/test/elected to withdraw since the subject did not show at the confinement period	1	No	N/AP
017	2007-01-30/test/elected to withdraw due to personal reason	2	No	N/AP
025	2007-01-22 15:11/test/elected to withdraw due to personal reason	1	No	N/AP
040	2007-01-29 15:50/test/was withdrawn due to concomitant medication	1	No	N/AP
045	2007-01-31 15:21/test/elected to withdraw due to adverse event (lower back pain) and concomitant medication	1	No	N/AP
046	2007-01-18 11:50/reference/was withdrawn due to adverse event (liquid stools)	1	No	N/AP
086	2007-02-07 14:00/test/elected to withdrawn due to adverse events (headache, back pain (all the back), runny nose)	1	No	N/AP
112	2007-02-08 05:32/test/was withdrawn due to a positive urine drug test to benzodiazepine	1	No	N/AP
114	2007-02-08 06:51/reference/was withdrawn due to difficulties with blood draws and catheter installation	1	No	N/AP
124	2007-01-25 21:26/test/elected to withdraw due to personal reason	1	No	N/AP

\*Time inconclusive (due to conflicting data)

**Table 29. Study Adverse Events, Fed Bioequivalence Study<sup>3</sup>**

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. 60652	
	Test N = 168	Reference N = 163
<b>Body as a Whole</b>		
Asthenia	1 (0.6%)	1 (0.6%)
Chills		1 (0.6%)
Flu synd	2 (1.2%)	4 (2.5%)
Headache	13 (7.7%)	15 (9.2%)
Hysn inject site	11 (6.5%)	12 (7.4%)
Inject site react	5 (3.0%)	3 (1.8%)
Injury accid	2 (1.2%)	2 (1.2%)
Mass inject site	2 (1.2%)	8 (4.9%)
Pain	3 (1.8%)	3 (1.8%)
Pain abdo	2 (1.2%)	5 (3.1%)
Pain back	5 (3.0%)	1 (0.6%)
Pain inject site	23 (13.7%)	15 (9.2%)
<b>Cardiovascular System</b>		
Syncope	1 (0.6%)	
Vasodilat	2 (1.2%)	2 (1.2%)
<b>Digestive System</b>		
Anorexia	1 (0.6%)	
Appetite inc	1 (0.6%)	
Constip	6 (3.6%)	5 (3.1%)
Diarrhea	2 (1.2%)	5 (3.1%)
Flatul	2 (1.2%)	3 (1.8%)
Nausea		5 (3.1%)
Stomatitis ulcer	1 (0.6%)	
Vomit		1 (0.6%)
<b>Hemic and Lymphatic System</b>		
Anemia hypochrom	1 (0.6%)	
Ecchymosis	2 (1.2%)	6 (3.7%)
Leukocytosis		1 (0.6%)
Leukopenia		1 (0.6%)

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Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. 60652	
	Test N = 168	Reference N = 163
<b>Metabolic and Nutritional Disorders</b>		
Edema	1 (0.6%)	
Hyperkalem	1 (0.6%)	
Hypoglycem	1 (0.6%)	
Thirst		1 (0.6%)
<b>Musculoskeletal System</b>		
Arthralgia	1 (0.6%)	1 (0.6%)
Myalgia	1 (0.6%)	1 (0.6%)
Myasthenia	1 (0.6%)	
<b>Nervous System</b>		
Dizziness		5 (3.1%)
Hemiplegia	1 (0.6%)	
Paralysis	1 (0.6%)	
Paresthesia	1 (0.6%)	
Somnolence	16 (9.5%)	9 (5.5%)
Speech dis	1 (0.6%)	
Tremor	1 (0.6%)	
<b>Respiratory System</b>		
Cough inc	2 (1.2%)	2 (1.2%)
Epistaxis	1 (0.6%)	
Pharyngitis		2 (1.2%)
Rhinitis	4 (2.4%)	1 (0.6%)
<b>Skin and Appendages</b>		
Acne	1 (0.6%)	
Nodule skin	1 (0.6%)	
Pruritus	1 (0.6%)	
Rash	3 (1.8%)	1 (0.6%)
Rash vesic bull	1 (0.6%)	
Skin dry	1 (0.6%)	
Sweat	1 (0.6%)	
<b>Special Senses</b>		
Blepharitis	1 (0.6%)	1 (0.6%)
Conjunctivitis	1 (0.6%)	1 (0.6%)

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Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. 60652	
	Test N = 168	Reference N = 163
<b>Urogenital System</b>		
Albuminuria	3 (1.8%)	1 (0.6%)
Hematuria	2 (1.2%)	2 (1.2%)
Pyuria	1 (0.6%)	1 (0.6%)
Urin abnorm	1 (0.6%)	
<b>Total</b>	81 (48.2%)	67 (41.1%)

**Table 30. Protocol Deviations, Fed Bioequivalence Study<sup>3</sup>**

Study No. 60652		
Type	Subject #s (Test)	Subject #s (Ref.)
During medication storage, the humidity of the storage facility fell beneath the accepted range, to as low as 27.39%RH, between December 29, 2006, and January 16, 2007.	001-170	001-170
<p>These subjects' blood collection tube (for balsalazide analysis) was centrifuged as much as 55 minutes after blood collection:</p> <p>-2.50 hour post-dose Period 1: Subjects No. 001, 002, 003.</p> <p>-0.750-hour post-dose Period 2: Subject No. 041.</p> <p>There is no impact since balsalazide is found to be stable in human EDTA K2 whole blood for 107 minutes at 4°C and in human EDTA K2 plasma erythrocytes for an additional 174 minutes at 4°C with a percentage of change of -3.12%. 5-ASA is found to be stable in human EDTA K2 whole blood for 109 minutes at 4°C and in human EDTA K2 plasma partitioned erythrocytes for an additional 182 minutes at 4°C with a percentage of change of -1.56%.</p>	001-003	041

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<b>Study No. 60652</b>		
<b>Type</b>	<b>Subject #s (Test)</b>	<b>Subject #s (Ref.)</b>
<p>These subjects' blood collection tube (for 5-aminosalicylic acid analysis) was centrifuged as much as 55 minutes after blood collection:</p> <ul style="list-style-type: none"> <li>- 27.0 hour post-dose Period 1: Subjects No. 013, 014, 015</li> <li>- 72.0-hour post-dose Period 1: Subject No. 058</li> <li>- 19.0-hour post-dose Period 2: Subjects No. 081 and 082</li> </ul> <p>There is no impact since balsalazide is found to be stable in human EDTA K2 whole blood for 107 minutes at 4°C and in human EDTA K2 plasma erythrocytes for an additional 174 minutes at 4°C with a percentage of change of -3.12%. 5-ASA is found to be stable in human EDTA K2 whole blood for 109 minutes at 4°C and in human EDTA K2 plasma partitioned erythrocytes for an additional 182 minutes at 4°C with a percentage of change of -1.56%.</p>	014, 015, 081	013, 058, 082
<p>This subject was dosed in Period 1 with approximately 239 mL of water instead of 240 mL as specified in the protocol (approximately 1 mL of water was lost). However, there is no impact since a mouth check was performed to ensure consumption of the medication.</p>	N/AP	072
<p>This subject consumed 240 mL of coffee 2 days 55 minutes after study drug administration, in Period 1.</p>	N/AP	011
<p>These subjects' post-study procedures were performed as much as 16 days after their last participation in the study. However, all post-study results were judged normal or not clinically significant by the physician.</p>	046	025
<p>During storage of the 60.0 and 72.0-hour post-dose 5-aminosalicylic acid plasma aliquots 2/2, the temperature of the freezer rose above the accepted range specified in the protocol, to as low as -49°C, on February 20, 2007 (durations: 1 hour 55 minutes). 5-aminosalicylic acid (5-ASA) and N-acetyl-5-aminosalicylic acid (5-ACASA) are found to be stable in acidified methanol for 167 days and 110 days at -20°C with % change of -0.44 and -9.46%, respectively. Therefore, the integrity of the samples is not affected.</p>	030-036, 038-040, 115-123, 125-131, 133-137, 139-147	030-036, 038, 039, 115-123, 125-131, 133-137, 139-147
<p>This subject consumed one sip of coca cola 2 days 6 hours 18 minutes after study drug administration, in Period 1.</p>	N/AP	037
<p>This subject consumed approximately 50 g of chocolate 2 days 12 hours 52 minutes after study drug administration, in Period 2.</p>	075	N/AP
<p>This subject consumed 2 chocolate cookies (Oreo), in period 2 (date and time inconclusive).</p>	092	N/AP
<p>These subjects' balsalazide plasma samples were processed as much as 91 minutes after the start of the centrifugation, in Periods 1 and 2. There is no impact since balsalazide is stable in human EDTA K2 plasma for 23 hours at room temperature.</p>	064-066, 149, 152, 153, 156*	067, 150, 154, 155, 157, 158*

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<b>Study No. 60652</b>		
<b>Type</b>	<b>Subject #s (Test)</b>	<b>Subject #s (Ref.)</b>
This subject consumed one piece (exact quantity unknown) of black forest chocolate cake 2 days 12 hours 54 minutes after study drug administration, in Period 1.	N/AP	158
This subject consumed approximately 40 mL of energy drink (Monster Beverage Co.) 2 days 13 hours 54 minutes after study drug administration, in Period 2.	158	N/AP
This subject consumed two chocolate almonds 2 days 11 hours 46 minutes after study drug administration, in Period 1.	162	N/AP

\*This deviation does not apply to all sampling time

**Comments on Adverse Events/Protocol Deviations:**

1. Ten (10) of the healthy male and female subjects did not complete the fed BE study (Table 28). Four (4) subjects (Nos. 40, 46, 112, and 114) were withdrawn from the study due to adverse events (AEs). While, six (6) subjects (Nos.01, 17, 25, 45, 86, and 124) elected to withdraw from the study. All of the subjects were discontinued in the study according to the firm’s protocol (Section 8.12).

According to the firm’s protocol a subject may be withdrawn from the study if they have an episode of diarrhea during the first 48 hours after dosing. In Period I, three (3) subjects (Nos. 46, 98, and 108) reported an episode of diarrhea within the allotted timeframe. However, only subject No. 46 was withdrawn from the study. The other two (2) subjects were dosed in Period 2 and allowed to complete the study.

Subject No.	Treatment	Period	Dosing Date and Time (hh:min)	Onset of AE Date and Time (hh:min)	Time Elapsed (hh:min)
46	B	I	01/18/2007 @ 07:10	01/18/2007 @ 11:40	03:30
98	A	I	01/25/2007 @ 07:34	01/25/2007 @ 07:42	00:08
108	B	I	01/25/2007 @ 07:54	01/25/2007 @ 17:50	09:57

\* Dosing time obtained from Study Drug Administration Log provided in the firm’s clinical report (Section 16.4)

\*\* Onset of AE obtained from AE event table provided in the firm’s clinical report (Section 16.2.7)

Therefore, the reviewer reevaluated the BE statistics with subject Nos. 98 and 108 excluded. The reviewer determined that the 90% confidence intervals for log-transformed AUC<sub>T</sub>, AUC<sub>I</sub>, C<sub>max</sub> are still within the acceptable range of 80-125% for balsalazide and 5-ASA.

2. Two-hundred and eight-one (281) AEs were reported during the fed BE study (Table 29). The data in Table 29 represents the number of AEs reported at least one time by a subject. One hundred and sixty-eight (168) AEs were reported after subjects received a single-oral dose of the test product. While, one-hundred and thirty-six (136) AEs were reported after subjects received a single-oral dose of the reference product.
3. According to the information provided in the firm’s clinical report, two (2) subjects (Nos. 26 and 40) reported experiencing SAEs during the fed BE study.
  - a. On February 04, 2007, subject No. 26 reported paralysis of the entire left side of the body, paralysis of legs, difficulty talking and muscular weakness on the left side. On January 30, 2007, the subject received a single-oral dose of the test product. The subject reported these AEs approximately 5 days after dosing. The subject went to the hospital and was hospitalized until (b) (6). The physician determined the AEs were from unknown origins. It was judged that the AEs were unrelated to the study medication. These serious adverse events resolved on February 5, 2007, with treatment, except for “Myasthenia” which was still unresolved on February 13, 2007. At that time, the severity of this adverse

event was judged as mild. The subject was not withdrawn from the study since all blood samples had been taken prior to the onset of the serious adverse events.

- b. Approximately nine (9) days after dosing in Period I, subject No. 40 reported experiencing serious pain at the left knee. The subject had knee surgery to remove a bump on the knee. The subject received the following concomitant medication for the treatment of pain:<sup>4</sup>

040	acetaminophen	1 x 325 mg	2007-01-12	09:00
	ibuprofen	1 x 300 mg	2007-02-05; 2007-02-06	unknown
			2007-02-07	10:15
			since 2007-01-26	each 4 hours
	acetaminophen/codeine phosphate	1 x 300 mg/ 30 mg	2007-02-07	10:15
			2007-02-05; 2007-02-06	unknown
			From 2007-01-30 to 2007-02-04	unknown
			7 x 300 mg/30 mg	unknown
	naproxen	1 x 375 mg	2007-02-05; 2007-02-06	unknown
			2007-02-07	10:15
2 x 300 mg/30 mg			unknown	

The AE was judged to be unrelated to the study medication. The subject was withdrawn from the study on January 29, 2007.

The reviewer agrees with the firm's decisions concerning subject Nos. 26 and 40.

5. According to the firm's protocol Section 6.5 Restrictions, subjects will be required to abstain from 'food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours prior to dosing until after the last sample collection of each period. However, approximately 2 days after dosing, subject Nos. 37, 75, 92, 158, and 162 consumed products containing xanthine ([Table 30](#)). The last blood sample collection time for balsalazide was at 48 hours, whereas for 5-ASA it was 72 hours. The reviewer determined that based on the review of the plasma concentration data and PK profiles for these subjects, it does not appear that it will have an impact on the outcome of the study for 5-ASA.

<sup>4</sup> A section of Non-Scheduled Medication Table provided in Section 16.2.7.1 of the clinical report.

**4.1.2.3 Bioanalytical Results**

**Table 31. Assay Validation – Within the Fed Bioequivalence Study<sup>3</sup>**

**A. Balsalazide**

Bioequivalence Study No. 60652NYV								
Balsalazide								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	1.00	2.00	20.03	100.16	200.32	300.48	400.64	500.80
Inter day Precision (%CV)	5.00	4.00	2.70	2.46	2.24	2.26	2.65	2.74
Inter day Accuracy (%)	100.00	100.00	101.70	100.69	99.82	100.53	98.51	98.85
Linearity	0.9953 to 0.9998							
Linearity Range (ng/mL)	1.00 to 500.80							
Sensitivity/LOQ (ng/mL)	1.00							

Bioequivalence Study No. 60652NYV				
Balsalazide				
Parameter	Quality Control Samples			
Concentration (ng/mL)	3.00	150.24	350.56	75.12
Inter day Precision (%CV)	7.21	2.67	2.61	3.46
Inter day Accuracy (%)	101.67	100.39	99.27	101.26

**B. Mesalamine (5-aminosalicylic acid, 5-ASA)**

Bioequivalence Study No. 60652OSA								
5-ASA								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	1.01	2.01	5.03	20.13	40.26	60.38	80.51	100.64
Inter day Precision (%CV)	7.14	5.26	3.61	3.37	3.71	3.38	2.91	3.33
Inter day Accuracy (%)	97.03	103.98	104.77	98.71	95.75	99.07	98.46	102.43
Linearity	0.9871 to 0.9996							
Linearity Range (ng/mL)	1.01 to 100.64							
Sensitivity/LOQ (ng/mL)	1.01							

Bioequivalence Study No. 60652OSA				
5-ASA				
Parameter	Quality Control Samples			
Concentration (ng/mL)	3.02	30.17	70.39	15.08
Inter day Precision (%CV)	124.09	4.97	4.18	18.99
Inter day Accuracy (%)	100.33	94.76	91.50	99.87

**Comments on Study Assay Validation:**

Acceptable.

Any interfering peaks in chromatograms?	No significant interfering peaks
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

**Comments on Chromatograms:**

Acceptable.

**Table 32. SOP's Dealing with Bioanalytical Repeats of Study Samples<sup>3</sup>**

SOP No.	Effective Date of SOP	SOP Title
ANI 156.09	2005-09-23	Sample Reassays and Reporting of Final Concentrations

**Table 33. Additional Comments on Repeat Assays**

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

**Summary/Conclusions, Study Assays:**

1. For 5-ASA, the inter day precision (% CV) for the quality control (QC) sample No. 1, 3.02 ng/mL and QC sample No. 4, 15.09 ng/mL was 124.09% and 18.99%, respectively ([Table 31-B](#)). The high % CV values were due to the outlier concentration values.
  - a. For QC sample No. 1, the outlier concentration values were 53.79, -0.05, 1.68 ng/mL, observed in analytical runs 22, 49 and 75, respectively.
  - b. For QC sample No. 4, the outlier concentration values were 49.26 and -0.01 ng/mL observed in analytical runs 22 and 49, respectively.

For QC sample No. 1 and 4, the firm stated that the calculated statistics without these values yield % CV of 6.75% and 14.95%, respectively. The reviewer agrees with the firm's assessment.

2. The study assay is acceptable.

#### 4.1.2.4 Pharmacokinetic Results

##### A. Balsalazide

**Table 34. Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in [Table 42](#) and [Figure 3](#)

<b>Fed Bioequivalence Study No. 60652</b>									
<b>Balsalazide</b>									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
<b>AUC<sub>0-t</sub> (hr *ng/ml)</b>	1812.26	61.95	501.13	7273.91	1796.61	50.53	653.56	5234.89	1.01
<b>AUC<sub>∞</sub> (hr *ng/ml)</b>	1983.75	57.74	555.18	7660.86	1961.40	47.35	726.70	5308.10	1.01
<b>C<sub>max</sub> (ng/ml)</b>	524.75	105.86	89.31	3582.76	538.64	92.33	87.28	3304.05	0.97
<b>T<sub>max</sub>* (hr)</b>	0.50	.	0.25	6.00	0.50	.	0.25	6.00	1.00
<b>Kel (hr<sup>-1</sup>)</b>	0.03	39.09	0.02	0.11	0.04	38.68	0.02	0.11	0.94
<b>T1/2 (hr)</b>	22.60	30.25	6.34	40.10	21.52	33.12	6.36	46.01	1.05

\* T<sub>max</sub> values are presented as median, range

**Table 35. Geometric Means and 90% Confidence Intervals - Firm Calculated**

<b>Balsalazide Disodium Capsules, 750 mg</b>				
<b>Dose (3 x 750 mg Capsules)</b>				
<b>Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals</b>				
<b>Balsalazide</b>				
<b>Fed Bioequivalence Study No. 60652</b>				
Parameter (units)	Test	Reference	% Ratio	90% C.I.
<b>AUC<sub>0-t</sub> (hr *ng/ml)</b>	1586.55	1595.01	99.47	95.72-103.37
<b>AUC<sub>∞</sub> (hr *ng/ml)</b>	1758.42	1761.23	99.84	96.14-103.68
<b>C<sub>max</sub> (ng/ml)</b>	366.27	386.61	94.74	87.17-102.97

**Table 36. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Balsalazide					
Fed Bioequivalence Study No. 60652					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (hr *ng/ml)	1586.55	1595.01	0.99	95.71	103.38
AUC <sub>∞</sub> (hr *ng/ml)	1758.42	1761.23	1.00	96.13	103.69
C <sub>max</sub> (ng/ml)	366.27	386.61	0.95	87.15	102.99

**Table 37. Additional Study Information, Fed BE Study No. 60652**

Root mean square error, AUC <sub>0-t</sub>	0.2077	
Root mean square error, AUC <sub>∞</sub>	0.2040	
Root mean square error, C <sub>max</sub>	0.4500	
	Test	Reference
Kel and AUC <sub>∞</sub> determined for how many subjects?	160	160
Do you agree or disagree with firm's decision?	--	--
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C <sub>max</sub>	0	0
Were the subjects dosed as more than one group?	Yes	Yes

Ratio of AUC <sub>0-t</sub> /AUC <sub>∞</sub>				
Treatment	n	Mean	Minimum	Maximum
Test	160	0.90	0.72	1.00
Reference	160	0.91	0.70	0.99

**B. Mesalamine (5-aminosalicylic acid, 5-ASA)**

**Table 38. Arithmetic Mean Pharmacokinetic Parameters**

Mean plasma concentrations are presented in [Table 42](#) and [Figure 3](#)

Fed Bioequivalence Study No. 60652									
5-ASA									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC <sub>0-t</sub> (hr *ng/ml)	1636.18	67.38	44.15	6362.76	1669.46	72.16	160.54	6949.94	0.98
AUC <sub>∞</sub> (hr *ng/ml)	1805.15	69.60	56.82	7002.29	1840.90	71.70	165.63	6960.40	0.98
C <sub>max</sub> (ng/ml)	93.44	81.38	3.39	513.01	94.85	84.78	11.16	608.01	0.99
T <sub>max</sub> * (hr)	19.00	.	8.00	60.00	23.00	.	6.00	59.98	0.83
K <sub>el</sub> (hr <sup>-1</sup> )	0.12	120.03	0.02	0.89	0.12	104.27	0.01	1.04	1.01
T <sub>1/2</sub> (hr)	11.07	75.59	0.78	42.46	10.37	80.24	0.67	49.85	1.07

\* T<sub>max</sub> values are presented as median, range

**Table 39. Geometric Means and 90% Confidence Intervals - Firm Calculated**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
5-ASA				
Fed Bioequivalence Study No. 60652				
Parameter (units)	Test	Reference	% Ratio	90% C.I.
AUC <sub>0-t</sub> (hr *ng/ml)	1297.99	1298.19	99.98	92.50-108.07
AUC <sub>∞</sub> (hr *ng/ml)	1404.82	1416.37	99.19	91.58-107.43
C <sub>max</sub> (ng/ml)	71.54	72.96	98.05	90.32-106.45

**Table 40. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

Balsalazide Disodium Capsules, 750 mg Dose (3 x 750 mg Capsules) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
5-ASA					
Fed Bioequivalence Study No. 60652					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC <sub>0-t</sub> (hr *ng/ml)	1292.99	1306.58	0.99	91.61	106.90
AUC <sub>∞</sub> (hr *ng/ml)	1421.52	1439.91	0.99	91.27	106.78
C <sub>max</sub> (ng/ml)	71.47	73.74	0.97	89.45	105.02

**Table 41. Additional Study Information, Fed BE Study No. 60652**

Root mean square error, AUC <sub>0-t</sub>	0.4116	
Root mean square error, AUC <sub>∞</sub>	0.3616	
Root mean square error, C <sub>max</sub>	0.4279	
	Test	Reference
Kel and AUC <sub>∞</sub> determined for how many subjects?		
Do you agree or disagree with firm's decision?	--	--
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	2	1
first measurable drug concentration as C <sub>max</sub>	0	0
Were the subjects dosed as more than one group?	Yes	Yes

Ratio of AUC <sub>0-t</sub> /AUC <sub>∞</sub>				
Treatment	n	Mean	Minimum	Maximum
Test	118	0.93	0.52	1.00
Reference	118	0.93	0.52	1.00

**Comments on Pharmacokinetic and Statistical Analysis:**

1. The firm assayed the plasma concentrations and provided the plasma profiles for balsalazide and 5-ASA.
2. Balsalazide is a highly-variable drug. The root-mean square error for LC<sub>max</sub> is 45%.
3. 5-ASA is a highly variable drug. The root-mean square error for LAUC<sub>T</sub>, LAUC<sub>I</sub> and LC<sub>max</sub> are 41%, 36% and 43%, respectively.

4. For balsalazide and 5-ASA, the firm and reviewer pooled the data for the four (4) groups to conduct BE statistical evaluations.
5. For balsalazide, the data for one-hundred (160) subjects were used in BE statistical evaluations.
6. For 5-ASA, the data for one-hundred and fifty-seven (157) subjects were used in BE statistical evaluations. In Period II, subject Nos. 55, 94 and 95 at time 0.0 hrs, had a pre-dose concentration values for 5-ASA which was greater than 5% of their  $C_{max}$ . The subjects pre-dose concentrations and  $C_{max}$  values are provided in the table below:

Subject	Treatment	Pre-dose concentration (ng/mL)	Cmax (ng/mL)
55	B	63.93	85.54
94	A	19.04	30.11
95	A	14.83	90.67

According to the FDA' Guidance to Industry, 2003 *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Consideration*, the subjects should be dropped from all BE statistical evaluations. Therefore, the firm did not include the three (3) subjects in BE statistical evaluations. The reviewer agrees with the firm's decision.

7. The firm and the reviewer calculated the PK parameters ( $AUC_{\infty}$ ,  $AUC_T$ ,  $C_{max}$ ,  $T_{max}$ , and  $K_{el}$ ) for balsalazide and 5-ASA. Statistical analysis was performed on the PK parameters using the GLM procedure of SAS with a 90% confidence interval. The reviewer agrees with the firm's results for balsalazide and 5-ASA.
8. For 5-ASA, the firm did not calculate the elimination rate constant,  $K_{el}$  and  $AUC_1$  for thirty-nine (39) subjects (Nos. 04, 05, 06, 09, 10, 11, 21, 23, 28, 31, 41, 44, 50, 51, 52, 59, 60, 65, 69, 70, 78, 81, 101, 109, 110, 116, 123, 126, 127, 129, 132, 137, 142, 144, 145, 147, 148, 149, and 161) due to either low correlation coefficients of ln-linear portion of the terminal elimination phase or an insufficient number of concentrations in the terminal phase. The reviewer agrees with the firm's decision.

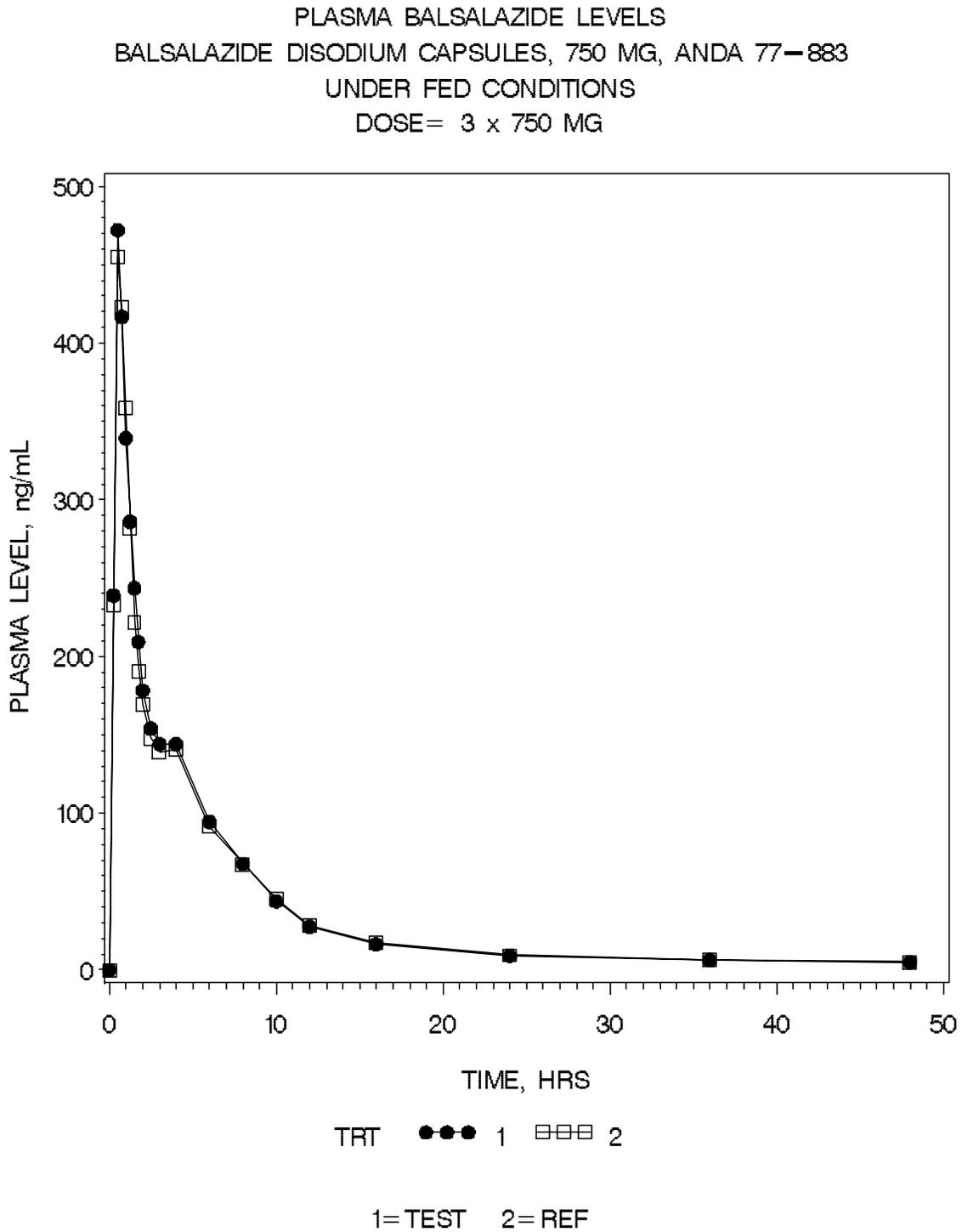
**Summary/Conclusions, Single-Dose Fed Bioequivalence Study:**

The single-dose fed bioequivalence study is acceptable.

**Table 42. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**

Balsalazide					
Time (hr)	Test (n=160)		Reference (n=160)		Ratio Mean (ng/mL)
	Mean (ng/mL)	CV%	Mean (ng/mL)	Time (hr)	
0.00	0.00	.	0.00	0.00	0.00
0.25	239.10	108.70	233.16	0.25	239.10
0.50	472.21	113.81	455.16	0.50	472.21
0.75	416.87	117.81	422.86	0.75	416.87
1.00	339.47	114.83	359.13	1.00	339.47
1.25	286.11	124.30	281.47	1.25	286.11
1.50	243.70	128.46	221.81	1.50	243.70
1.75	209.41	117.94	190.97	1.75	209.41
2.00	178.44	94.42	169.77	2.00	178.44
2.50	154.14	73.92	147.81	2.50	154.14
3.00	144.34	57.68	139.01	3.00	144.34
4.00	144.24	48.19	140.87	4.00	144.24
6.00	94.62	65.44	92.02	6.00	94.62
8.00	67.73	61.75	67.70	8.00	67.73
10.00	43.94	75.17	45.18	10.00	43.94
12.00	27.73	69.15	28.14	12.00	27.73
16.00	16.49	77.18	17.58	16.00	16.49
24.00	9.23	60.11	9.44	24.00	9.23
36.00	6.30	53.82	6.39	36.00	6.30
48.00	4.96	54.07	5.08	48.00	4.96

**Figure 3. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**



**Table 43. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**

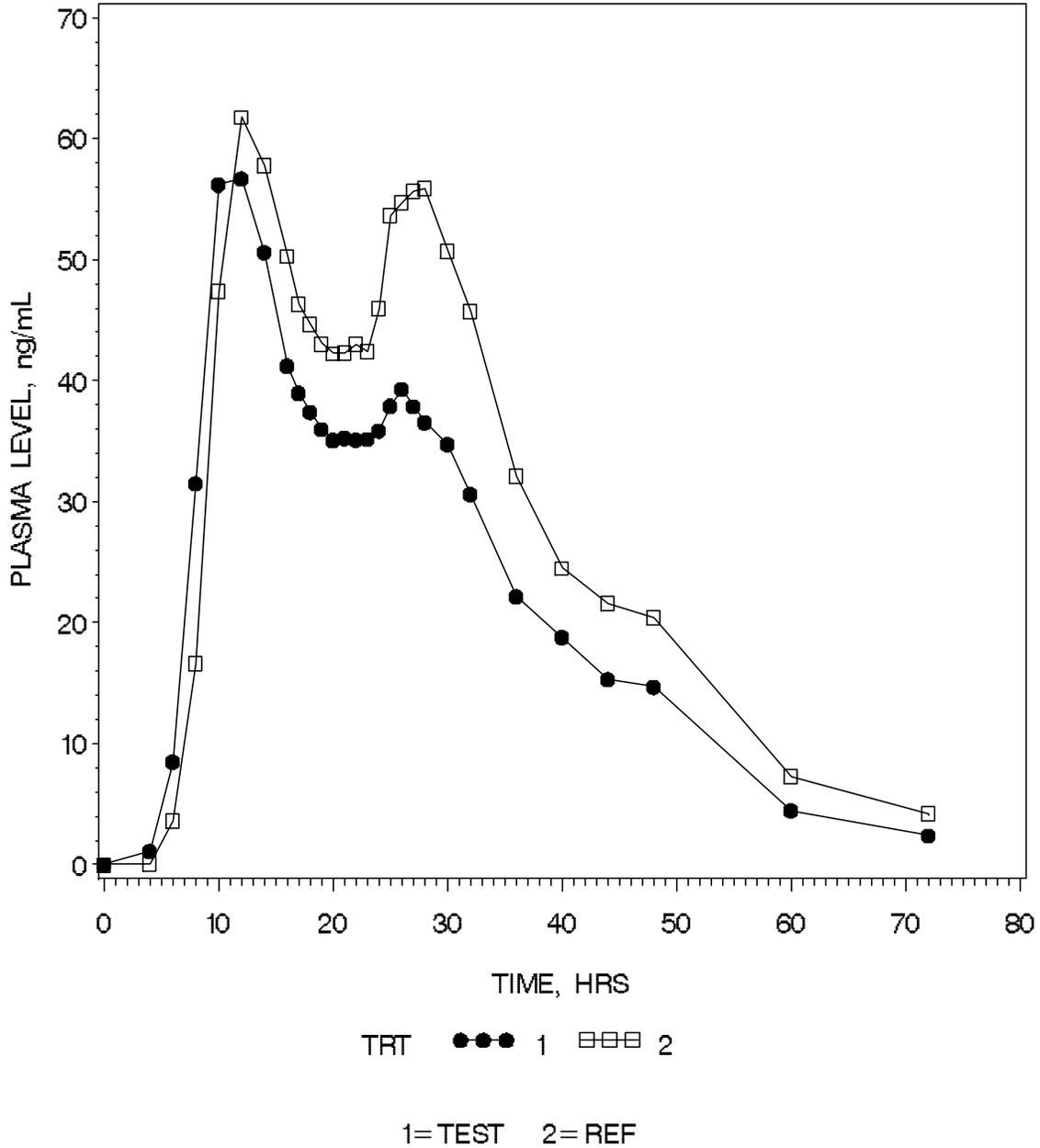
5-ASA					
Time (hr)	Test (n=157)		Reference (n=157)		Ratio Mean (ng/mL)
	Mean (ng/mL)	CV%	Mean (ng/mL)	Time (hr)	
0.00	0.00	.	0.00	0.00	0.00
4.00	1.10	715.67	0.05	4.00	1.10
6.00	8.48	283.72	3.64	6.00	8.48
8.00	31.50	185.76	16.66	8.00	31.50
10.00	56.19	121.27	47.37	10.00	56.19
12.00	56.69	98.20	61.77	12.00	56.69
14.00	50.60	88.98	57.76	14.00	50.60
16.00	41.21	85.90	50.30	16.00	41.21
17.00	38.97	86.67	46.32	17.00	38.97
18.00	37.39	85.55	44.63	18.00	37.39
19.00	35.98	88.62	43.06	19.00	35.98
20.00	35.05	87.98	42.25	20.00	35.05
21.00	35.24	86.32	42.27	21.00	35.24
22.00	35.10	79.15	43.03	22.00	35.10
23.00	35.16	75.77	42.45	23.00	35.16
24.00	35.85	69.08	46.00	24.00	35.85
25.00	37.89	75.91	53.67	25.00	37.89
26.00	39.29	76.16	54.69	26.00	39.29
27.00	37.88	76.51	55.64	27.00	37.88
28.00	36.55	82.37	55.87	28.00	36.55
30.00	34.73	89.66	50.76	93.40	0.68
32.00	30.59	94.88	45.75	94.77	0.67
36.00	22.15	116.22	32.16	95.89	0.69
40.00	18.79	129.32	24.51	104.58	0.77
44.00	15.29	123.31	21.62	104.67	0.71
48.00	14.68	124.38	20.44	117.20	0.72

ANDA 77-883  
Single-Dose Fed Bioequivalence Study Review

60.00	4.45	214.01	7.25	216.56	0.61
72.00	2.39	238.21	4.17	239.50	0.57

**Figure 4. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study**

PLASMA MESALAMINE (5-ASA) LEVELS  
BALSALAZIDE DISODIUM CAPSULES, 750 MG, ANDA 77-883  
UNDER FED CONDITIONS  
DOSE= 3 x 750 MG



## 4.2 Formulation Data<sup>3,5</sup>

Ingredient	Amount (mg)/Capsule	Amount (%) 750 mg Capsule
	750 mg	
(b) (4)		
Balsalazide Disodium Dihydrate	750	99.3
Colloidal Silicon Dioxide	(b) (4)	(b) (4)
Magnesium Stearate		
(b) (4)		-
Hard Gelatin Capsule - white/white opaque		-
<b>Coating</b>		
None	N/A	-
Total	755	100
(b) (4)		
*Detailed composition of Capsules and Printing Ink can be found in module section 3.2.P.4 (Control of Excipients).		

<b>Is there an overage of the active pharmaceutical ingredient (API)?</b>	NO
<b>If the answer is yes, has the appropriate chemistry division been notified?</b>	N/A
<b>If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?</b>	N/A
<b>Comments on the drug product formulation:</b>	The formulation is acceptable. The Division of Chemistry previously reviewed the firm's formulation data.

- <sup>5</sup> 1. Division of System Files v 2.0. ANDA #77-883. Bioequivalence Review. Biopharmaceutics. N 000 03-Nov-2005 and N 077883 N 000 AB 16-Oct-2006.  
 2. Division of System Files v 2.0. ANDA #77-883. ---. Chemist. N 077883 N 000 AC 15-Jun-2006.

### 4.3 Dissolution Data

<b>Dissolution Review Path</b>	<ol style="list-style-type: none"> <li>V:\DIVISION\BIO\Bio Temporary-Ra\77883D0805.doc</li> <li>Division of System Files v 2.0. ANDA #77-883. Bioequivalence Review. Biopharmaceutics. N 000 03-Nov-2005 and N 077883 N 000 AB 16-Oct-2006.</li> </ol>
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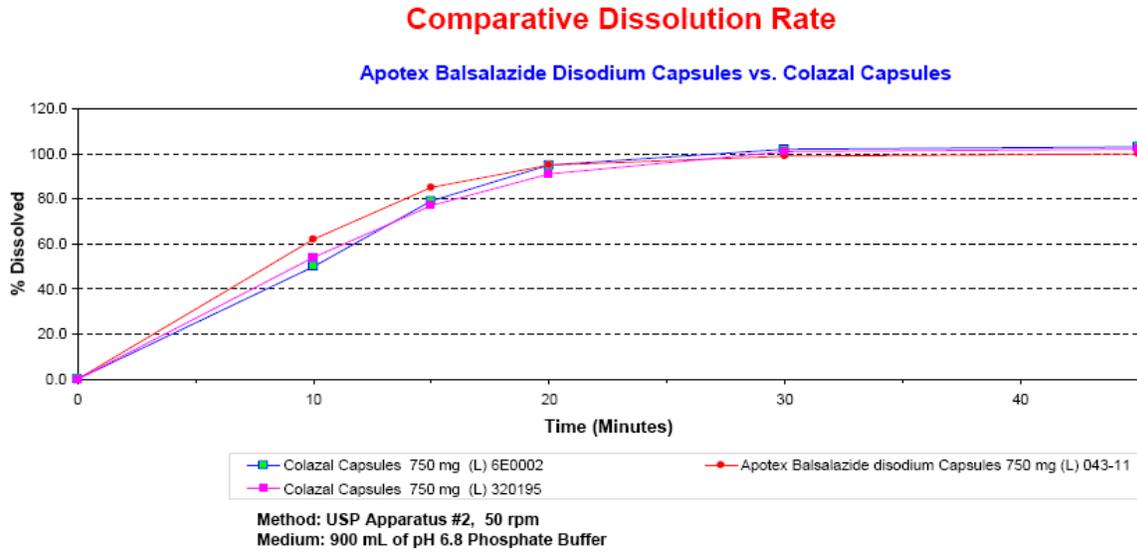
**Table 44. Dissolution Data<sup>3</sup>**

Dissolution Conditions		Apparatus:		USP Dissolution Apparatus #2							
		Speed of Rotation:		50 rpm							
		Medium:		Potassium Phosphate Buffer							
		Volume:		900 mL							
		Temperature:		37 ± 0.5°C							
Firm's Proposed Specifications		Q <sup>(b)</sup> <sub>(4)</sub> in 30 minutes									
Dissolution Testing Site (Name, Address)		Apotex Inc. 150 Signet Drive, Toronto Ontario M9L 1T9, Canada									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)					Study Report Location
						10	15	20	30	45	
Fasting Study No. 70038 and Fasting Study No. 60652	May 2005	<b>Product ID:</b> Balsalazide Disodium Capsules  <b>Batch No.:</b> 043-11  <b>Manufacturing Date:</b> June 2005  <b>Expiration Date:</b> June 2007	750 mg Capsules	12	Mean	62	85	95	99	100	Section 5.3.1.3
					Range	53-71	75-97	88-101	96-102	96-104	
					%RSD	10	8	4	2	2	
Fasting Study No. 70038	March 2007	<b>Product ID:</b> Colazal® Capsules, 750 mg  <b>Batch No.</b> 320195  <b>Manufacturing Date:</b> Not Available  <b>Expiration Date:</b> July 2009	750 mg Capsules	12	Mean	54	77	91	101	102	Section 5.3.1.3
					Range	39-68	62-86	72-101	83-105	85-106	
					%RSD	15	10	9	6	6	

**Table 34. Dissolution Data (continued)**

Dissolution Conditions		Apparatus:		USP Dissolution Apparatus #2							
		Speed of Rotation:		50 rpm							
		Medium:		Potassium Phosphate Buffer							
		Volume:		900 mL							
		Temperature:		37 ± 0.5 C							
Firm's Proposed Specifications		Q <sup>(b)</sup> <sub>(4)</sub> % in 30 minutes									
Dissolution Testing Site (Name, Address)		Apotex Inc. 150 Signet Drive, Toronto Ontario M9L 1T9, Canada									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)					Study Report Location
						10	15	20	30	45	
Fed Study No. 60652	Nov 2006	<b>Product ID:</b> Colazal® Capsules, 750 mg  <b>Batch No.</b> 6E0002  <b>Manufacturing Date:</b> Not Available  <b>Expiration Date:</b> March 2009	750 mg Capsules	12	Mean	50	79	95	102	103	
					Range	15-69	48-102	81-105	96-110	95-110	
					%RSD	30	19	9	4	4	

Figure 5. Dissolution Profiles<sup>6</sup>



<sup>6</sup> The figure is provided by the firm.

#### 4.4 Detailed Regulatory History (If Applicable)

*Location: Division of System Files v 2.0. ANDA #77-883. Bioequivalence Review. Biopharmaceutics. N 000 03-Nov-2005 and N 077883 N 000 AB 16-Oct-2006.*

On November 03, 2005, the firm submitted its application for Balsalazide Disodium Capsules, 750 mg. The application contained only a fasting BE study comparing its Balsalazide Disodium Capsules, 750 mg to the reference-listed drug (RLD), Colazal<sup>®</sup> Capsules, 750 mg by Salix Pharmaceuticals, Inc. The fasting BE study No. 50526 was designed as a two-way, **two-group** crossover study in healthy, adult males subjects (Treatment Group No. 01, N = 36, Treatment Group No. 02, N =41). The male subjects received a single oral dose of 3 x 750 mg capsules. In this study there was no statistical significant group-by-treatment effect. The subjects were combined into one group for pharmacokinetic and statistical analyses, N=72 (5 subjects voluntarily withdrew).

Statistical analysis of the plasma concentration data for the parent compound demonstrated bioequivalence. However, statistical analyses of the plasma concentration data of the active metabolite, 5-ASA did not demonstrate bioequivalence. The 90% CI for  $LAUC_T$ ,  $LAUC_I$ , and  $LC_{max}$  were as follows:

PK Parameter	90% CI
$LAUC_T$	<b>73.94-105.42%</b>
$LAUC_{\infty}$	<b>79.16-100.23%</b>
$LC_{max}$	<b>74.25-100.30%</b>

The firm concluded that one of the subjects (No. 34) in the study had aberrant plasma 5-ASA concentrations in the fasting BE study therefore a re-dosing study (No. 60045) was conducted. The re-dosing study did confirm the firm's assessment and the subject was subsequently dropped from the study. The study failed demonstrate bioequivalence. The 90% confidence intervals for  $LAUC_{\infty}$  was **79.16-100.23%**. However, after the DBE applied the Studentized Residual Outlier test, it was determined that another subject (No. 78) was an outlier as well. The firm did not exclude this subject from BE statistical evaluations. After excluding Subject Nos. 34 and 78 from statistical analyses of the study, plasma concentration data for 5-ASA still did not demonstrate bioequivalence. The 90% confidence intervals for  $LAUC_I$ , and  $LC_{max}$  were outside the range of 80-125%. The 90% confidence intervals for  $LAUC_{\infty}$  was **79.16-100.23%**, and  $LC_{max}$  was **78.62-96.85%**. Therefore, the firm was advised to either redose subject No. 78 or alternatively submit a new fasting BE study. Also, the firm's analytical reports were insufficient for its fasting BE study.

At the time of the original review, the firm's *in vitro* dissolution testing was incomplete due to the fact that the firm had not acknowledged and accepted the FDA-recommended dissolution method for its test product.

In addition, the labeling for the RLD product, Colazal<sup>®</sup> (balsalazide disodium) Capsules had been amended on September 21, 2006 to include statement pertaining to a food effect on absorption. As per the CDER Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance for Industry (posted January 31, 2003) the FDA recommends a

bioequivalence study under fed conditions for all orally administered immediate-release drug products if the RLD label makes statements about the effect of food on absorption or administration. Therefore, the firm was advised to conduct a single dose, two-way crossover fed in-vivo bioequivalence study comparing Balsalazide Disodium Capsules, 750mg to the reference listed drug, Colazal ® Capsules 750mg.

#### **4.5 Consult Reviews**

None.

Following this page, 279 pages withheld in full- (b)(4) SAS Output

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-883  
APPLICANT: Apotex, Inc.  
DRUG PRODUCT: Balsalazide Capsules, 750 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you have accepted the following FDA-recommended dissolution method and specification for your test product, Balsalazide Capsules, 750 mg:

Medium: Phosphate Buffer, pH 6.8  
Volume: 900 mL  
Temperature: 37°C ± 0.5°C  
USP Apparatus: II (Paddle)  
Rotational Speed: 50 rpm  
Sampling Times: 10, 15, 20, 30, and 45 minutes

The test product should meet the following specification:

NLT  $\frac{(b)}{(4)}\%$  (Q) of the labeled amount of balsalazide in the dosage form should be dissolved in 30 minutes.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

## 4.8 Outcome Page

ANDA: 77-883

1.	<b>Fasting Study</b>	Strength:	750 mg
	(STF)	Outcome:	<b>AC</b>
	Submission Date(s)	August 22, 2007	
	Clinical Site:	Anapharm, 2050, boul. René-Lévesque Ouest, Québec (Québec), Canada G1V 2K8	
	Analytical Site:	Anapharm, 2500, rue Einstein, Québec (Québec), Canada, G1P 0A2	
2.	<b>Fed Study</b>	Strength:	750 mg
	(STP)	Outcome:	<b>AC</b>
	Submission Date(s)	August 22, 2007	
	Clinical Site:	Anapharm, 2050, boul. René-Lévesque Ouest, Québec (Québec), Canada G1V 2K8	
	Analytical Site:	Anapharm, 2050, boul. René-Lévesque Ouest, Québec (Québec), Canada G1V 2K8	
3.	<b>Study Amendment</b>	Strength(s):	750 mg
	(STA)	Outcome:	<b>WC</b>
	Submission Date(s)	September 21, 2007	
	Clinical Site:	--	
	Analytical Site:	--	

<b>BIOEQUIVALENCE OUTCOME DECISIONS:</b>	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit
--	--

**COMPLETED ASSIGNMENT FOR 077883 ID: 551**

**10/4/2007 9:07:21 AM**

**Reviewer:** Braddy, April

**Date Completed:**

**Verifier:**

**Date Verified:**

**Division:** Division of Bioequivalence

**Description:**

---

*Productivity:*

<i>ID</i>	<i>Date Entered</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Productivity Weight</i>	<i>Subtotal</i>
551	8/22/2007	Bioequivalence Study	Fasting Study	1	1	1
551	8/22/2007	Bioequivalence Study	Fed Study	1	1	1
551	9/21/2007	Other	Study Amendment Without Credit (WC)	0	1	0
				<b>Bean Total:</b>		<b>2</b>

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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April Braddy  
10/5/2007 07:28:56 AM  
BIOPHARMACEUTICS

Moheb H. Makary  
10/5/2007 07:33:46 AM  
BIOPHARMACEUTICS

Dale Conner  
10/10/2007 10:08:21 AM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 77-883**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

November 3, 2005

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

*PTN  
- Falls Back  
McIntyre  
9/20/2006*

To Whom It May Concern,

**Re: Original Abbreviated New Drug Application  
Balsalazide Disodium Capsules, 750 mg  
Pre-Assigned ANDA No 077-883**

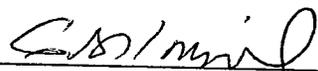
Apotex Inc. is hereby submitting an Original Abbreviated New Drug Application seeking approval to market Balsalazide Disodium Capsules, 750 mg. This product is bioequivalent to Colazal® Capsules manufactured by Salix Pharmaceuticals pursuant to NDA No 020610. Comparative, randomized, 2-way crossover bioavailability studies of Apotex Inc's Balsalazide Disodium Capsules and Colazal® Capsules under fasting conditions are included in this application.

A comparability protocol has been included in Section 3.2.R.2.P. In addition, the ANDA checklist has been included in Section 1.2 for screening purposes.

The eCTD is provided on a CD and original signed documents are attached.

Please direct any communications regarding this application to Kalpesh Shroff at Apotex Corp., the authorized US agent for Apotex Inc. at telephone (847) 279-7748 or fax: (847) 353-2982, or for any concerns related to the eCTD format, please do not hesitate to contact me by telephone at (416) 675-0338 ext. 4122 or fax: (416) 675-8410.

Sincerely,



Gloria Imperial  
Project Leader, Regulatory Affairs

RECEIVED  
NOV 07 2005  
OGD/CDER

**ANDA CHECKLIST**  
**FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION**

ANDA Nbr: 77-883      FIRM NAME: APOTEX INC.

**RELATED APPLICATION(S):**

First Generic Product Received? NO

DRUG NAME: BALSALAZIDE DISODIUM

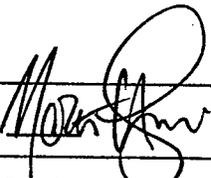
DOSAGE FORM: CAPSULES, 750 MG

<b>Bio Assignments:</b>		<input type="checkbox"/> Micro Review
<input checked="" type="checkbox"/> BPH	<input type="checkbox"/> BCE	
<input type="checkbox"/> BST	<input checked="" type="checkbox"/> BDI	

Random Queue: 7

Chem Team Leader: M. Scott Furness      PM: Yoon Kong      Labeling Reviewer: Koung Lee

Letter Date: NOVEMBER 3, 2005	Received Date: NOVEMBER 7, 2005
Comments: EC - 1 YES	On Cards: YES
Therapeutic Code: 8030700 ANTI-ULCER	
Archival Format: ELECTRONIC	Sections I (356H Sections per EDR Email)
Review copy: YES	E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections	
Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive)	NO
(Required for Non-USP drugs)	
Cover Letter YES	Table of Contents YES
PART 3 Combination Product Category	N Not a Part3 Combo Product
(Must be completed for ALL Original Applications)      Refer to the Part 3 Combination Algorithm	

<b>Reviewing</b> CSO/CST    Arianne Camphire  Date    5JAN06	<b>Recommendation:</b>  <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE to RECEIVE
<b>Supervisory Concurrence/Date:</b> 	<b>Date:</b> 9 JAN 2006
<b>ADDITIONAL COMMENTS REGARDING THE ANDA:</b> Kalpesh Shroff 954.349.4217 Does not meet bio requirements.	
<b>Top 200 Drug Product:</b>	



Study Type	<b>IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO</b> a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	<input type="checkbox"/>
Study Type	<b>TRANSDERMAL DELIVERY SYSTEMS NO</b> a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	<input type="checkbox"/>
Study Type	<b>NASALLY ADMINISTERED DRUG PRODUCTS NO</b> a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	<input type="checkbox"/>
Study Type	<b>TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES) NO</b> a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	<input type="checkbox"/>
Sec. VII	<b>Components and Composition Statements</b> 1. Unit composition and batch formulation x 2. Inactive ingredients as appropriate ok per IIG	<input checked="" type="checkbox"/>

<p><b>Sec. VIII</b></p>	<p><b>Raw Materials Controls</b></p> <p><b>1. Active Ingredients</b></p> <p>a. Addresses of bulk manufacturers x</p> <p>b. Type II DMF authorization letters or synthesis # (b) (4)</p> <p>c. COA(s) specifications and test results from drug substance mfg(s) x</p> <p>d. Applicant certificate of analysis x</p> <p>e. Testing specifications and data from drug product manufacturer(s) x</p> <p>f. Spectra and chromatograms for reference standards and test samples x</p> <p>g. CFN numbers</p> <p><b>2. Inactive Ingredients</b></p> <p>a. Source of inactive ingredients identified x</p> <p>b. Testing specifications (including identification and characterization) x</p> <p>c. Suppliers' COA (specifications and test results) x</p> <p>d. Applicant certificate of analysis x</p>	<p><input checked="" type="checkbox"/></p>
<p><b>Sec. IX</b></p>	<p><b>Description of Manufacturing Facility</b></p> <p>1. Full Address(es) of the Facility(ies) x</p> <p>2. CGMP Certification: yes</p> <p>3. CFN numbers</p>	<p><input checked="" type="checkbox"/></p>
<p><b>Sec. X</b></p>	<p><b>Outside Firms Including Contract Testing Laboratories</b></p> <p>1. Full Address x</p> <p>2. Functions x</p> <p>3. CGMP Certification/GLP yes</p> <p>4. CFN numbers</p>	<p><input checked="" type="checkbox"/></p>
<p><b>Sec. XI</b></p>	<p><b>Manufacturing and Processing Instructions</b></p> <p>1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) x</p> <p>2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Scale up = (b) (4)</p> <p>3. If sterile product: Aseptic fill / Terminal sterilization</p> <p>4. Filter validation (if aseptic fill)</p> <p>5. Reprocessing Statement yes</p>	<p><input checked="" type="checkbox"/></p>
<p><b>Sec. XII</b></p>	<p><b>In-Process Controls</b></p> <p>1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation</p> <p>Exhibit # GX0434</p> <p>TY = (b) (4)</p> <p>AY =</p> <p>AP =</p> <p>2. In-process Controls - Specifications and data yes</p>	<p><input checked="" type="checkbox"/></p>

<b>Sec. XIII</b>	<b>Container</b> 1. Summary of Container/Closure System (if new resin, provide data) x 2. Components Specification and Test Data (Type III DMF References) yes 3. Packaging Configuration and Sizes x 4. Container/Closure Testing x 5. Source of supply and suppliers address x	<input checked="" type="checkbox"/>
<b>Sec. XIV</b>	<b>Controls for the Finished Dosage Form</b> 1. Testing Specifications and Data x 2. Certificate of Analysis for Finished Dosage Form x	<input checked="" type="checkbox"/>
<b>Sec. XV</b>	<b>Stability of Finished Dosage Form</b> 1. Protocol submitted x 2. Post Approval Commitments x 3. Expiration Dating Period x 4. Stability Data Submitted complete a. 3 month accelerated stability data x b. Batch numbers on stability records the same as the test batch x	<input checked="" type="checkbox"/>
<b>Sec. XVI</b>	<b>Samples - Statement of Availability and Identification of:</b> 1. Drug Substance x 2. Finished Dosage Form x 3. Same lot numbers	<input checked="" type="checkbox"/>
<b>Sec. XVII</b>	<b>Environmental Impact Analysis Statement</b> yes	<input checked="" type="checkbox"/>
<b>Sec. XVIII</b>	<b>GDEA (Generic Drug Enforcement Act)/Other:</b> 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) yes	<input checked="" type="checkbox"/>

ANDA # 77-883

**IIG – Oral Administration  
Inactive Ingredient Search Results  
(Approved Drug Products not withdrawn for safety or efficacy)**

SILICON DIOXIDE, COLLOIDAL ORAL; TABLET 007631869 2109 (b) (4)

MAGNESIUM STEARATE ORAL; TABLET 000557040 4709 (b) (4)

ANDA 77883 Final Check List for Branch Chief

- 1) Check letter date and stamp date of ANDA vs. drafted letter.
- 2) Check for any NG arriving post stamp date but prior to Reg. Review.
- 3) Check for gross errors in letter.
- PTN 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)
- 5) Check address and contact person on letter vs. 356h.
- 6) Check for any t-cons and verify date and correspondence date.
- 7) Check Patent Certification information entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.
- 8) Check for any comments or problems raised by reviewer on Check List.
- NIA 9) If first generic, copy BE review and file.
- 10) Sign Check List.
- 11) Check electronic Orange Book to verify current patent information and correct RLD. Colateral
- NIA 12) Check for MOU patents
- 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.
- 14) Review Basis for Submission.
- 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.
- 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.
- PTN 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.
- 18) Pull USP information. (USP  yes  no)
- 19) Final Grammar review on letter.
- 20) Verify information in OGD Patent Tracking System.
- 21) EES slip.
- 22) Document in record book.

Signature

Mark H. [Signature]

date

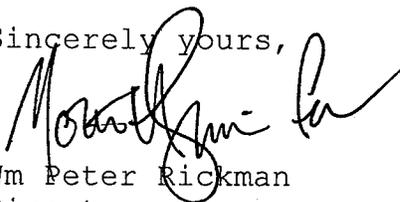
9/10/2006



Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Arianne Camphire  
Project Manager  
(301) 827-5837

Sincerely yours,

A handwritten signature in black ink, appearing to read "Wm Peter Rickman". The signature is fluid and cursive, with a large initial "W" and "P".

Wm Peter Rickman  
Director

Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA 77-883

DUP/Jackets  
HFD-600/Division File  
Field Copy  
HFD-610  
HFD-143/OIM/DRM

Endorsement:

HFD-615/M.Shimer, Chief, RSB

*Mona R...*

date

*9 Jan 2006*

HFD-615/A.Camphire, CSO

*Jean Min for Camphire*

date

*1/8/06*

Word File v:\FIRMSAM\APOTEX\LTRS&REV\77883.RTF.DOC

F/T

Refuse to Receive Letter

June 15, 2006

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

N/AC

To Whom It May Concern,

**Re: Balsalazide Disodium Capsules, 750 mg  
Pre-Assigned ANDA No 077-883  
Response to FDA Refuse To File Biequivalency Letter dated January 9, 2006.**

Apotex Inc. is hereby filing an amendment to ANDA No. 077-883 for Balsalazide Disodium Capsules 750 mg. This amendment is being submitted in response to the Refusal to file letter dated January 9, 2006.

A signed application form (FDA 356h) is provided.

The Amendment is in the eCTD format and is included on the enclosed CD. Original signed documents are attached.

I trust the additional information provided will be satisfactory. If you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at (416) 675-0338 ext. 4122, by fax at (416) 675-0340 or by e-mail at [gimperia@apotex.com](mailto:gimperia@apotex.com).

Sincerely,

  
for Gloria Imperial  
Project Leader, Regulatory Affairs–Solid Dose US, Apotex Inc.

cc: Bernice Tao, Associate Director, Regulatory Affairs-Solid Dose US, Apotex Inc.

**ANDA CHECKLIST  
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION**

ANDA Nbr: 77-883      FIRM NAME: APOTEX INC.

RELATED APPLICATION(S):

First Generic Product Received? NO

DRUG NAME: BALSALAZIDE DISODIUM

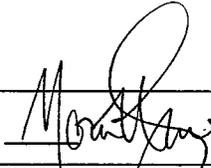
DOSAGE FORM: CAPSULES, 750 MG

<b>Bio Assignments:</b>		<input type="checkbox"/> Micro Review
<input checked="" type="checkbox"/> BPH	<input type="checkbox"/> BCE	
<input type="checkbox"/> BST	<input checked="" type="checkbox"/> BDI	

Random Queue: 7

Chem Team Leader: M. Scott Furness      PM: Yoon Kong      Labeling Reviewer: Koung Lee

Letter Date: NOVEMBER 3, 2005		Received Date: NOVEMBER 7, 2005	
Comments: EC - 1 YES		On Cards: YES	
Therapeutic Code: 8030700 ANTI-ULCER			
Archival Format: ELECTRONIC		Sections I (356H Sections per EDR Email)	
Review copy: YES		E-Media Disposition: YES SENT TO EDR	
Not applicable to electronic sections			
Field Copy Certification (Original Signature) YES			
Methods Validation Package (3 copies PAPER archive)		NO	
(Required for Non-USP drugs)			
Cover Letter YES		Table of Contents YES	
PART 3 Combination Product Category		N Not a Part3 Combo Product	
(Must be completed for ALL Original Applications)		Refer to the Part 3 Combination Algorithm	

<b>Reviewing</b> CSO/CST    Kwadwo Awuah  Date      8/10/06	<b>Recommendation:</b>  <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE to RECEIVE
<b>Supervisory Concurrence/Date:</b> 	Date: <u>15 Aug 2006</u>
<b>ADDITIONAL COMMENTS REGARDING THE ANDA:</b> ANDA was originally "RTF" on January 9, 2006 due to a deficiency in the BE Study. RTF letter in Volume 1.1. Apotex sent in an amendment dated June 15, 2006 addressing the Bioequivalence deficiency that was identified in the original ANDA. As per the email from DBE dated August 10, 2006, this application is acceptable for filing. All other BE issues will be addressed during the technical review. A copy of the referenced email has been placed in Volume 2.1 of the ANDA.	
<b>Contact Person: Tammy McIntire 954.349.4217</b>	
<b>Top 200 Drug Product:</b>	

Sec. I	<b>Signed and Completed Application Form (356h)</b> YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	<b>Basis for Submission</b> NDA# : 20-610 Ref Listed Drug: COLAZAL Firm: SALIX PHARMACEUTICALS INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. <p style="text-align: right;">Wavier Granted:</p>	☒
Sec. III	<b>Patent Certification</b> 1. Paragraph: III to '992 2. Expiration of Patent: 7/8/2006 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? <b>Exclusivity Statement:</b> YES	☒
Sec. IV	<b>Comparison between Generic Drug and RLD-505(j)(2)(A)</b> 1. Conditions of use x 2. Active ingredients x 3. Route of administration x 4. Dosage Form x 5. Strength x How Supplied (30's, 280, 350's and UD 10 x 10)	☒
Sec. V	<b>Labeling</b> (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL x 2. 1 RLD label and 1 RLD container label x 3. 1 side by side labeling comparison with all differences annotated and explained x 4. Was a proprietary name request submitted? no (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	<b>Bioavailability/Bioequivalence</b> <b>1. Financial Certification (Form FDA 3454) and Disclosure Statement (Form 3455)</b> YES <b>2. Request for Waiver of In-Vivo Study(ies):</b> NA <b>3. Formulation data same?</b> (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) <b>4. Lot Numbers of Products used in BE Study(ies):</b> Lot # 043-11 Ref # 311208 <b>5. Study Type: IN-VIVO PK STUDY(IES)</b> (Continue with the appropriate study type box below)	☒
Study Type	<b>IN-VIVO PK STUDY(IES)</b> (i.e., fasting/fed/sprinkle) FASTING ONLY a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) <i>BE data for 5-ASA out of 90% CI</i> No b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES complete	☒

Study Type	<p><b>IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO</b></p> <p>a. Properly defined BE endpoints (eval. by Clinical Team)</p> <p>b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120)</p> <p>c. Summary results indicate superiority of active treatments (test &amp; reference) over vehicle/placebo (p&lt;0.05) (eval. by Clinical Team)</p> <p>d. EDR Email: Data Files Submitted</p>	<input type="checkbox"/>
Study Type	<p><b>TRANSDERMAL DELIVERY SYSTEMS NO</b></p> <p>a. <u>In-Vivo PK Study</u></p> <ol style="list-style-type: none"> <li>1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC)</li> <li>2. In-Vitro Dissolution</li> <li>3. EDR Email: Data Files Submitted</li> </ol> <p>b. <u>Adhesion Study</u></p> <p>c. <u>Skin Irritation/Sensitization Study</u></p>	<input type="checkbox"/>
Study Type	<p><b>NASALLY ADMINISTERED DRUG PRODUCTS NO</b></p> <p>a. <u>Solutions</u> (Q1/Q2 sameness):</p> <ol style="list-style-type: none"> <li>1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming &amp; Repriming, Tail Off Profile)</li> </ol> <p>b. <u>Suspensions</u> (Q1/Q2 sameness):</p> <ol style="list-style-type: none"> <li>1. In-Vivo PK Study <ol style="list-style-type: none"> <li>a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC)</li> <li>b. EDR Email: Data Files Submitted</li> </ol> </li> <li>2. In-Vivo BE Study with Clinical EndPoints <ol style="list-style-type: none"> <li>a. Properly defined BE endpoints (eval. by Clinical Team)</li> <li>b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120)</li> <li>c. Summary results indicate superiority of active treatments (test &amp; reference) over vehicle/placebo (p&lt;0.05) (eval. by Clinical Team)</li> <li>d. EDR Email: Data Files Submitted</li> </ol> </li> <li>3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming &amp; Repriming, Tail Off Profile)</li> </ol>	<input type="checkbox"/>
Study Type	<p><b>TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES) NO</b></p> <p>a. Pilot Study (determination of ED50)</p> <p>b. Pivotal Study (study meets BE criteria 90%CI or 80-125)</p>	<input type="checkbox"/>
Sec. VII	<p><b>Components and Composition Statements</b></p> <p>1. Unit composition and batch formulation x</p> <p>2. Inactive ingredients as appropriate ok per IIG</p>	<input checked="" type="checkbox"/>

<p><b>Sec. VIII</b></p>	<p><b>Raw Materials Controls</b></p> <p><b>1. Active Ingredients</b></p> <p>a. Addresses of bulk manufacturers x</p> <p>b. Type II DMF authorization letters or synthesis # (b) (4)</p> <p>c. COA(s) specifications and test results from drug substance mfgr(s) x</p> <p>d. Applicant certificate of analysis x</p> <p>e. Testing specifications and data from drug product manufacturer(s) x</p> <p>f. Spectra and chromatograms for reference standards and test samples x</p> <p>g. CFN numbers</p> <p><b>2. Inactive Ingredients</b></p> <p>a. Source of inactive ingredients identified x</p> <p>b. Testing specifications (including identification and characterization) x</p> <p>c. Suppliers' COA (specifications and test results) x</p> <p>d. Applicant certificate of analysis x</p>	<p>☒</p>
<p><b>Sec. IX</b></p>	<p><b>Description of Manufacturing Facility</b></p> <p>1. Full Address(es) of the Facility(ies) x</p> <p>2. CGMP Certification: yes</p> <p>3. CFN numbers</p>	<p>☒</p>
<p><b>Sec. X</b></p>	<p><b>Outside Firms Including Contract Testing Laboratories</b></p> <p>1. Full Address x</p> <p>2. Functions x</p> <p>3. CGMP Certification/GLP yes</p> <p>4. CFN numbers</p>	<p>☒</p>
<p><b>Sec. XI</b></p>	<p><b>Manufacturing and Processing Instructions</b></p> <p>1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) x</p> <p>2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Scale up = (b) (4)</p> <p>3. If sterile product: Aseptic fill / Terminal sterilization</p> <p>4. Filter validation (if aseptic fill)</p> <p>5. Reprocessing Statement yes</p>	<p>☒</p>
<p><b>Sec. XII</b></p>	<p><b>In-Process Controls</b></p> <p>1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation</p> <p>Exhibit # GX0434</p> <p>TY = (b) (4)</p> <p>AY =</p> <p>AP =</p> <p>2. In-process Controls - Specifications and data yes</p>	<p>☒</p>

Sec. XIII	<b>Container</b> 1. Summary of Container/Closure System (if new resin, provide data) x 2. Components Specification and Test Data (Type III DMF References) yes 3. Packaging Configuration and Sizes x 4. Container/Closure Testing x 5. Source of supply and suppliers address x	<input checked="" type="checkbox"/>
Sec. XIV	<b>Controls for the Finished Dosage Form</b> 1. Testing Specifications and Data x 2. Certificate of Analysis for Finished Dosage Form x	<input checked="" type="checkbox"/>
Sec. XV	<b>Stability of Finished Dosage Form</b> 1. Protocol submitted x 2. Post Approval Commitments x 3. Expiration Dating Period x 4. Stability Data Submitted complete a. 3 month accelerated stability data x b. Batch numbers on stability records the same as the test batch x	<input checked="" type="checkbox"/>
Sec. XVI	<b>Samples - Statement of Availability and Identification of:</b> 1. Drug Substance x 2. Finished Dosage Form x 3. Same lot numbers	<input checked="" type="checkbox"/>
Sec. XVII	<b>Environmental Impact Analysis Statement</b> yes	<input checked="" type="checkbox"/>
Sec. XVIII	<b>GDEA (Generic Drug Enforcement Act)/Other:</b> 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) yes	<input checked="" type="checkbox"/>

ANDA # 77-883

**IIG – Oral Administration  
Inactive Ingredient Search Results  
(Approved Drug Products not withdrawn for safety or efficacy)**

SILICON DIOXIDE, COLLOIDAL ORAL; TABLET 007631869 2109 (b) (4)

MAGNESIUM STEARATE ORAL; TABLET 000557040 4709 (b) (4)

ANDA 77-883

AUG 16 2006

Apotex Corp.  
U.S. Agent for: Apotex Inc.  
Attention: Tammy McIntire  
2400 North Commerce Parkway, Suite 400  
Weston, FL 33326

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the "Refuse to Receive" letter dated January 9, 2006 and your amendment dated June 15, 2006.

NAME OF DRUG: Balsalazide Disodium Capsules, 750 mg

DATE OF APPLICATION: November 3, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 16, 2006

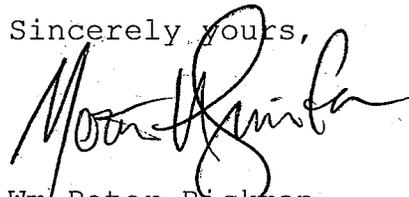
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Yoon Kong  
Project Manager  
301-827-5791

Sincerely yours,

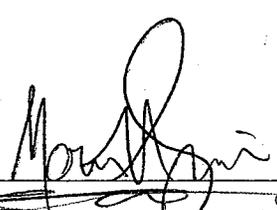


Wm Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA 77-883  
DUP/Jackets  
HFD-600/Division File  
Field Copy  
HFD-610  
HFD-143/OIM/DRM

Endorsement:

HFD-615/M. Shimer, Chief, RSB  
HFD-615/K. Awuah, CSO

  
~~\_\_\_\_\_~~ date 16 Aug 2006  
~~\_\_\_\_\_~~ date 8/16/06

Word File V:\FIRMSAM\APOTEX\LTRS&REV\77883.ACK.doc

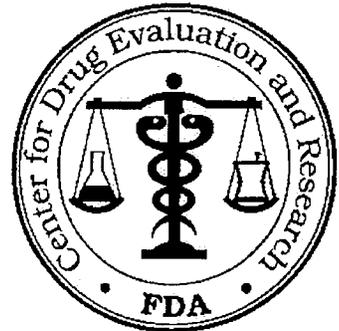
F/T by KAA 8/14/06

**ANDA Acknowledgment Letter!**

# BIOEQUIVALENCY AMENDMENT

ANDA 77-883

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Apotex Corp.  
U.S. Agent for Apotex Inc.

TEL: 954-349-4217

ATTN: Tammy McIntire

FAX: 954-349-4233

FROM: Christina Thompson *CT*

PROJECT MANAGER: 301-827-5847

**OCT 03 2006**

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on June 15, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Balsalazide Disodium Capsules, 750 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 9 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

### SPECIAL INSTRUCTIONS:

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

*CT*

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-883

APPLICANT: Apotex Inc.

DRUG PRODUCT: Balsalazide Disodium Capsules, 750 mg

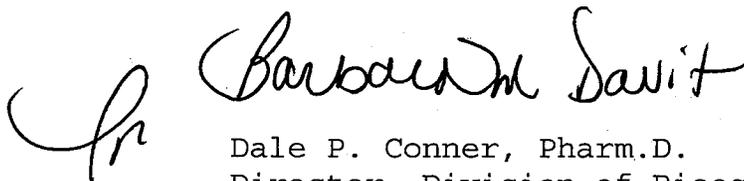
The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence study will be conducted later.

Your proposed dissolution method is not acceptable. Please conduct and submit dissolution testing using the following FDA-recommended method:

The dissolution testing should be conducted in 900 mL of Potassium Phosphate Buffer, pH 6.8, at 37°C using USP Apparatus 2 (paddle) with sinkers at 50 rpm. The samples should be taken at 5, 10, 15, 20, 30, 45, 60, 80 and 120 minutes.

In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file in Microsoft Word. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

Sincerely yours,



Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

## Templates for CTD Summary Tables

**Table 1. Summary of Bioavailability Studies**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)						Study Report Location
					C <sub>max</sub> (units/mL)	T <sub>max</sub> (hr)	AUC <sub>0-t</sub> (units)	AUC <sub>∞</sub> (units)	T <sub>1/2</sub> (hr)	K <sub>el</sub> (hr <sup>-1</sup> )	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M ± S.D.	Mn or Md	M ± S.D.	M ± S.D.	Mean	Mean	Vol. # p. #
			Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]		M ± S.D.	No SD	M ± S.D.	M ± S.D.	No SD	No SD	
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean y (range)	M ± S.D.	Mn or Md	M ± S.D.	M ± S.D.	Mean	Mean	Vol. # p. #
			Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]		M ± S.D.	No SD	M ± S.D.	M ± S.D.	No SD	No SD	

**Table 2. Statistical Summary of the Comparative Bioavailability Data**

Drug Dose (# x mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC <sub>0-t</sub>				
AUC <sub>∞</sub>				
C <sub>max</sub>				
Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC <sub>0-t</sub>				
AUC <sub>∞</sub>				
C <sub>max</sub>				

**Table 3. Bioanalytical Method Validation**

<b>Information Requested</b>	<b>Data</b>
<b>Bioanalytical method validation report location</b>	Provide the volume(s) and page(s)
<b>Analyte</b>	Provide the name(s) of the analyte(s)
<b>Internal standard (IS)</b>	Identify the internal standard used
<b>Method description</b>	Brief description of extraction method; analytical method
<b>Limit of quantitation</b>	LOQ, units
<b>Average recovery of drug (%)</b>	%
<b>Average recovery of IS (%)</b>	%
<b>Standard curve concentrations (units/mL)</b>	Standard curve range and appropriate concentration units
<b>QC concentrations (units/mL)</b>	List all the concentrations used
<b>QC Intraday precision range (%)</b>	Range or per QC
<b>QC Intraday accuracy range (%)</b>	Range or per QC
<b>QC Interday precision range (%)</b>	Range or per QC
<b>QC Interday accuracy range (%)</b>	Range or per QC
<b>Bench-top stability (hrs)</b>	hours @ room temperature
<b>Stock stability (days)</b>	days @ 4°C
<b>Processed stability (hrs)</b>	hours @ room temperature; hours @ 4°C
<b>Freeze-thaw stability (cycles)</b>	# cycles
<b>Long-term storage stability (days)</b>	17 days @ -20°C (or other)
<b>Dilution integrity</b>	Concentration diluted X-fold
<b>Selectivity</b>	No interfering peaks noted in blank plasma samples

**Table 4. Summary of In Vitro Dissolution Studies**

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Dissolution: Apparatus Speed of Rotation: rpm Medium: Volume: mL Temperature: °C	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap./Susp.		12					

**Table 5. Formulation Data**

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
<b>Cores</b>				
<b>Coating</b>				
<b>Total</b>			100.00	100.0

**Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study**

	Study No.	
	Treatment Groups	
	Test Product N =	Reference Product N =
<b>Age (years)</b>		
<b>Mean ± SD</b>		
<b>Range</b>		
<b>Groups</b>		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
<b>Sex</b>		
Female	N(%)	N(%)
Male	N(%)	N(%)
<b>Race</b>		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
<b>Other Factors</b>		



**Table 8. Reanalysis of Study Samples**

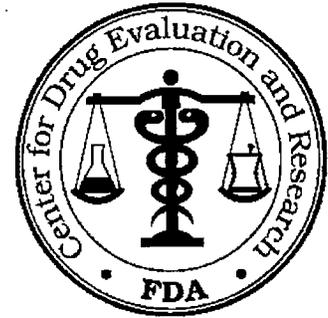
Study No. Additional information in Volume(s), Page(s)									
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis				
	Actual number		% of total assays		Actual number		% of total assays		
	T	R	T	R	T	R	T	R	
Pharmacokinetic <sup>1</sup>									
Reason A (e.g. below LOQ)									
Reason B									
Reason C									
Etc.									
Total									

<sup>1</sup> If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

**MINOR AMENDMENT**

ANDA 77-883

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Apotex Corp.  
U.S. Agent for Apotex Inc.

TEL: 954-349-4217

ATTN: Tammy McIntire

FAX: 954-349-4233

FROM: Yoon Kong

PROJECT MANAGER: (301) 827-5791

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 3, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Balsalazide Disodium Capsules, 750 mg.

Reference is also made to your amendment dated June 15, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments ( 2  pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

**SPECIAL INSTRUCTIONS:**

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**36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 77-883

APPLICANT: Apotex Inc.

DRUG PRODUCT: Balsalazide Disodium Capsules, 750 mg

A. The deficiencies presented below represent MINOR deficiencies.

1.

(b) (4)

2.

3.

4.

5.

6.

7.

8.

9.

10.

B. Comments:

1. Please provide updated stability data for the exhibit batches.
2. The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

Sincerely yours,

*{See appended electronic signature page}*

Florence Fang, Ph.D.  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Michael S Furness  
10/12/2006 01:54:46 PM

ORIG AMENDMENT

N/A/B

October 16, 2006

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

To Whom It May Concern,

**Re: Balsalazide Disodium Capsules 750 mg**  
**ANDA No 077-883**  
**BIOEQUIVALENCY AMENDMENT**  
**Response to FDA Deficiency Letter Dated October 3, 2006.**

Apotex Inc. is hereby filing an amendment to ANDA No. 077-883 for Balsalazide Disodium Capsules 750 mg. This amendment is being submitted in response to the bioequivalency deficiency letter dated October 3, 2006.

A signed application form (FDA 356h) is provided.

This amendment is provided for electronically in the eCTD format on the enclosed CD.

I trust the additional information provided will be satisfactory. If you have any questions or concerns regarding the enclosed, please do not hesitate to contact me by telephone at (416) 401-7889, by fax: (416) 401-3809, or email [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



\_\_\_\_\_  
Bernice Tao  
Director, Regulatory Affairs Solid Dose US

RECEIVED  
OCT 17 2006  
OGD / CDER



November 8, 2006

ORIG AMENDMENT

*N-000-AM*

Office of Generic Drugs  
CDER, Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

To Whom It May Concern:

**Re: MINOR AMENDMENT**  
**Balsalazide Disodium Capsules, 750 mg**  
**ANDA No. 077-883**

Apotex Inc. is hereby submitting a Minor Amendment to ANDA No. 077-883 for Balsalazide Disodium Capsules, 750 mg in response to the FDA Deficiency Letter dated October 12, 2006.

The Amendment is in eCTD format and is included on the enclosed CD. Both a pdf and MS Word copy of the amendment is provided. A signed Form FDA 356h is also provided.

I trust the additional information provided will be satisfactory. Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at (416) 401-7889, by fax at (416) 401-3807 or via email at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,

---

Berrice Tao  
Director, Regulatory Affairs – Solid Dose US

RECEIVED  
NOV 13 2006  
OGD / CDER



# BIOEQUIVALENCY AMENDMENT

ANDA 77-883

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Apotex Corp. U.S. Agent for Apotex Inc.

TEL: 905-884-2050

ATTN: Kalpesh Shroff

FAX: 905-508-2359 or 954-349-4233

FROM: Aaron Sigler

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on June 15, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Balsalazide Disodium Capsules, 750 mg.

Reference is also made to your amendment dated October 16, 2006.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-883

APPLICANT: Apotex Inc.

DRUG PRODUCT: Balsalazide Disodium Capsules, 750 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The DBE agrees with your decision to conduct a re-dosing study based on a hypothesis that Subject No. 34 showed aberrant mesalamine plasma concentrations during study #50256. However, the DBE noted that, based on the test/reference {AUC, or Cmax} ratios, Subject No. 78 may have also had an aberrant response. Thus, Subject no. 78 should have been re-dosed as well but was not included in the re-dosing study. Therefore, Subject No. 78 could have been excluded from the re-dosing study with bias toward favorable bioequivalence outcome. You are advised to re-dose Subject No.78 with several subjects (control group) chosen at random from the same study (study #50256). Alternatively, you may conduct a new fasting bioequivalence study. Therefore, the fasting BE study and the re-dosing study are incomplete.
2. Please provide a SOP for selecting suspected subjects with anomalous/outlying pharmacokinetic parameters for re-dosing study.
3. Please provide the bioanalytical summary tables for balsalazide and mesalamine for fasting BE Study No. 50256.

For balsalazide, the following tables are missing from Section 16.2.51 of the Bioanalytical Report:

Table 2A. Plasma EDTA K3 Balsalazide Concentrations (ng/mL) in Humans

Table 2B. Plasma EDTA K3 Balsalazide Concentrations (ng/mL) in Humans

Table 3. Repeat Analysis Results for Balsalazide in Human Plasma EDTA K3

Table 4. Summary of Study Sample Reassays

Table 5A and 5B. Summary of Analytical Runs  
Table 6. Calibration Curve Parameters for Balsalazide  
Calibration Standards in Human Plasma EDTA K3  
Table 7. Analytical Performance: Back-Calculated  
Concentration (ng/mL) of Balsalazide Calibration Curve  
Standard in (Human) (Plasma EDTA K3)  
Table 8. Analytical Performance of Balsalazide  
Quality Control Samples in Human Plasma EDTA K3

For mesalamine, the following tables are missing from  
Section 16.2.5.1 of the Bioanalytical Report:

Table 10A. Plasma EDTA K3 5-ASA Concentrations  
(ng/mL) in Humans  
Table 10B. Plasma EDTA K3 5-ASA Concentrations  
(ng/mL) in Humans  
Table 11. Repeat Analysis Results for 5-ASA in  
Human Plasma EDTA K3  
Table 12. Summary of Study Sample Reassays  
Table 13A and 13B. Summary of Analytical Runs  
Table 14. Calibration Curve Parameters for 5-ASA  
Calibration Standards in Human Plasma EDTA K3  
Table 15. Analytical Performance: Back-Calculated  
Concentration (ng/mL) of 5-ASA Calibration Curve Standard  
in (Human) (Plasma EDTA K3)  
Table 16. Analytical Performance of Balsalazide  
Quality Control Samples in Human Plasma EDTA K3

4. For the re-dosing fasting study No. 60045, please provide the bioanalytical method validation summary tables for balsalazide and mesalamine.
5. Please acknowledge the following dissolution method and specification.

The dissolution testing should be conducted in phosphate buffer, pH 6.8 at 37°C ± 0.5°C using apparatus II (Paddles) at 50 rpm with sinkers. The test product should meet the following specification:

Not less than  $\frac{(b)}{(4)}$  (Q) of the labeled amount of balsalazide in the dosage form is dissolved in 30 minutes

6. The labeling for the reference listed drug (RLD), Colazal® (balsalazide disodium) capsules, 750 mg has been changed to include statements about the effect of food on

absorption or administration of the capsule product. As per the CDER Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance for Industry (posted January 31, 2003) the FDA recommends a bioequivalence study under fed conditions for all orally administered immediate-release drug products if the RLD label makes statements about the effect of food on absorption or administration.

Therefore, please perform a single dose, two-way crossover fed in-vivo bioequivalence study comparing Balsalazide Disodium Capsules, 750mg to the reference listed drug, Colazal ® Capsules 750mg.

Please measure plasma concentrations of both balsalazide (parent) and mesalamine (metabolite) using an appropriate assay. For an acceptable fed bioequivalence study, the 90% confidence intervals of the test/reference geometric mean ratios for AUC and Cmax of both balsalazide and mesalamine should fall within the range of 0.8 to 1.25.

Sincerely yours,

*(See appended electronic signature page)*

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Barbara Davit  
12/12/2006 03:40:21 PM  
Signing for Dale P Conner

# **A** APOTEX CORP.

April 12, 2007

Mr. Gary Buehler, Director  
Office of Generic Drugs, CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

*N/MC*

**RE: ANDA # 77-883  
Balsalazide Disodium Capsules 750mg  
US Agent Change in Contact Information**

We would like to notify FDA (Office of Generic Drugs) of a change in the contact information of our US Agent, effective April 1, 2007 in relation to the above-mentioned ANDA application.

The new contact information is as follows:

Kiran Krishnan, MPharm, RAC  
Project Leader, Regulatory Affairs  
Apotex Corp.  
2400 N. Commerce Parkway Suite 400  
Weston FL  
33326

Telephone: (954) 384-3986  
Fax: (954) 349-4233

Should you have any questions, please do not hesitate to contact myself at tel: (416) 401-7889 or fax: (416) 401-3807.

Sincerely,

*Bernice Tao*  
Bernice Tao  
Director, Regulatory Affairs (US)

**RECEIVED  
APR 13 2007  
OGD / CDER**

Enclosure- Change in US Agent and Point Of Contact Information Letter

Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AB

To Whom It May Concern,

Re: **BIOEQUIVALENCY AMENDMENT**  
**Balsalazide Disodium Capsules 750 mg**  
**ANDA No 077-883**  
**Response to FDA Deficiency Letter Dated December 12, 2006**

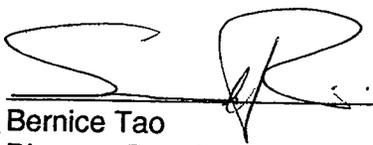
Apotex Inc. is hereby submitting a bioequivalency amendment to ANDA 077-883, Balsalazide Disodium Capsules 750 mg in response to the FDA deficiency letter dated December 12, 2006.

A signed application form (FDA 356h) is provided.

This amendment is submitted in the eCTD format on the enclosed compact disc. Apotex Inc. certifies that the media being submitted with this application is virus free and was scanned with McAfee VirusScan software.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp, the authorized US agent for Apotex Inc, by telephone at (954) 384-3986, or by fax at (954) 349-4223. For any other concerns, please do not hesitate to contact me by phone at (416) 401-7889, by fax at (416) 401-3809, or by e-mail at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,

  
for Bernice Tao  
Director, Regulatory Affairs US

Aug. 22, 2007.  
Date  
**RECEIVED**  
AUG 24 2007

N/XP

Office of Generic Drugs  
CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Re: **PATENT/EXCLUSIVITY AMENDMENT**  
**Balsalazide Disodium Capsules 750 mg**  
**ANDA No. 077-883**

To Whom It May Concern,

Apotex Inc. is hereby filing an exclusivity amendment to ANDA no. 077-883 for Balsalazide Disodium Capsules 750 mg. This amendment is being submitted to provide the FDA with an updated patent certification and revised exclusivity statement to include the NPP and ODE exclusivities and its corresponding pediatric (PED) exclusivity, as per the Electronic Orange Book.

The updated patent and revised exclusivity statement is included in section 1.3.5 Patent Exclusivity. Please note that revised Final Printed Labeling will be provided as a result of this revised exclusivity statement.

I trust that the information provided will be satisfactory. Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp, the authorized US agent for Apotex Inc, by telephone at (954) 384-3986, or by fax at (954) 349-4223. For any other concerns, please do not hesitate to contact me by phone at (416) 401-7889, by fax at (416) 401-3809, or by e-mail at [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



\_\_\_\_\_  
Bernice Tao  
Director, Regulatory Affairs US

Sept. 21, 2007  
Date:

**RECEIVED**

SEP 25 2007

**OGD**

ORIG AMENDMENT  
N/AB

Aaron Sigler  
Office of Generic Drugs  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Dear Aaron

Re: **BIOEQUIVALENCY TELEPHONE AMENDMENT**  
**Balsalazide Disodium Capsules 750 mg**  
**ANDA No 077-883**  
**Response to Telephone request dated September 10, 2007**

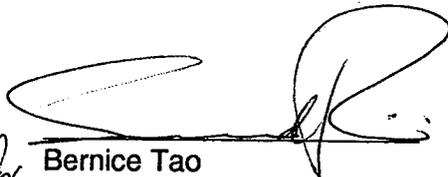
Apotex Inc. is hereby submitting a bioequivalency telephone amendment to ANDA 077-883, Balsalazide Disodium Capsules 750 mg in response to your telephone request on September 10, 2007 to Kiran Krishnan, our US Agent.

A signed application form (FDA 356h) is provided.

This amendment is submitted in the eCTD format on the enclosed compact disc. Apotex Inc. certifies that the media being submitted with this application is virus free and was scanned with McAfee VirusScan software.

We trust that the information provided is satisfactory. Should you have any questions, please do not hesitate to contact me by phone at (416) 401-7889, by fax at (416) 401-3809.

Sincerely,

  
for. Bernice Tao  
Director, Regulatory Affairs US

Sept. 21, 2007  
Date

**RECEIVED**

SEP 25 2007

**OGD**

Office of Generic Drugs  
CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

*N-000-AF*

To Whom It May Concern,

**Re: Labeling Amendment  
Balsalazide Disodium Capsules 750 mg  
ANDA No. 077-883**

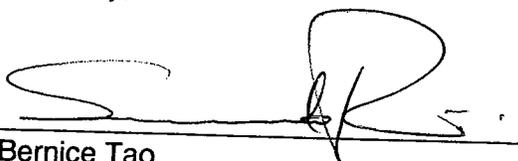
Apotex Inc is hereby submitting a label amendment to ANDA No. 077-883 for Balsalazide Disodium Capsules 750 mg. The amendment is being filed in response to the FDA generic labeling template for Balsalazide Disodium Capsules, dated September 13, 2007.

The revised labeling includes the physician's insert labeling in Word format as well as final printed labeling in pdf format. A side-by-side comparison of the physician's insert has also been provided.

This amendment is submitted in the eCTD format on the CD attached. Apotex Inc. certifies that the media being submitted with this application is virus free and was scanned with McAfee VirusScan software.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., at telephone (954) 984-3986 or fax: (954) 349-4233, or for any other concerns, please do not hesitate to contact me by telephone at (416) 401-7889, by fax: (416) 401-3809, or email [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



*for* Bernice Tao  
Director, Regulatory Affairs US  
Apotex Inc.

*Sept. 24, 2007*  
Date

**RECEIVED**

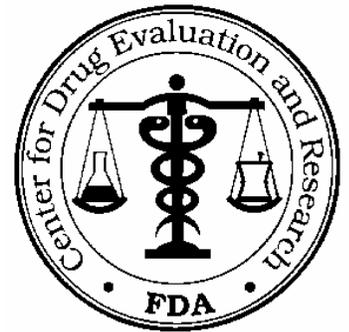
**SEP 26 2007**

**OGD**

# Telephone Fax

ANDA 77-883

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park  
North I  
7520 Standish Place  
Rockville, MD 20855-2773  
**240-276-8986**



TO: Apotex Corp,  
U.S. Agent for Apotex Inc.

TEL: 905-384-3986

ATTN: Kiran Krishnan

FAX: 954-349-4233

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Balsalazide Disodium Capsules, 750 mg.

Pages (including cover): 4

**SPECIAL INSTRUCTIONS:**

*Labeling Comments*

**REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

---

ANDA Number: 77-883      Dates of Submission: November 3, 2005, September 24, 2007

Applicant's Name: Apotex, Inc.

Established Name: Balsalazide Disodium Capsules, 750 mg

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Labeling Deficiencies:

1. CONTAINER (Bottles of 30s, 280s, and 350s):

Please separate the strength from the net quantity statement by inserting "Rx only" statement between them.

2. CARTON (10 X 10)

See CONTAINER comment above.

3. BLISTER

Please revise the individual blister to read "Balsalazide Disodium Blister" since only one capsule will be packaged in one blister.

2. INSERT:

a. GENERAL COMMENTS:

i. Please use italicized font for phrases such as "*in vivo*" and "*in vitro*" throughout the text.

ii. Revise "µg" to "mcg".

iii. Please justify the amount of sodium (approximately 86 mg) on the label.

b. HIGHLIGHTS

i. Add "Initial U.S. Approval: 2000" please refer to the template.

ii. Add the "RECENT MAJOR CHANGES" section, please refer to the template.

c. FULL PRESCRIBING INFORMATION: CONTENTS\*

Please separate this section from the HIGHLIGHTS and FULL PRESCRIBING INFORMATION sections by lines. Please refer to the template.

d. FULL PRESCRIBING INFORMATION

i. 1 INDICATIONS AND USAGE

Revise "Balsalazide" to "Balsalazide disodium capsules"

ii. Add margin markers to 2.2 and 5.1.

iii. 11 DESCRIPTION

Please add components of printing ink and "titanium dioxide" to the list of inactive ingredients

iv. 12.3 Pharmacokinetics

Elimination, penultimate paragraph, revise "3-6 g" to "3 to 6 g".

Submit labels and labeling electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

*{See appended electronic signature page}*

---

Wm. Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Lillie Golson  
10/25/2007 04:49:12 PM  
Lillie Golson for Wm. Peter Rickman

Ann Vu  
Office of Generic Drugs  
CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

*N-000-AF*

Dear Ms. Vu,

**Re: Labeling Amendment  
Balsalazide Disodium Capsules 750 mg  
ANDA No. 077-883**

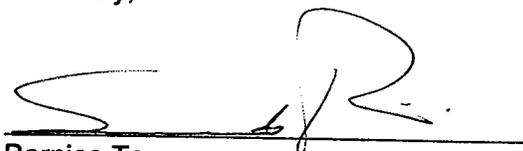
Apotex Inc is hereby submitting a label amendment to ANDA No. 077-883 for Balsalazide Disodium Capsules 750 mg. The amendment is being filed in response to the FDA telephone deficiency dated October 25, 2007.

The revised labeling includes the physician's insert (in Word format), container, carton and blister labels provided as final printed labeling in pdf format. A side-by-side comparison of the physician's insert has also been provided.

This amendment is submitted in the eCTD format on the CD attached. Apotex Inc. certifies that the media being submitted with this application is virus free and was scanned with McAfee VirusScan software.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., at telephone (954) 384-3986 or fax: (954) 349-4223, or for any other concerns, please do not hesitate to contact me by telephone at (416) 401-7889, by fax: (416) 401-3809, or email [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



*for* Bernice Tao  
Director, Regulatory Affairs US  
Apotex Inc.

*Oct. 31/07.*  
Date

**RECEIVED**

NOV 01 2007

**OGD**

Ann Vu  
Office of Generic Drugs  
CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**MAJ AMENDMENT**

*MAJ*

Dear Ms Vu

**Re: Labeling Amendment  
Balsalazide Disodium Capsules 750 mg  
ANDA No. 077-883**

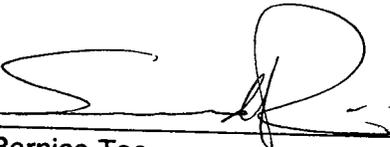
Apotex Inc is hereby submitting a labeling amendment to ANDA No. 077-883 for Balsalazide Disodium Capsules 750 mg. The amendment is being filed in response to your e mail request dated November 07, 2007 to Kiran Krishnan to update our labeling as per RLD labeling approved on November 02, 2007.

The revised labeling includes the physician's insert in Word format, as well as final printed labeling in pdf format. A side-by-side comparison of the physician's insert has also been provided. Please note there have been no changes to the container/carton labels since our last amendment. We have provided a representative container label for completeness.

This amendment is submitted in the eCTD format on the CD attached. Apotex Inc. certifies that the media being submitted with this application is virus free and was scanned with McAfee VirusScan software.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., at telephone (954) 384-3986 or fax: (954) 349-4233, or for any other concerns, please do not hesitate to contact me by telephone at (416) 401-7889, by fax: (416) 401-3809, or email [btao@apotex.com](mailto:btao@apotex.com).

Sincerely,



*for* Bernice Tao  
Director, Regulatory Affairs US  
Apotex Inc.

Nov. 09, 2007  
Date

**RECEIVED**

NOV 13 2007

**OGD**

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-883 Applicant Apotex Inc.  
Drug Balsalazide Disodium Capsules

Strength(s) 750 mg

APPROVAL  TENTATIVE APPROVAL  SUPPLEMENTAL APPROVAL (NEW STRENGTH)  OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. **Martin Shimer**

Chief, Reg. Support Branch

Date 21 DEC 07

Date \_\_\_\_\_

Initials MHS

Initials \_\_\_\_\_

Contains GDEA certification: Yes  No  Determ. of Involvement? Yes  No   
(required if sub after 6/1/92) Pediatric Exclusivity System

Patent/Exclusivity Certification: Yes  No

RLD = \_\_\_\_\_ NDA# \_\_\_\_\_

Date Checked \_\_\_\_\_

If Para. IV Certification- did applicant

Nothing Submitted

Notify patent holder/NDA holder Yes  No

Written request issued

Was applicant sued w/in 45 days: Yes  No

Study Submitted

Has case been settled: Yes  No

Date settled: \_\_\_\_\_

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes  No

Date of latest Labeling Review/Approval Summary \_\_\_\_\_

Any filing status changes requiring addition Labeling Review Yes  No

Type of Letter: Full Approval

Comments: At the time this ANDA was filed the applicant provided a PIII certification to the '992 patent which has since expired. On 9/21/2007, the ANDA sponsor amended their ANDA with an Exclusivity Statement expressing their intent to carve out the NPP+ped exclusivity and the ODE+ped exclusivity. Since these exclusivities have been omitted from the sponsor's labeling and there are no remaining unexpired patents this ANDA is eligible for Full Approval.

2. **Project Manager, Theresa Liu Team 7**  
Review Support Branch

Date 11/23/07

Date \_\_\_\_\_

Initials stcl

Initials \_\_\_\_\_

Original Rec'd date 11/3/05

EER Status Pending  Acceptable  OAI

Date Acceptable for Filing 6/16/06

Date of EER Status 10/24/06

Patent Certification (type) pIII

Date of Office Bio Review 10/24/07

Date Patent/Exclus. expires 7/8/06

Date of Labeling Approv. Sum 11/20/07

Citizens' Petition/Legal Case Yes  No   
(If YES, attach email from PM to CP coord)

Labeling Acceptable Email Rec'd Yes  No   
Labeling Acceptable Email filed Yes  No

First Generic Yes  No

Date of Sterility Assur. App. \_\_\_\_\_

Priority Approval Yes  No

Methods Val. Samples Pending Yes  No

(If yes, prepare Draft Press Release, Email it to Cecelia Parise)

MV Commitment Rcd. from Firm Yes  No

Acceptable Bio reviews tabbed Yes  No

Modified-release dosage form: Yes  No

Bio Review Filed in DFS: Yes  No

Interim Dissol. Specs in AP Ltr: Yes

Suitability Petition/Pediatric Waiver Yes

Pediatric Waiver Request Accepted  Rejected  Pending

Previously reviewed and tentatively approved  Date \_\_\_\_\_

Previously reviewed and CGMP def. /NA Minor issued  Date \_\_\_\_\_

Comments:

3. **Labeling Endorsement**

Reviewer:

Labeling Team Leader:

Date 11/26/07

Date 11/26/07

Name/Initials av

Name/Initials lg

Comments:

Hi Theresa,

From a labeling standpoint, this application is acceptable for approval. Please endorse the AP routing form on behalf of Ann and me.

Thanks

Lillie

Theresa,

Please sign off for me. I checked DSS, OB, and USP.

Thanks  
Ann

4. David Read (**PP IVs Only**) Pre-MMA Language included   
OGD Regulatory Counsel, Post-MMA Language Included  Date \_\_\_\_\_  
Comments: Initials \_\_\_\_\_
5. Div. Dir./Deputy Dir. Date 11/29/2007  
Chemistry Div. II Initials RCA  
Comments: CMC OK, see attached spreadsheet
6. Frank Holcombe **First Generics Only** Date \_\_\_\_\_  
Assoc. Dir. For Chemistry Initials \_\_\_\_\_  
Comments: (First generic drug review)
7. Vacant Date \_\_\_\_\_  
Deputy Dir., DLPS Initials \_\_\_\_\_
8. Peter Rickman Date 12/21/2007  
Director, DLPS Initials swpr  
Para.IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No   
Comments: applicant will carve out the NPP+ped and ODE indications from their  
proposed labeling; patent has expired; labeling acceptable 11/20/07 and e-mail from  
TL 11/26/07; bio acceptable 10/24/07; EER acceptable 10/24/2006  
OKAY for FULL APPROVAL
- OR**
8. Robert L. West Date \_\_\_\_\_  
Deputy Director, OGD Initials \_\_\_\_\_  
Para.IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No   
Press Release Acceptable   
Comments:
9. Gary Buehler Date \_\_\_\_\_  
Director, OGD Initials \_\_\_\_\_  
Comments:  
First Generic Approval  PD or Clinical for BE  Special Scientific or Reg.Issue   
Press Release Acceptable
10. Project Manager, Theresa Liu Team 7 Date 12/28/07  
Review Support Branch Initials tcl  
\_\_\_\_\_ Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

11 am Time notified of approval by phone 11 am Time approval letter faxed

FDA Notification:

12/28/07 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

12/28/07 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Theresa Liu

12/28/2007 11:02:54 AM