

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-807

Name: Balsalazide Disodium Capsules, 750 mg

Sponsor: Mylan Pharmaceuticals, Inc.

Approval Date: December 28, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-807

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-807

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-807

Mylan Pharmaceuticals Inc.
Attention: Wayne Talton
Vice President Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 18, 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 December 15, 2005, January 19, April 6, and June 9, 2006, April 16 and 18, and September 14, 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 Ammendale 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.**

/s/

Robert L. West
12/28/2007 10:10:18 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

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 disodium capsules.

Balsalazide disodium capsules
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES	
Dosage and Administration, Administration Alternatives (2.2)	09/2006
Warnings and Precautions, Exacerbations of Ulcerative Colitis (5.1)	12/2006
Drug Interactions (7)	11/2007

INDICATIONS AND USAGE

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

DOSAGE 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)

DOSAGE FORMS AND STRENGTHS

- Capsules: 750 mg (3)

CONTRAINDICATIONS

Patients with hypersensitivity to salicylates or to any of the components of balsalazide

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
 - Adult Dose
 - Administration Alternatives
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Exacerbations of Ulcerative Colitis
 - Pyloric Stenosis
 - Renal
- ADVERSE REACTIONS
 - Clinical Studies Experience
 - Post-marketing Experience
- DRUG INTERACTIONS
- USE IN SPECIFIC POPULATIONS
 - Pregnancy
 - Nursing Mothers
 - Pediatric Use

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 disodium 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 in sprinkle form with food.

3 DOSAGE FORMS AND STRENGTHS

Balsalazide disodium capsules are available as a 750 mg capsules with an orange opaque cap/orange opaque body, hard-shell gelatin capsule filled with orange to yellow powder. The capsule is axially printed with MYLAN over 6750 in black ink on both the cap and body.

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 was reported 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 Mylan Pharmaceuticals Inc. Toll free at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>.

DRUG INTERACTIONS

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 CYP3A4/5). (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

BALZ-R5
Revised: Nov 2007

10 OVERDOSAGE

11 DESCRIPTION

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- Important Precautions Regarding Balsalazide
- What Patients Should Know About Adverse Reactions
- What Patients Should Know About Taking Balsalazide with Other Medication

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

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 Exacerbations of Ulcerative Colitis

In the adult clinical trials, 3 out of 259 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 disodium 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 disodium in four controlled trials.

In the four controlled clinical trials patients receiving a balsalazide disodium 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 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	6 (2%)	0%
Fatigue	6 (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 Post-marketing 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

Post-marketing adverse reactions of hepatotoxicity have been reported, including elevated liver function tests (SGOT/AST, SGPT/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-aminobenzoyl- β -alanine (4-ABA) and N-acetyl-4-aminobenzoyl- β -alanine (N-Ac-4-ABA)] were not shown to inhibit the major CYP enzymes evaluated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5). Therefore, balsalazide and its metabolites are not expected to inhibit the metabolism of other drugs which are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

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 fetus 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.

8.3 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.

8.4 Pediatric Use

Pediatric use information is protected by marketing exclusivity.

10 OVERDOSAGE

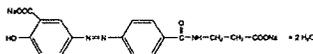
No case of overdose has occurred with balsalazide. A 3 year old boy is reported

to have ingested 2 g of another mesalamine product. He was treated with ipecac and activated charcoal with no adverse reactions.

If an overdose occurs with balsalazide disodium, 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 produce mesalamine (5-aminosalicylic acid or 5-ASA), an anti-inflammatory drug. Each capsule of balsalazide disodium (750 mg) is equivalent to 267 mg of mesalamine. Balsalazide disodium has the chemical name (E)-5-[[4-[[[2-carboxyethyl] amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate. Its structural formula is:



Molecular Weight: 437.32

Molecular Formula: $C_{17}H_{13}N_3O_6Na_2 \cdot 2H_2O$

Balsalazide disodium is a stable, odorless orange to yellow 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-shell gelatin capsule contains, colloidal silicon dioxide, D&C Red No. 28, D&C Yellow No. 10, FD&C Red No. 40, gelatin, magnesium stearate, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide.

The imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol and shellac glaze.

The sodium content of each capsule is approximately 87 mg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Balsalazide disodium 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 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 production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanooids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyicosatetraenoic acids, 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 disodium 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 Disodium Capsules Following a Fast, a High-Fat Meal, and Drug Contents Sprinkled on Applesauce (Mean \pm SD)

	Fasting n = 17	High-Fat Meal n = 17	Sprinkled n = 17
C_{max} (mcg/mL)			
Balsalazide	0.51 \pm 0.32	0.45 \pm 0.39	0.21 \pm 0.12
5-ASA	0.22 \pm 0.12	0.11 \pm 0.136	0.29 \pm 0.17
N-Ac-5-ASA	0.88 \pm 0.39	0.64 \pm 0.534	1.04 \pm 0.57
AUC _{0-12h} (mcg-hr/mL)			
Balsalazide	1.35 \pm 0.73	1.52 \pm 1.01	0.87 \pm 0.48
5-ASA	2.59 \pm 1.46	2.10 \pm 2.58	2.99 \pm 1.70
N-Ac-5-ASA	17.8 \pm 8.14	17.7 \pm 13.7	20.0 \pm 11.4
T_{max} (h)			
Balsalazide	0.8 \pm 0.85	1.2 \pm 1.11	1.6 \pm 0.44
5-ASA	8.2 \pm 1.98	22.0 \pm 8.23	8.7 \pm 1.99
N-Ac-5-ASA	9.9 \pm 2.49	20.2 \pm 8.94	10.8 \pm 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_{max} and AUC_{0-12h} were lower, while t_{max} was markedly prolonged, under fed (high-fat meal) compared to fasted conditions. Moreover, the data suggest that dosing 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 one year, systemic drug exposure, based on mean AUC values, was up to 60 times greater (0.008 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 \geq 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 disodium (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.

In a multiple-dose study in healthy subjects receiving a balsalazide disodium 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, 65% of a single 2.25 g dose of balsalazide disodium 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 disodium daily for more than one 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⁺/-) forward mutation test, or mouse micronucleus test. However, it was genotoxic in the *in vitro* Chinese hamster lung cell (CH V79/HGPRT) 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⁺/-) 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⁺/-) 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 disodium demonstrated no nephrotoxic effects in rats or dogs.

Overdosage

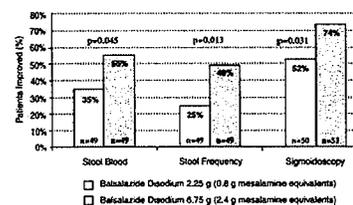
A single oral dose of balsalazide disodium at 5 g/kg or 4-aminobenzoyl- β -alanine, a metabolite of balsalazide disodium, at 1 g/kg was non-lethal in mice and rats. No symptoms of acute toxicity were seen at these doses.

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 doses of balsalazide disodium (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 a 750 mg capsule.

The 750 mg capsule is an orange opaque cap/orange opaque body, hard-shell gelatin capsule filled with orange to yellow powder. The capsule is axially printed with MYLAN over 6750 in black ink on both the cap and body. They are available as follows:

NDC 0378-6750-82
bottles of 280 capsules
NDC 0378-6750-05
bottles of 500 capsules

Storage

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

17.1 Important Precautions Regarding Balsalazide

- Instruct patients not to take balsalazide if they have a hypersensitivity to salicylates (e.g., aspirin).
- Patients should be instructed to contact their healthcare 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 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.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

N
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0378-6750-82
5



750 mg

Each capsule contains:
Balsalazide disodium 750 mg



MYLAN®

**BALSALAZIDE
DISODIUM
CAPSULES**
750 mg

NDC 0378-6750-82

280 CAPSULES



Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Usual Adult Dosage: See accompanying prescribing information.

This container is not intended for dispensing for household use.

**Mylan Pharmaceuticals Inc.
Morgantown, WV 26505**

RM6750AE

N
3
0378-6750-05
4



750 mg

Each capsule contains:
Balsalazide disodium 750 mg



MYLAN®

**BALSALAZIDE
DISODIUM
CAPSULES**
750 mg

NDC 0378-6750-05

500 CAPSULES



Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Usual Adult Dosage: See accompanying prescribing information.

This container is not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM6750B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-807

LABELING REVIEWS

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

ANDA Number: 77-807 Date of Submission: July 18, 2005 (Original)

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Balsalazide Disodium Capsules, 750 mg

Labeling Deficiencies:

1. CONTAINER:
 - a. Please ensure your labels comply with the bar code requirements prior to full approval.
 - b. Please revise "Each tablet contains..." to " Each capsule contains..."
2. INSERT:
 - a. DESCRIPTION, Inactive Ingredients: Add "gelatin".
 - b. OVERDOSAGE: Second paragraph, first sentence, revise "duse" to "use".
 - c. HOW SUPPLIED: Please add your storage conditions (temperature storage).

Please revise your label and labeling as described above and submit electronically. The immediate container labels may be submitted either electronically or in hard copy.

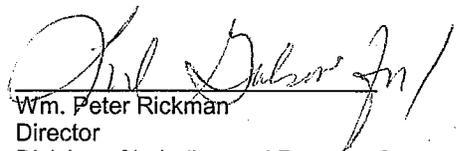
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Kyoung Lee at 301-827-7336.

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.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained


Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?			X
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim		X	

supported?			
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING- This review is based on the labeling of Colazal ® Capsules of Salix Pharmaceuticals, Inc., NDA 20-610/S-013 approved March 10, 2006.

2. PATENT/ EXCLUSIVITIES

Patent Data – for NDA 20-610

No	Expiration	Use Code	Use	File	Labeling Impact
4412992	July 8, 2006			III	None

Exclusivity Data – for NDA 20-610

Code/sup	Expiration	Use Code	Description	Labeling Impact
NCE	July 28, 2005			None

3. MANUFACTURING FACILITY

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

[Vol B1.1, pg. 6873]

4. SCORING:

NDA - N/A
ANDA - N/A

5. STORAGE CONDITIONS:

NDA - Store at 20° to 25° C (68° to 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) [See USP Controlled Room Temperature].

6. DISPENSING RECOMMENDATIONS:

NDA - None listed in labeling.
ANDA - Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed.

7. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.
[Vol. B1.1, pg.6703]

The inactive ingredients for the drug product are:

capsule contents- colloidal silicon dioxide, magnesium stearate, sodium starch glycolate
capsule shell- gelatin, titanium dioxide D&C Red #28, D&C Yellow #10, FD&C Red #40, sodium lauryl sulfate
Capsule imprinted with- edible black ink containing black iron oxide, D&C Yellow #10 aluminum lake, FD&C Blue #1 aluminum lake, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, propylene glycol and shellac glaze.

Iron oxide is in the ink only and not in the capsule. Thus, the iron content is too negligible to count in regards of the elemental iron intake issue.

8. PACKAGING CONFIGURATIONS:

NDA- Bottles of 280
Bottles of 500

ANDA- Bottles of 280
Bottles of 500

[Vol B1.1, pg. 7017]

9. CONTAINER/CLOSURE SYSTEM:

280s- 24 oz oblong, beige HDPE bottles with 53mm fine-ribbed beige plastic closure. Not CRC.
500s- 36 oz oblong, beige HDPE bottles with 53mm fine-ribbed beige plastic closure. Not CRC.
[Vol B1.1, pg. 7021]

10. The tablet 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- Orange opaque cap/orange opaque body, hard shell gelatin capsule filed with orange to yellow powder. The capsule axially printed with MYLAN over 6750 in black ink on both the cap and body. [Vol B1.1, pg. 7062]

11. Insert states that effect of food intake was not studied (PHARMACOKINETICS, Absorption)
Bioequivalence review is pending as 5/17/06.
12. NDC numbers: 280 capsules- NDC 0378-6750-82
NDC numbers: 500 capsules- NDC 0378-6750-05

Date of Review: May 19, 2006

Date of Submission: July 18, 2005

Primary Reviewer: Thuyanh Vu 

Date: 5/25/06

Team Leader: Lillie Golson 

Date: 5/25/06

cc: ANDA: 77-807
DUP/DIVISION FILE
HFD-613/TVu/
HFD-613/LGolson (no cc)
V:\FIRMSAMMYLAN\LTRS&REV\77807.na1.LABELING.DOC
Review

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

ANDA Number: 77-807 Date of Submission: June 9, 2006

Applicant's Name: Mylan Pharmaceutical, Inc.

Established Name: Balsalazide Disodium Capsules, 750 mg

BASIS OF TENTATIVE APPROVAL:

TENTATIVE APPROVAL SUMMARY (*Satisfactory in draft as of June 9, 2006 submission*)

Container Labels: (Bottles of 280, and 500)

Labeling Piece	File Path	Decision
280	\\Cdsub1\77807\N_000\2006-06-09\Labeling\Proposed BL1.pdf	Tentatively Approve
500	\\Cdsub1\77807\N_000\2006-06-09\Labeling\Proposed BL1.pdf	Tentatively Approve

Professional Package Insert Labeling:

\\Cdsub1\77807\N_000\2006-06-09\Labeling\Proposed OT.pdf

Revisions needed post-approval:

Please calculate the amount of sodium in your capsules and revise your labeling as necessary.

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 #: March 10, 2006/S-013

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

Basis of Approval for the Carton Labeling: side-by-side

Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?			X
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim		X	

supported?			
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

Chemist Shanaz Read's email dated 6/12/06: I calculated the amount of Sodium from the drug and it should be 79 mg (same as (b) (4)). The others, including the RLD appear to be incorrect, unless they have an additional source of Sodium which I do not see from the Component/Composition tables that I have reviewed. The best thing would be if you could ask them to justify the amount of Sodium on the label.

FOR THE RECORD:

1. MODEL LABELING- This review is based on the labeling of Colazal ® Capsules of Salix Pharmaceuticals, Inc., NDA 20-610/S-013 approved March 10, 2006. As of 6/26/06, Salix Pharmaceuticals submitted an efficacy supplement requesting pediatric exclusivity which will extend the expiry date of the patent six months. Waiting for the listing in the OB.

2. PATENT/ EXCLUSIVITIES

Patent Data – for NDA 20-610

No	Expiration	Use Code	Use	File	Labeling Impact
4412992	July 8, 2006			III	None

Exclusivity Data – for NDA 20-610

Code/sup	Expiration	Use Code	Description	Labeling Impact
NCE	July 28, 2005			None

3. MANUFACTURING FACILITY

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

[Vol B1.1, pg. 6873]

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) [See USP Controlled Room Temperature].

6. DISPENSING RECOMMENDATIONS:

NDA - None listed in labeling.
ANDA - Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed.

7. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.
[Vol. B1.1, pg.6703]

The inactive ingredients for the drug product are:

capsule contents- colloidal silicon dioxide, magnesium stearate, sodium starch glycolate
Capsule shell- gelatin, titanium dioxide D&C Red #28, D&C Yellow #10, FD&C Red #40, sodium lauryl sulfate
Capsule imprinted with- edible black ink containing black iron oxide, D&C Yellow #10 aluminum lake, FD&C Blue #1 aluminum lake, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, propylene glycol and shellac glaze.

Iron oxide is in the ink only and not in the capsule. Thus, the iron content is too negligible to count in regards of the elemental iron intake issue.

8. PACKAGING CONFIGURATIONS:

NDA- Bottles of 280
Bottles of 500

ANDA- Bottles of 280
Bottles of 500

[Vol B1.1, pg. 7017]

9. CONTAINER/CLOSURE SYSTEM:

280s- 24 oz oblong, beige HDPE bottles with 53mm fine-ribbed beige plastic closure. Not CRC.

500s- 36 oz oblong, beige HDPE bottles with 53mm fine-ribbed beige plastic closure. Not CRC.
[Vol B1.1, pg. 7021]

10. The tablet 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- Orange opaque cap/orange opaque body, hard shell gelatin capsule filed with orange to yellow powder. The capsule axially printed with MYLAN over 6750 in black ink on both the cap and body.
[Vol B1.1, pg. 7062]

11. Insert states that effect of food intake was not studied (PHARMACOKINETICS, Absorption)
Bioequivalence review is acceptable as of 6/20/06.

12. NDC numbers: 280 capsules- NDC 0378-6750-82
NDC numbers: 500 capsules- NDC 0378-6750-05

Date of Review: June 27, 2006

Date of Submission: June 9, 2006

Primary Reviewer: Thuyanh Vu

Date:

6/30/06

Team Leader:

Lillie Golson

Date:

6/30/06

cc:

ANDA: 77-807
DUP/DIVISION FILE
HFD-613/TVu/
HFD-613/LGolson (no cc)
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Review

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
Supercedes TA summary dated 6/30/06**

ANDA Number: 77-807 Dates of Submission: April 18 and September 14, 2007

Applicant's Name: Mylan Pharmaceutical, Inc.

Established Name: Balsalazide Disodium Capsules, 750 mg

BASIS OF APPROVAL:

APPROVAL SUMMARY

Container Labels: (Bottles of 280, and 500)
Satisfactory in final print as of June 9, 2006

Professional Package Insert Labeling:
Satisfactory in final print as of September 14, 2007

Revisions needed post-approval:

1. HIGHLIGHTS OF PRESCRIBING INFORMATION, RECENT MAJOR CHANGES: Delete "Indications and Usage (1) and Dosage and Administration (2).
2. HIGHLIGHTS OF PRESCRIBING INFORMATION, DOSAGE AND ADMINISTRATION: Second bullet, revise "(2.3)" to "(2.2)".
3. FULL PRESCRIBING INFORMATION: CONTENTS*, 2 DOSAGE AND ADMINISTRATION, revise "2.3 Administration Alternatives" to "2.2 Administration Alternatives".
4. FULL PRESCRIBING INFORMATION, add margin markers to 2.2 and 5.1.
5. FULL PRESCRIBING INFORMATION, 11 DESCRIPTION: Refer to the RLD labeling (20-610/S-016) and revise the first two sentences accordingly.
6. FULL PRESCRIBING INFORMATION, 12.3 Pharmacokinetics, Absorption: first sentence, revise "Table 3" to "Table 2"
7. Please justify the amount of sodium (approximately 87 mg) on the label.

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 #: December 20, 2006, S-016

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:

Chemist Shanaz Read's email dated 6/12/06: I calculated the amount of Sodium from the drug and it should be 79 mg (same as (b) (4)). The others, including the RLD appear to be incorrect, unless they have an additional source of Sodium which I do not see from the Component/Composition tables that I have reviewed. The best thing would be if you could ask them to justify the amount of Sodium on the label.

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. 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**

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

[Vol B1.1, pg. 6873]

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) [See USP Controlled Room Temperature].

6. **DISPENSING RECOMMENDATIONS:**

NDA - None listed in labeling.
ANDA - Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed.

7. **INACTIVE INGREDIENTS:**

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

[Vol. B1.1, pg.6703]

The inactive ingredients for the drug product are:

capsule contents- colloidal silicon dioxide, magnesium stearate, sodium starch glycolate
Capsule shell- gelatin, titanium dioxide D&C Red #28, D&C Yellow #10, FD&C Red #40, sodium lauryl sulfate
Capsule imprinted with- edible black ink containing black iron oxide, D&C Yellow #10 aluminum lake, FD&C Blue #1 aluminum lake, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, propylene glycol and shellac glaze.

Iron oxide is in the ink only and not in the capsule. Thus, the iron content is too negligible to count in regards of the elemental iron intake issue.

8. PACKAGING CONFIGURATIONS:

NDA- Bottles of 280
Bottles of 500

ANDA- Bottles of 280
Bottles of 500

[Vol B1.1, pg. 7017]

9. CONTAINER/CLOSURE SYSTEM:

280s- 24 oz oblong, beige HDPE bottles with 53mm fine-ribbed beige plastic closure. Not CRC.
500s- 36 oz oblong, beige HDPE bottles with 53mm fine-ribbed beige plastic closure. Not CRC.

[Vol B1.1, pg. 7021]

10. The tablet 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- Orange opaque cap/orange opaque body, hard shell gelatin capsule filled with orange to yellow powder. The capsule axially printed with MYLAN over 6750 in black ink on both the cap and body.
[Vol B1.1, pg. 7062]

11. Insert states that effect of food intake was not studied (PHARMACOKINETICS, Absorption)
Bioequivalence review is acceptable as of 5/3/07.

12. NDC numbers: 280 capsules- NDC 0378-6750-82
NDC numbers: 500 capsules- NDC 0378-6750-05

Date of Review: September 26, 2007

Dates of Submission: April 18 and September 14, 2007

Primary Reviewer: Thuyanh Vu

Date:

Team Leader: Lillie Golson

Date:

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

/s/

Thuyanh Vu
9/27/2007 07:39:16 AM
LABELING REVIEWER

Lillie Golson
9/28/2007 12:16:24 PM
LABELING REVIEWER

**APPROVAL SUMMARY #2
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
Supersedes AP Summary dated September 28, 2007**

ANDA Number: 77-807 Date of Submission: November 9, 2007

Applicant's Name: Mylan Pharmaceutical, Inc.

Established Name: Balsalazide Disodium Capsules, 750 mg

BASIS OF APPROVAL:

APPROVAL SUMMARY

Container Labels: (Bottles of 280, and 500)
Satisfactory in final print as of June 9, 2006

Professional Package Insert Labeling:
Satisfactory in final print as of November 9, 2007

Revisions needed post-approval:

1. HIGHLIGHTS OF PRESCRIBING INFORMATION, RECENT MAJOR CHANGES: Revise the corresponding date of "Drug Interactions (7)" to "2/2007".
2. HIGHLIGHTS OF PRESCRIBING INFORMATION: Delete the margin markers within this section.

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 #: S-017, approved November 2, 2007
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:

Chemist Shanaz Read's email dated 6/12/06: I calculated the amount of Sodium from the drug and it should be 79 mg (same as (b) (4)). The others, including the RLD appear to be incorrect, unless they have an additional source of Sodium which I do not see from the Component/Composition tables that I have reviewed. The best thing would be if you could ask them to justify the amount of Sodium on the label.

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 November 2, 2007. 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

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

[Vol B1.1, pg. 6873]

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) [See USP Controlled Room Temperature].

6. DISPENSING RECOMMENDATIONS:

NDA - None listed in labeling.

ANDA - Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed.

7. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

[Vol. B1.1, pg.6703]

The inactive ingredients for the drug product are:

capsule contents- colloidal silicon dioxide, magnesium stearate, sodium starch glycolate
Capsule shell- gelatin, titanium dioxide D&C Red #28, D&C Yellow #10, FD&C Red #40, sodium lauryl sulfate
Capsule imprinted with- edible black ink containing black iron oxide, D&C Yellow #10 aluminum lake, FD&C Blue #1 aluminum lake, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, propylene glycol and shellac glaze.

Iron oxide is in the ink only and not in the capsule. Thus, the iron content is too negligible to count in regards of the elemental iron intake issue.

Mylan provided justification to the sodium quantity in AF dated 11/9/07. Mylan calculated the sodium content to be 87 mg.

8. PACKAGING CONFIGURATIONS:

NDA- Bottles of 280
Bottles of 500

ANDA- Bottles of 280

Bottles of 500

[Vol B1.1, pg. 7017]

9. CONTAINER/CLOSURE SYSTEM:

280s- 24 oz oblong, beige HDPE bottles with 53mm fine-ribbed beige plastic closure. Not CRC.
500s- 36 oz oblong, beige HDPE bottles with 53mm fine-ribbed beige plastic closure. Not CRC.

[Vol B1.1, pg. 7021]

10. The tablet 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- Orange opaque cap/orange opaque body, hard shell gelatin capsule filled with orange to yellow powder. The capsule axially printed with MYLAN over 6750 in black ink on both the cap and body.
[Vol B1.1, pg. 7062]

11. Insert states that effect of food intake was not studied (PHARMACOKINETICS, Absorption)
Bioequivalence review is acceptable as of 5/3/07.

12. NDC numbers: 280 capsules- NDC 0378-6750-82
NDC numbers: 500 capsules- NDC 0378-6750-05

Date of Review: November 15, 2007

Dates of Submission: November 9, 2007

Primary Reviewer: Thuyanh Vu

Date:

Team Leader: Lillie Golson

Date:

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

/s/

Thuyanh Vu
11/19/2007 08:44:02 AM
LABELING REVIEWER

Koung Lee
11/19/2007 09:29:31 AM
LABELING REVIEWER
Signing for Lillie Golson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-807

CHEMISTRY REVIEWS



#1

ANDA 77-807

Balsalazide Disodium Capsules, 750 mg

Mylan Pharmaceuticals Inc.

**Shahnaz Read
Chemistry Division II**

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Chemistry Review Data Sheet

1. ANDA 77-807
2. REVIEW #: 1
3. REVIEW DATE: December 7, 2005
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS: NA
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original Submission

Document Date
July 18, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals Inc.
Address:	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Representative:	S. Wayne Talton
Telephone:	304-599-2595 ext. 6551
Fax number:	304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

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

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 certifies that in its opinion and to the best of its knowledge U.S. patent 4,412,992 will expire on July 8, 2006 and seeks

Chemistry Review Data Sheet

approval after expiration of the patent (Paragraph III certification). 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

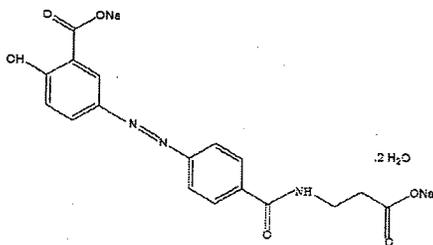
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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: $C_{10}H_7Cl_2N_3O.HCl.H_2O$;

Molecular Weight: 401.32 (437.32 for the dihydrate, 357.32 for the di-acid)

Chemical Structure:



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/21/05	Information Request
	IV			4	NA		
	IV			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		

¹ 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")

² 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	9/14/2005	S. Ferguson
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	NA		
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 77-807

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- β -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 manufacturing process involves (b) (4)

encapsulated and packaged.

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- β -alanine. The recommended dose of 6.75 g/day provides 2.4 g of free 5-aminosalicylic acid (mesalamine).

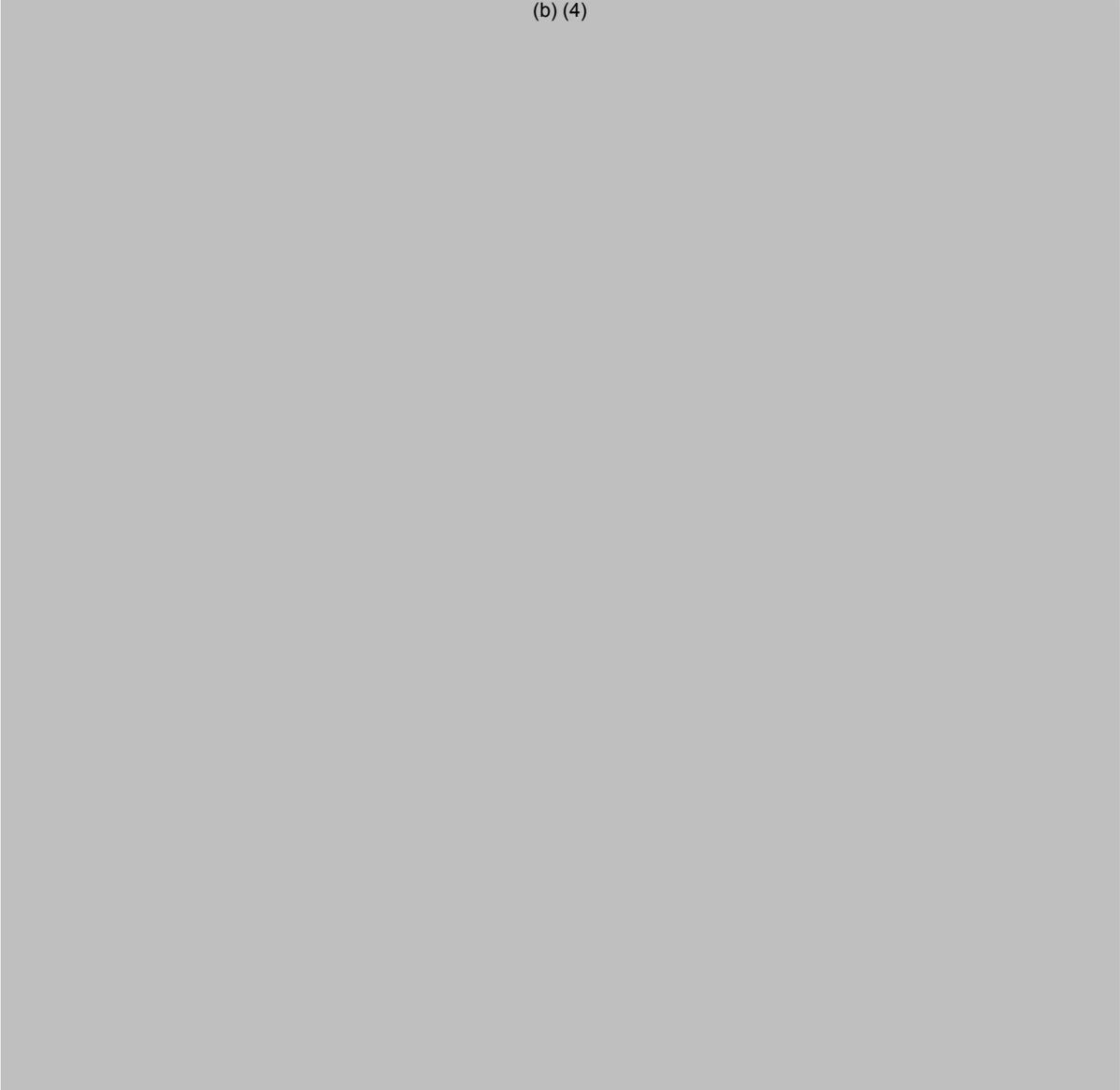


C. Basis for Approvability or Not-Approval Recommendation

The firm needs to resolve issues related to drug substance and drug product specifications and methods.

Following this page, 8 pages withheld in full (b)(4)-Chemistry review #1

Chemistry Assessment Section

(b) (4)
**30. MICROBIOLOGY**

NA

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

NA

32. LABELING

Pending



33. ESTABLISHMENT INSPECTION

Acceptable

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).

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-807

APPLICANT: Mylan Pharmaceuticals 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.

B. Comments:

The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

Sincerely yours,

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



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 77-807
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/ *SR* 12/17/05

HFD-645/SFurness/12/14/05 *M. S. Furness 12/14/05*

HFD-617/YKong/12/15/05 *YK 12/15/05*

F/T by: rad12/15/05

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TYPE OF LETTER: MINOR

ANDA 77-807

Balsalazide Disodium Capsules, 750 mg

Mylan Pharmaceuticals Inc.

**Shahnaz Read
Chemistry Division II**



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Chemistry Review Data Sheet

1. ANDA 77-807
2. REVIEW #: 2
3. REVIEW DATE: April 17, 2006
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS: NA

Submission(s) Reviewed
Original Submission

Document Date
July 18, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Minor Amendment
Telephone Amendment

Document Date
January 19, 2006
April 6, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Mylan Pharmaceuticals Inc.
Address: 781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Representative: S. Wayne Talton, Vice President, Regulatory
Affairs
Telephone: 304-599-2595 ext. 6551
Fax number: 304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

c) British adopted name (BAN): Balsalazide

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 certifies that in its opinion and to the best of its knowledge U.S. patent 4,412,992 will expire on July 8, 2006 and seeks approval after expiration of the patent (Paragraph III certification). 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, dihydrate salt.

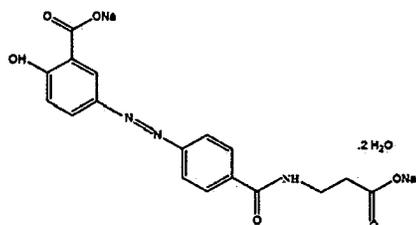
Molecular Formula: $C_{17}H_{13}N_3Na_2O_6 \cdot 2H_2O$

Molecular Weight: 437.32 for the disodium dihydrate salt, (357.32 for the di-acid)

Chemical Structure:

CHEMISTRY REVIEW

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	3/29/06	Adequate
	IV			4	NA		
	IV			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		

¹ 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")

² 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	9/5/07	S. Ferguson
Methods Validation	NA		
Labeling	Acceptable	9/28/07	A. Vu
Bioequivalence	Acceptable	5/2/07	C. Chaurasia
EA	Exclusion		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 77-807

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- β -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 manufacturing process involves a (b) (4)

encapsulated and packaged.

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

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Chemistry Assessment Section

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

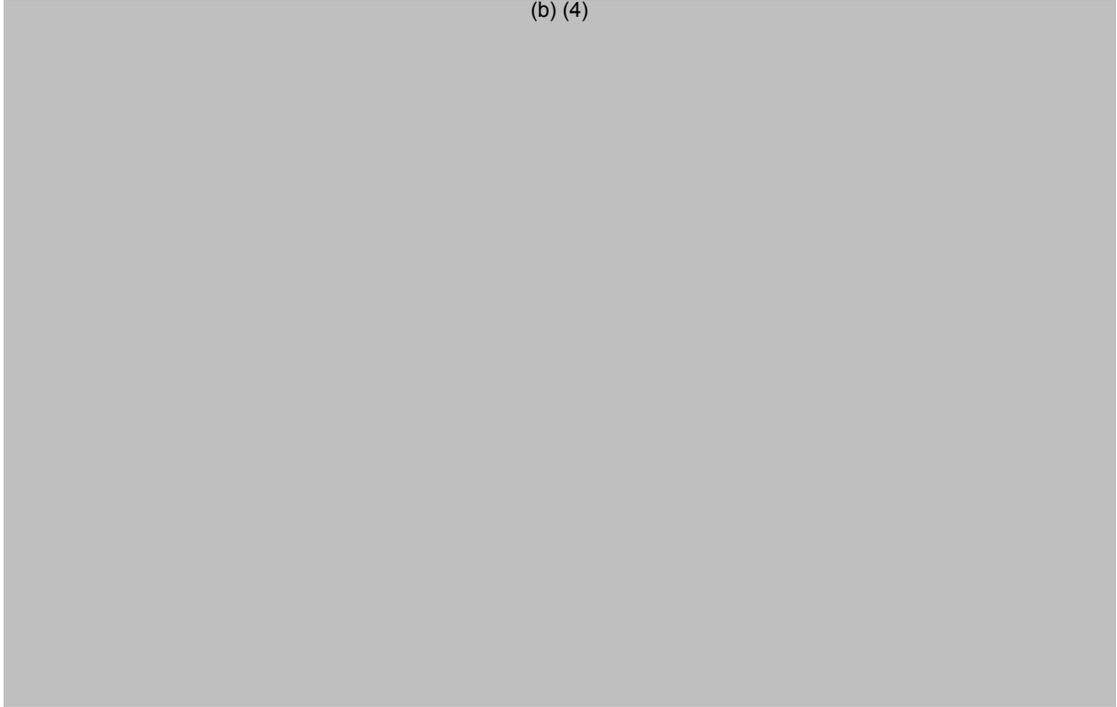
The firm has resolved all CMC issues.

Following this page, 9 pages withheld in full- (b)(4) Chemistry review #2

CHEMISTRY REVIEW

Chemistry Assessment Section

(b) (4)



30. MICROBIOLOGY

NA

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

NA

32. LABELING

Acceptable 9/28/07

33. ESTABLISHMENT INSPECTION

Acceptable 9/5/07

34. BIOEQUIVALENCE

Acceptable 5/2/07

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 REVIEW

Chemistry Assessment Section

cc: ANDA 77-807
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/4/17/06

HFD-645/SFurness/4/24/06

HFD-617/YKong/4/25/05/TLiu/10/1/07

TYPE: Approvable

**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
10/17/2007 10:42:38 AM
CHEMIST

Michael S Furness
10/21/2007 01:29:57 PM
CHEMIST

Theresa Liu
10/22/2007 09:03:50 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-807

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-807
Drug Product Name	Balsalazide Disodium Capsules
Strength	750 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Submission Date(s)	07/18/2005
First Generic	No
Reviewer	Paul Seo, Ph.D.
File Location	V:\firmsam\Mylan\ltrs&rev\77807D0705.doc
Clinical Site	PRACS Institute, Ltd. 4801 Amber Valley Parkway, Fargo, ND 58104
Analytical Site	Mylan Pharmaceuticals Inc. 3711 Collins Ferry Rd., Morgantown, WV 26504

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 submitted summary biotables to EDR.

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

RLD METHOD

Medium	Potassium Phosphate buffer, pH 6.8
Volume	900 ml
Temperature	37°C
Apparatus	2 (paddle) with sinkers
Rotational Speed	50 rpm
Specification	NLT ^(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)

Medium	0.1N HCl, pH 4.5 Buffer, pH 6.8 Buffer, and pH 7.4 Buffer
Volume	900 ml
Temperature	37°C
Apparatus	1 (basket)
Rotational Speed	100 rpm
Submitted by Firm?	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						Study Report Location	
					Mean %Dissolved (Range)							
					5 min	10 min	15 min	20 min	30 min	45 min	60 min	
Not submitted	Mylan/R1M0787	750 mg Caps	Dissolution: Apparatus 1 (basket) Speed of Rotation: 100 rpm Medium: Water	12	19 (8-32)	61 (36-83)	93 (81-100)	102 (96-106)	103 (100-108)	104 (100-109)	104 (100-110)	V 1.12 p. 6695
	Colazal® / 308512	750 mg Caps	Volume: 900 mL Temperature: 37°C	12	35 (22-)	65 (49-)	87 (77-)	101 (95-)	104 (101-)	104 (101-)	104 (101-)	

					48)	76)	101)	106)	108)	109)	109)	
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Table 2. SAS Transport Files

Are the SAS files located in the EDR ? (Yes/No)	
Fasting BE Study	
Plasma Data	Yes
PK data	Yes
Fed BE Study	
Plasma Data	NA
PK Data	NA

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 (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. 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 (f_2) to compare test and reference dissolution profiles. To determine f_2 , 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:

Medium Potassium Phosphate buffer, pH 6.8
Volume 900 ml

Temperature	37°C
Apparatus	2 (paddle) with sinkers
Rotational Speed	50 rpm
Specification	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.

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 and 80 minutes.

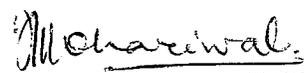
RECOMMENDATIONS:

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



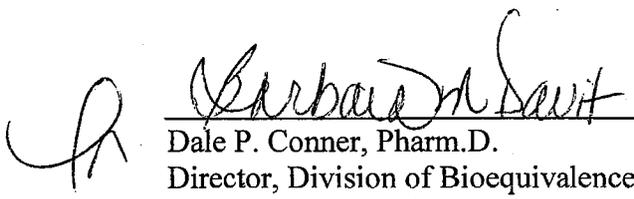
11/29/05

Paul Seo, Ph.D. Date
Reviewer, Branch IV
Division of Bioequivalence



11/29/05

Kuldeep R. Dhariwal, Ph.D. Date
Team Leader, Branch IV
Division of Bioequivalence



11/29/05

Dale P. Conner, Pharm.D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-807

APPLICANT: Mylan Pharmaceuticals Inc.

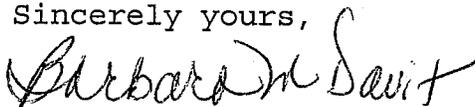
DRUG PRODUCT: Balsalazide Disodium Capsules, 750 mg

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 and 80 minutes.

Sincerely yours,

fr


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

CC: ANDA #: 77-807
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ P. Seo
HFD/650/ B. Fabian-Fritsch

V:\firmsam\Mylan\ltrs&rev\77807D0705.doc

Endorsements: (Final with Dates)

HFD-650/Seo *PS 11/29/05*

HFD-650/Dhariwal *MS 11/29/05*

HFD/650/Fabian-Fritsch

HFD-650/Conner *BN 11/30/05*

SR

BIOEQUIVALENCE - INCOMPLETE

Submission date: 7/18/2005

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

1. DISSOLUTION (Dissolution Data)

Strength: 750 mg

Outcome: IC

Outcome Decisions: IC -- Incomplete

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No. 77-807
Drug Product Name Balsalazide Disodium Capsules
Strength 750 mg
Applicant Name Mylan Pharmaceuticals Inc.
Submission Date(s) 12/15/2005
First Generic No
Reviewer Paul Seo, Ph.D.
File Location V:\firmsam\Mylan\ltrs&rev\77807D1205.doc
Clinical Site PRACS Institute, Ltd.
4801 Amber Valley Parkway, Fargo, ND 58104
Analytical Site Mylan Pharmaceuticals Inc.
3711 Collins Ferry Rd., Morgantown, WV 26504

Review of a Dissolution Review Amendment

EXECUTIVE SUMMARY

This amendment was submitted in response to a request from the Division of Bioequivalence (DBE) about dissolution testing. The firm conducted dissolution testing using a non-FDA-recommended method on the test and reference products. The firm submitted new dissolution data using the FDA-recommended method: 900 ml of Potassium Phosphate Buffer, pH 6.8, using apparatus 2 (paddle) with sinkers at 50 rpm, with sampling times at 5, 10, 15, 20, 30, 45, 60, and 80 minutes. The firm's dissolution data meets the FDA-recommended specification of NLT ^(b) ₍₄₎ % (Q) in 30 minutes at the S1 level. The dissolution testing is incomplete as the firm needs to acknowledge if they accept the DBE's proposed dissolution method and specification.

The DBE will review the bioequivalence study at a later date.

REVIEW OF SUBMISSION

Deficiency 1: 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 and 80 minutes.

Firm's Response: The firm conducted dissolution testing on test and reference products using the FDA-recommended dissolution method: 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 and 80 minutes. The dissolution data is presented below.

Sampling Time (min)	Test Product, 750 mg Lot No. R1M0787			Reference Product, 750 mg Lot No. 308512		
	Mean	%CV	Range	Mean	%CV	Range
5	26	26.0	18-38	40	14.4	32-52
10	75	12.0	60-90	69	5.1	64-75
15	92	7.0	82-101	85	6.2	76-95
20	99	1.9	95-101	95	4.6	85-100
30	100	2.0	96-103	101	1.8	98-103
45	100	1.9	97-103	101	1.4	98-103
60	100	2.0	96-103	101	1.6	98-103
80	100	2.0	97-103	102	1.8	99-104

Reviewer's Comment: The firm conducted dissolution testing using the FDA-recommended method. The test product meets the FDA-recommended specification of NLT $\frac{(b)}{(4)}\%$ (Q) in 30 minutes at the S1 level. The firm did not propose a dissolution specification. The firm should acknowledge the FDA-recommended specification.

DEFICIENCY COMMENTS:

1. The firm conducted dissolution testing using the FDA-recommended method of 900 mL of Potassium Phosphate Buffer, pH 6.8, at 37°C using USP Apparatus 2 (paddle) with sinkers at 50 rpm with sampling times of 5, 10, 15, 20, 30, 45, 60 and 80 minutes. The firm should acknowledge the FDA-recommended specification of NLT $\frac{(b)}{(4)}\%$ (Q) in 30 minutes.

RECOMMENDATIONS:

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

Paul Seo

12/19/2005

Paul Seo, Ph.D.
Reviewer, Branch IV
Division of Bioequivalence

Date

Kuldeep R. Dhariwal

12/19/2005

Kuldeep R. Dhariwal, Ph.D.
Team Leader, Branch IV
Division of Bioequivalence

Date

fr

Dale P. Conner

12/22/05

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs

Date

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-807

APPLICANT: Mylan Pharmaceuticals 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.

We acknowledge that the dissolution testing is conducted using the following FDA-recommended method:

Apparatus: 2 (paddle) with sinkers
Speed: 50 rpm
Volume: 900 mL
Medium: Potassium Phosphate Buffer, pH 6.8
Temperature: 37°C
Sampling Times: 5, 10, 15, 20, 30, 45, 60 and 80 minutes.

We recommend that the test product should meet the following specification:

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

With your response to the above deficiency, please indicate if you accept the above dissolution specification.

Sincerely yours,



Dale P. Conner

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

CC: ANDA #: 77-807
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ P. Seo
HFD/650/ B. Fabian-Fritsch

V:\firmsnz\Mylan\ltrs&rev\77807A1205.doc

Endorsements: (Final with Dates)
HFD-650/Seo PS 12/14/2005
HFD-650/Dhariwal ~~MD~~ 12/19/05
HFD/650/Fabian-Fritsch
HFD-650/Conner ~~MD~~ 12/22/05

fr

BIOEQUIVALENCE - INCOMPLETE

Submission date: 12/15/2005

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

1. DISSOLUTION (Dissolution Data)

Strength: 750 mg
Outcome: IC

Outcome Decisions: IC – Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-807
Drug Product Name	Balsalazide Disodium Capsules
Strengths	750 mg
Applicant Name	Mylan Pharmaceuticals, Inc.
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Submission Date(s)	July 18, 2005, January 19, 2006
Amendment Date(s)	December 15, 2005 (Dissolution Amendment)
Reviewer	Chandra S. Chaurasia, Ph.D.
First Generic	No
File Location	V:\Firmsam\Mylan\ltrs&rev\77807N0705.doc

Executive Summary

The firm has submitted a randomized, single-dose, two-way crossover bioequivalence (BE) study under fasted conditions comparing the test product, balsalazide disodium capsules, 750 mg, with the reference listed drug (RLD), Colazal® (balsalazide disodium) capsules, 750 mg, manufactured by Salix Pharmaceuticals.

The fasting BE study was conducted in 77 healthy adult male and female subjects at a dose of 3x750 mg (total single dose of 2250 mg) per treatment. The PK analyses were based on plasma parent drug balsalazide and its metabolite mesalamine concentrations. The results for balsalazide (point estimate, 90% CI) of the study are: LAUC_t of 0.96, 89%-105%; LAUC_i of 0.96, 88%-104% and LC_{max} of 0.89, 82%-96%. Study results for mesalamine (point estimate, 90% CI) of the study are: LAUC_t of 0.95, 88%-103%; LAUC_i of 0.96, 82%-112% and LC_{max} of 1.05, 94%-117%. The results of the fasting study for the parent drug and its metabolite are acceptable.

Per OGD recommendations, the firm has also submitted comparative dissolution profiles in four media 0.1N HCl, pH 4.5 buffer, pH 6.8 buffer, and pH 7.4 buffer in support of establishing bioequivalency between the test and reference drugs. Evaluation of these dissolution data is considered significant in determining whether an equivalent amount of drug from each formulation, test and reference, is delivered to GI sites of action because balsalazide acts locally within the GI tract rather than systemically. Results of the comparative dissolution testing suggest that both test and reference formulations would be acid resistant for at least one hour and equally dissolved by the time balsalazide reaches the lumen of the colon, the site of action for this drug. Thus, BE dissolution data are acceptable. In addition, the firm has also submitted acceptable dissolution testing for the quality control and stability program of the test product using the FDA-recommended method.

The application is acceptable with no deficiencies.

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III. Submission Summary

A. Drug Product Information

Test Product: Balsalazide Disodium, 750 mg.
 Reference Product: Colazal® (Balsalazide Disodium) Capsules, 750 mg (July 18, 2000)
 RLD Manufacturer: Salix Pharmaceuticals
 NDA No.: 20-610
 RLD Approval Date: July 18,, 2000
 Indication: Balsalazide disodium is an oral prodrug that results in the in vivo formation of mesalamine (5-aminosalicylic acid), and indicated for the treatment of mild to moderately active ulcerative colitis

B. PK/PD Information

Mechanism of Action	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.
Bioavailability	According to the Colazal® label, systemic absorption of intact balsalazide is low and variable, although its absolute bioavailability is unknown. Both balsalazide and mesalamine are measurable in plasma following an oral dose of Colazal®.
Food Effect	The Colazal® label states that the effect of food on Colazal® absorption was not studied.
Tmax	Peak plasma concentrations of balsalazide occur from 1 to 2 hours post-dosing, whereas peak plasma concentrations of mesalamine occurs at about 10 hours post-dosing.
Metabolism	Extensive colorectal metabolism (bacterial) of balsalazide; Metabolites: Mesalamine (5-aminosalicylic acid; 5-ASA) = active 4-aminobenzoyl-beta-alanine (4-ABA) = inactive 5-acetylaminosalicylic acid (Ac-5-ASA) = activity uncertain
Excretion	Renal: <1% of parent, ≤ 25% as metabolites Fecal: <1% of parent; > 65% excreted as metabolites
Half-life	Balsalazide: cannot be determined, large intersubject variability Mesalamine: ~1 hour

Relevant OGD or DBE History

OGD Recommendations for Bioequivalence Assessment of Balsalazide Disodium Capsules (Source: OGD Protocol 05-006, v:\firmsnz\ (b) (4) protocols\ 05006p0105.doc). The OGD convened a working group of CDER scientists and physicians to recommend approaches for bioequivalence assessment of 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 is bioequivalent to the RLD Colazal®:

1. 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. 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:

0.1N HCl

pH 4.5 buffer

pH 6.8 buffer

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.

2. In addition, the applicant should conduct a bioequivalence study with pharmacokinetic endpoints comparing its Balsalazide Disodium Capsules to the RLD Colazal®. This study will provide additional assurance that the generic and RLD formulations are bioequivalent. The applicant should measure plasma concentrations of balsalazide and mesalamine. Plasma balsalazide should be measured because balsalazide is the parent drug, and plasma parent drug concentrations are sensitive to changes in formulation performance. Plasma mesalamine should be measured because its absorption from the colon reflects availability of the active moiety at the site of activity. The 90% confidence intervals of the test/reference geometric mean ratios for AUC and C_{max} of BOTH balsalazide and mesalamine should fall within the range of 0.8 to

	<p>1.25. This is an exception to the guidance provided in the BA/BE Guidance, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. The OGD recommends that firm's use a dose of 2250 mg (3 capsules of 750 mg) in the study.</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. A fed BE study is not requested.</p> <p>5. For its stability and quality controls program, the applicant should perform dissolution testing of its Balsalazide Disodium Capsules using the FDA-recommended dissolution method* (see #7 below):</p> <p style="padding-left: 40px;">Medium: Water Volume: 900 mL Temperature: 37°C Apparatus: USP 1 (Basket) with sinkers Rotational Speed: 50 rpm Specification: NLT $\frac{(b)}{(4)}$ % (Q) in 30 min</p> <p>6. 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.</p> <p>*7. Recently, the dissolution method for the RLD was revised as follows (V:\firmsam\ (b) (4) \ltrs&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 $\frac{(b)}{(4)}$ % (Q) in 30 minutes <i>*Source of Method: NDA# 20-610/SCS-011 Chemistry Review-Jul 20, 2005.</i></p>
Agency Guidance:	None
Drug Specific Issues (if any):	None

C. Contents of Submission

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

D. Pre-Study Bioanalytical Method Validation

D.1. For Balsalazide

Report Location	Volume 2, Pages 448-2595
Analyte	Balsalazide (BALS)
Internal Standard (IS)	(b) (4)
Method Description	Protein Precipitation and On-line Extraction; Positive Ion APCI LC/MS/MS
Limit of Quantitation (ng/mL)	6.0
Average Recovery of Drug (%)	60.30
Average Recovery of IS (%)	67.87
Standard Curve Concentrations (ng/mL)	6.0, 12, 18, 30, 60, 120, 240, 360, 480 and 600
QC Concentrations (ng/mL)	6.0, 18, 60 and 360
QC Intraday Precision Range (%)	1.70 to 5.27
QC Intraday Accuracy Range (%)	-0.56 to 6.88
QC Interday Precision Range (%)	2.22 to 5.03
QC Interday Accuracy Range (%)	1.39 to 4.38
Bench-Top Stability (hrs)	6 hours @ room temperature
Stock Stability (days)	28 days @ 4°C
Processed Stability (hrs)	96 hours @ room temperature
Freeze-Thaw Stability (cycles)	5 cycles
Long-Term Storage Stability (days)	141 days @ -70°C
Dilution Integrity	Concentration diluted 2-fold
Selectivity	No interfering peaks noted in blank plasma samples

D.2. For Mesalamine

Report Location	Volume 6, Pages 2708-4511
Analyte	Mesalamine (MESA)
Internal Standard (IS)	(b) (4)
Method Description	Derivatization with solid phase extraction, Reversed-phase HPLC with Fluorescence detection
Limit of Quantitation (ng/mL)	10
Average Recovery of Drug (%)	Low Control: 67.20% Mid Control: 71.43% High Control: 73.33%
Average Recovery of IS (%)	55.50%
Standard Curve Concentrations (ng/mL)	10, 20, 40, 80, 160, 320, 400, 500, 600, and 800
QC Concentrations (ng/mL)	10, 40, 320, and 600
QC Intraday Precision Range (%)	6.01 to 6.92%
QC Intraday Accuracy Range (%)	-2.51 to 17.31%
QC Interday Precision Range (%)	6.02 to 10.83%
QC Interday Accuracy Range (%)	-0.55 to 15.58%
Bench-Top Stability (hrs)	7 hours @ room temperature
Stock Stability (days)	28 days @ 4°C
Processed Stability (hrs)	117 hours @ room temperature
Freeze-Thaw Stability (cycles)	3 cycles
Long-Term Storage Stability (days)	382 days @ -70°C
Dilution Integrity	Concentration diluted 2-fold
Selectivity	No interfering peaks noted in blank plasma samples

E. In Vivo Studies

E.1. Single-dose Fasting Bioequivalence Study No. BALS-0431

Study Summary	
Study No.	BALS-0431
Study Design	open-label, single-dose, randomized, two-period, two-treatment crossover under fasting conditions
No. of subjects enrolled	80
No. of subjects completing	77
No. of subjects analyzed	77
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 39 Female: 41
Test product	Balsalazide Disodium Capsules
Reference product	Colazal® Capsules
Strength tested	750 mg
Dose	3x750 mg (2250 mg) administered with 240 mL of water at room temperature

Summary of Statistical Analysis As Reported by the Firm Balsalazide Disodium 2250 mg (3x750 mg)*		
Fasting BE Study BALS-431 (N=77)		
Balsalazide		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	0.96	89%-105%
AUC _∞	0.96	88%-104%
C _{max}	0.89	82%-96%
Mesalamine		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	0.95	88%-103%
AUC _∞	0.96	82%-112%
C _{max}	1.05	94%-117%

*The reviewer's calculated values were same as reported by the firm.

Reanalysis of Study Samples: Balsalazide and Mesalamine

BALS-0431-Fasting Study Balsalazide Additional Information in Volume 2, pages 384-388								
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	0	0	0%	0%	0	0	0%	0%
Reason A	28	38	0.57%	0.77%	28	38	0.57%	0.77%
Reason B	5	7	0.10%	0.14%	5	7	0.10%	0.14%
Reason C	0	0	0%	0%	0	0	0%	0%
Total	33	45	0.67%	0.91%	33	45	0.67%	0.91%

BALS-0431-Fasting Study Mesalamine Additional Information in Volume 6, page 2638								
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	0	0	0%	0%	0	0	0%	0%
Reason A	0	1	0%	0.02%	0	1	0%	0.02%
Reason B	2	2	0.04%	0.04%	2	2	0.04%	0.04%
Reason C	1	0	0.02%	0%	1	0	0.02%	0%
Total	3	3	0.06%	0.06%	3	3	0.06%	0.06%

- A Sample Outside Limits of Curve Range (ALQ)
- B Abnormal Internal Standard (IS) Response
- C No Original Assay

Total numbers of samples assayed for study BALS-0431 were 4973.

Did use of recalculated plasma concentration data change study outcome?

No, there were no pharmacokinetic repeats and no recalculations were performed for either the parent drug balsalazide or the metabolite mesalamine.

F. Formulation

Location in appendix	Section B, Page 25
Are inactive ingredients within IIG limits?	Yes
If yes, list ingredients outside of limits	N/A
If a tablet, is the product scored?	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A: Capsule Dosage Form
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

To help establish BE, the current FDA-recommended method is as follows: ¹

Source of Method (USP, FDA or Firm)	FDA
Media*	1) 0.1N HCl 2) pH 4.5 buffer 3) pH 6.8 buffer 4) pH 7.4 buffer
Volume (mL)	900 mL
Temperature	37 ± 0.5°C
USP Apparatus type	1 (basket)
Rotation (rpm)	100
Recommended sampling times (min)	5, 10, 15, 20, 30, 45, and 60
f2 metric calculated?	NO
If no, why not?	Inapplicable; >20% CV of early time points resulted in too few samples for appropriate f2 calculation (please see also comments with data below)
Is method acceptable?	Yes ²
If no, why not?	---
Are dissolution results acceptable?	YES
If not, then why?	---
Location in Appendix	See Section IV.C below

¹ Protocol #05-006, Balsalazide Disodium Capsules

² Dissolution Amendment, ANDA 77-807, submitted 01/19/06

*In addition, the firm has also provided dissolution testing results in water

Reviewer's comment: Both test and reference products are equally acid resistant and would be expected to remain intact through the stomach (for at least 1 hour). Despite the discrepancies in the dissolution rate between the test and reference products at the early time points (i.e., 5 min, 10 min, and 15 min), the extent of drug dissolution after 20 min is nearly identical across all three buffer (pH 4.5, 6.8, and 7.4) and water media. Because the transit time through the small intestine is three hours (irrespective of the fed

or fasted state) at a pH of 5.0-7.0, these data suggest that both test and reference formulations would be equally dissolved by the time balsalazide reaches the lumen of the colon, the site of action for this drug. These observations are supported by the fact that this product shows bioequivalence to the RLD in vivo with respect to both the parent prodrug balsalazide and the active metabolite mesalamine. One factor contributing to in vivo bioequivalence between test and reference products will be the rate of balsalazide dissolution throughout the GI tract, which will in turn influence the rate of balsalazide uptake at the site of activity (the enterocytes of the colon). Thus, BE dissolution data are acceptable.

For issues related to quality controls and stability, the current FDA-recommended dissolution testing method is:

Medium	Potassium Phosphate Buffer, pH 6.8
Volume	900 mL
Temperature	37 ± 0.5 °C
USP Apparatus	2 (Paddles) with sinkers
Rotational Speed	50 rpm
Specification	NLT ^(b) ₍₄₎ % (Q) in 30 min

The firm conducted QC/Stability dissolution testing per the FDA recommendation. These data were submitted as dissolution amendment on December 15, 2005 and found acceptable by the Division (Source V:\firmsam\mylan\ltrs&rev\77807D1205.doc). Please also see the Appendix in section IV.C. Dissolution.

Reviewer's Comments: Quality controls and stability dissolution data, as reviewed previously,³ meet the FDA-recommended specification of NLT ^(b)₍₄₎ % (Q) dissolved in 30 min. These results are acceptable. On January 19, 2006, the firm acknowledged the dissolution method and specification.

³. Dissolution Amendment V:\firmsam\mylan\ltrs&rev\77807D1205.doc

H. Waiver Request(s): N/A

I. Deficiency Comments

None

J. Recommendations

1. The single-dose, fasting study conducted by Mylan Pharmaceuticals, Inc. on its Balsalazide Disodium Capsules, 750 mg (Lot # R1M0787), comparing it to Colazal® (balsalazide disodium) Capsules, 750 mg (Lot # 308512), manufactured by Salix Pharmaceuticals, is acceptable.
2. The in vitro dissolution testing conducted by Mylan Pharmaceuticals, Inc. on its Balsalazide Disodium Capsules 750mg strength, Lot No. R1M0787 is acceptable. The dissolution testing should be conducted in 900 mL of potassium phosphate buffer, pH 6.8 at 37 °C using Apparatus II (Paddle) with sinkers at 50 rpm. The test product should meet the following specification:

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

From the bioequivalence viewpoint, the firm has submitted acceptable information regarding in vivo bioequivalence and in vitro dissolution testing.

The firm should be informed of the above recommendations.

Chandra S. Chaurasia 6/12/2006
Chandra S. Chaurasia, Ph.D., Reviewer, Branch 1 Date

Moheb H. Makary 6/12/06
Moheb H. Makary, Ph.D., Team Leader, Branch 1 Date

Dale P. Conner 6/12/06
Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	BALS-0431
Study Title	Single dose Fasting In Vivo Bioequivalence Study of Balsalazide Disodium Capsules (750 mg; Mylan) and Colazal® Capsules (750 mg; Salix) in Healthy Volunteers
Clinical Site	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period I: May 7, 2004-May 11, 2004 Period II: May 21, 2004 –May 25, 2004
Analytical Site	Mylan Pharmaceuticals Inc. 3711 Collins Ferry Road, WV 26504
Analytical Director	(b) (6)
Analysis Dates	Balsalazide Phase: July 1, 2004 –September 23, 2004 Mesalamine Phase: July 29, 2004-August 27, 2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	Balsalazide: 140 days Mesalamine Phase: 114 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Balsalazide Disodium Capsules	Colazal® (Balsalazide Disodium) Capsules
Manufacturer	Mylan	Salix Pharma
Batch/Lot No.	R1M0787	308512
Manufacture Date	03/31/04	N/A
Expiration Date	TBE	4/2006
Strength	750 mg	750 mg
Dosage Form	Capsules	Capsules
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	99.9%	101.0%
Content Uniformity (mean, %CV)	100%, 2.4%	101%, 1.9%
Formulation	See Appendix Section 0	
Dose Administered	3x750 mg (2250 mg) with 240-mL of water at room temp.	3x750 mg (2250 mg) mg with 240-mL of water at room temp.
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 2,3,5,6,9,13,17,18,19,20,21,23,25,28,30,33,34,35,37,39,41, 42*,43,44,46,51,52*,53,56,57,61,62,65,67,70,71,72,73,75,77 BA: 1,4,7,8,10,11,12,14,15*,16,22,24,26,27,29,31,32,36,38,40,45, 47,48,49,50,54,55,58,59,60,63,64,66,68,69,74,76,78,79,80
Blood Sampling Times	Pre dose (0), 0.167,0.33, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8,9, 10, 11,12, 14,16,20,24,29,34,39,48,60 AND 72 hours post-dose
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	After collection in vacutainers with K3 EDTA, blood samples were placed in an ice water bath, and centrifuged under refrigeration. The plasma was then separated, transferred to polypropylene tubes, and immediately stored at -70°C ±15°C pending assay.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours
Length of Confinement	Overnight before pre-dose until after the 24-hour after dosing for each study period.
Safety Monitoring	Blood pressure, pulse rate and respiration rate were measured within 60 min prior to dosing and 12 and 24 hours post-dosing.

Sub #15 was discontinued from the study during Period 1 due to adverse events

Sub #42 was discontinued from the study prior to Period 2 dosing due to a positive pregnancy screen

Sub #52 withdrew from the study due to difficult phlebotomy during Period 1

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 1. Demographic Profile for Subjects Completing Balsalazide Disodium Bioequivalence Study

Fasting Bioequivalence Study BALS-0431		
	Treatment Groups	
	Balsalazide Disodium 15 mg N=77	Mobic® 15 mg N=77
Age (years)		
Mean ± SD	25.6 ± 9.1	25.6 ± 9.1
Range	18-72	18-72
Groups		
<18	0 (0%)	0 (0%)
18-40	70 (91%)	70 (91%)
41-64	6 (8%)	6 (8%)
65-75	1 (1%)	1 (1%)
>75	0 (0%)	0 (0%)
Sex		
Female	38 (49%)	38 (49%)
Male	39 (51%)	39 (51%)
Race		
Asian/Pacific	3 (4%)	3 (4%)
Black	5 (6.5%)	5 (6.5%)
Caucasian	64 (83%)	64 (83%)
Hispanic	5 (6.5%)	5 (6.5%)
Other	0 (0%)	0 (0%)

Table 2 Dropout Information

Subject No	Reason	Period	Replaced ?
15	Discontinued from the study during Period 1 due to adverse events – dizziness, syncope, and emesis	Per 1	No
42	Discontinued from the study prior to Period 2 dosing due to a positive pregnancy screen	Per 2	No
52	Withdrew from the study due to difficult phlebotomy during Period 1	Per 1	No

Table 3. Incidence of Adverse Events in Balsalazide Disodium Bioequivalence Study

Fasting Bioequivalence Study BALS-0431		
Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Test	Reference
Musculoskeletal and Connective Tissue Disorders		
Hematoma Left Arm Antecubital Space	0 (0%)	1 (4%)
Muscular Weakness	0 (0%)	1 (4%)
Reproductive System and Breast Disorders		
Menstrual Cramps	0 (0%)	1 (4%)
Itchy Vaginal Walls	1 (3%)	0 (0%)
Respiratory, Thoracic, and Mediastinal Disorders		
Head Cold	1 (3%)	1 (4%)
Sore Throat	1 (3%)	0 (0%)
Itchy Eyes	0 (0%)	1 (4%)
Blood and Lymphatic System Disorder		
Swollen Glands	0 (0%)	1 (4%)
Gastrointestinal Disorders		
Stomachache	2 (7%)	2 (8%)
Vomiting	1 (3%)	0 (0%)
Constipation	1 (3%)	0 (0%)
Diarrhea	1 (3%)	2 (8%)
Abdominal Cramping	1 (3%)	0 (0%)
Stomach Pain	0 (0%)	1 (4%)
Nausea	0 (0%)	1 (4%)
Upset Stomach	0 (0%)	1 (4%)
Emesis	0 (0%)	1 (4%)
Nervous System Disorders		
Headache	8 (27%)	5 (20%)
Dizziness	3 (10%)	0 (0%)
Lightheadedness	2 (7%)	4 (16%)
Funny taste in Mouth	1 (3%)	0 (0%)
Syncope	0 (0%)	1 (4%)
Renal and Urinary Disorders		
Burning Upon Urination	1 (3%)	0 (0%)
Strong Urine Smell	1 (3%)	0 (0%)
General Disorders and Administration Site Conditions		
Fatigue	1 (3%)	0 (0%)
Pallor	1 (3%)	1 (4%)
Pain near Tailbone	1 (3%)	0 (0%)
Weak	1 (3%)	0 (0%)
Pregnancy, Puerperium, and Perinatal Conditions		
Pregnancy	1 (3%)	0 (0%)
Total	30	25

Protocol Deviations

Twenty-two subjects in Treat A (Test) and 20 subjects in Treat B exhibited protocol deviations related to blood draw time (for details please see Tables on pages 4540 and 4541 Clinical Report, Volume 1.9). These deviations were minor and had no effect on the outcome of the study.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were 55 adverse events experienced by 32 subjects – 30 with test and 25 with the reference drug. Thirty-two AEE were either remotely or non-related to study medications. Forty-three AEs were listed mild in severity and 12 were listed as moderate in severity.
- One subject (Sub #36, Test drug, Per 2) vomited three times between study hours 10.75 to 11 of Period 2. The median Tmax for mesalamine for the Test product was calculated to be 8 hours. Since mesalamine Tmax for this subject was 16 hr, per BA/BE Guidance, this reviewer reanalyzed mesalamine data excluding Sub #36. There were no changes in the point ratios and confidence intervals for AUCt and Cmax values compared to those obtained with all subjects. No PK recalculation for the parent drug balsalazide was necessary as the balsalazide Tmax for subject 36 (test product) was 0.5 hr same as the median Tmax for balsalazide.
- Subject #15 (Ref drug, Per I) reported emesis during Period 1 at approximately study hour 0.5. The subject was withdrawn from the study due to AEE (dizziness and syncope), and was not included in the statistical analysis.
- Subject #42 was withdrawn from the study prior to Period II dosing secondary to a positive pregnancy screen.
- All adverse events resolved. There were no serious AE reported in this study.
- The adverse events and protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 4 Assay Quality Control – Within Study for Balsalazide and Mesalamine

	Parent (Balsalazide)									
QC Conc. (ng /mL)	18	60	60	360	360					
Intra day Precision (%CV)	6.9	5.2	0.86	6.8	4.7					
Intra day Accuracy (%)	0.22	-0.03	6.3	1.7	7.4					
Cal. Standards Conc. (ng /mL)	6.00	12.0	18.0	30.0	60.0	120.0	240.0	360.0	480.0	600.0
Inter day Precision (%CV)	1.8	2.9	3.3	2.9	3.2	3.1	3.1	3.0	2.9	3.0
Inter day Accuracy (%)	0.98	-2.3	0.17	0.27	0.17	-0.33	-1.3	1.1	2.5	-1.4
Linearity Range (range of R ² values)	0.9917-0.9993									

	Metabolite (Mesalamine)									
QC Conc. (ng /mL)	15	30	40	80	160	300	320	600		
Intra day Precision (%CV)	2.5	6.6	3.3	0.88	0.62	3.3	0.62	2.3		
Intra day Accuracy (%)	11.8	3.2	0.64	2.6	-0.63	2.2	1.1	0.76		
Cal. Standards Conc. (ng /mL)	10.0	20.0	40.0	80.0	160.0	320.0	400.0	500.0	600.0	800.0
Inter day Precision (%CV)	1.4	2.6	2.5	1.7	2.0	2.2	1.3	1.5	2.6	1.8
Inter day Accuracy (%)	0.49	-0.21	-1.1	-1.0	-0.12	-0.10	0.15	-0.54	1.6	0.92
Linearity Range (range of R ² values)	0.99780-0.99973									

Comments on Study Assay Quality Control:

Any interfering peaks in chromatograms?	None
Were 20% of chromatograms included?	YES
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: For both the analyte and internal standard, there were no interfering peaks. Peak shapes and baseline formation were satisfactory for the internal standard and the analyte.

Table 5 SOP's dealing with analytical repeats of study samples for balsalazide and mesalamine

SOP No.	Date of SOP	SOP Title
D-400-04	03/29/2004	Reassay of Reinjection of Clinical Samples

Table 6 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

- There were a total of 78 sample (33 test and 45 reference) re-assays for balsalazide in the study, representing 1.6% of the total study assays. For mesalamine, there were a total of 6 (3 each for test and ref) in the study, representing 0.12% of the total study samples. All re-assays were performed in accordance with the SOP.
- Analytical method and data are acceptable.

d) Pharmacokinetic Results

Table 7 Arithmetic Mean Balsalazide Pharmacokinetic Parameters

PARAMETER	MEAN1	CV1	MEAN2	CV2	RMEAN12
AUCT	1029.19	68.27	1088.75	69.79	0.95
AUCI	1053.26	66.92	1111.18	69.08	0.95
C _{MAX}	380.19	52.33	426.72	52.91	0.89
T _{MAX}	0.56	47.16	0.54	65.26	1.03
K _E	0.59	25.97	0.57	31.09	1.03
T _{1/2}	1.27	28.04	1.36	39.29	0.93
LAUCT	871.27	0.07	906.09	0.07	0.96
LAUCI	898.38	0.06	928.51	0.06	0.97
LC _{MAX}	334.66	0.15	378.41	0.13	0.88

Table 8 Geometric Means and 90% Confidence Intervals Balsalazide

PARAMETER	Test	Reference	T/R	90% CI	
				Lower	Upper
AUCT	1031.34	1089.17	0.95	84.57	104.81
AUCI	1042.25	1103.22	0.94	84.24	104.71
C _{MAX}	380.70	426.66	0.89	81.88	96.57
LAUCT	872.50	906.63	0.96	88.52	104.62
LAUCI	882.91	922.30	0.96	88.09	104.03
LC _{MAX}	335.09	378.48	0.89	82.04	95.55

Table 9 Additional Study Information for Balsalazide

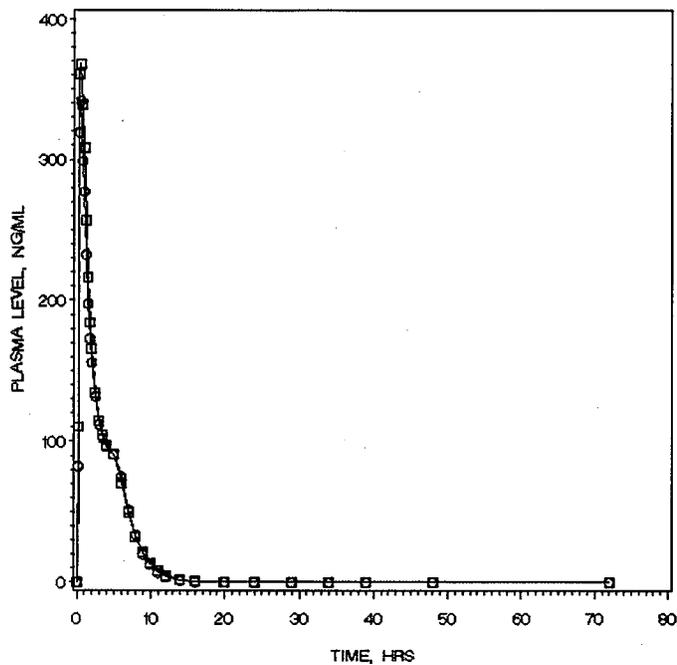
Root mean square error, AUC	0.3112
Root mean square error, C _{max}	0.2838
Ke and AUC _i determined for how many subjects?	75
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C _{max}	None
Were the subjects dosed as more than one group?	No

Table 10 Mean Plasma Balsalazide Concentrations, Single-Dose Fasting Bioequivalence Study

Time	Test (n=77)		Reference (n=77)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	
0.17	82.27	96.48	110.53	74.90	0.74
0.33	319.47	58.37	360.94	46.24	0.89
0.5	341.61	54.20	367.87	50.46	0.93
0.75	298.92	51.51	339.15	63.08	0.88
1	277.28	55.70	308.42	71.95	0.90
1.25	232.60	58.86	257.39	73.12	0.90
1.5	197.73	63.01	216.24	75.46	0.91
1.75	172.96	65.56	184.48	73.63	0.94
2	155.88	66.05	165.62	70.15	0.94
2.5	131.86	78.05	134.59	73.95	0.98
3	112.08	77.37	114.48	71.14	0.98

3.5	102.29	80.90	104.84	72.31	0.98
4	96.12	77.20	97.31	78.00	0.99
5	90.79	77.52	90.80	81.00	1.00
6	74.71	102.93	70.22	101.62	1.06
7	51.44	122.26	49.98	116.55	1.03
8	33.72	137.04	32.79	133.63	1.03
9	20.22	155.91	21.49	159.67	0.94
10	12.29	174.84	13.72	193.96	0.90
11	6.75	207.87	8.16	230.55	0.83
12	3.53	244.83	4.41	297.78	0.80
14	1.11	328.85	1.62	425.79	0.68
16	0.24	621.27	0.70	558.61	0.34
20	0.00	.	0.28	636.74	0.00
24	0.00	.	0.00	.	.
29	0.00	.	0.00	.	.
34	0.00	.	0.00	.	.
39	0.00	.	0.24	871.78	0.00
48	0.00	.	0.00	.	.
72	0.00	.	0.00	.	.

PLASMA BALSALAZIDE PARENT LEVELS
BALSALAZIDE PARENT CAPSULE, 750 MG ANDA # 77807
UNDER FAST CONDITIONS
DOSE=3 X 750 MG (= 2250 MG)



11 000 1 000 2

1=TEST 2=REF

Table 11: Arithmetic Mean Mesalamine Pharmacokinetic Parameters

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCT	2798.99	62.76	2918.11	58.76	0.96
AUCI	3697.84	57.90	4148.03	77.58	0.89
C _{MAX}	200.24	67.53	199.84	76.11	1.00
T _{MAX}	10.99	71.28	11.87	72.86	0.93
KE	0.07	66.58	0.07	54.79	1.01
T _{HALF}	15.28	77.12	16.23	109.5 3	0.94
LAUCT	2342.54	0.03	2461.60	0.02	0.95
LAUCI	3203.18	0.02	3367.51	0.02	0.95
LC _{MAX}	167.56	0.35	159.70	0.42	1.05

Table 12 Geometric Means and 90% Confidence Intervals Mesalamine

PARAMETER	Test	Reference	T/R	90% CI	
				Lower	Upper
AUCT	2799.68	2920.52	0.96	88.46	103.26
AUCI	3853.87	3959.57	0.97	82.43	112.23
C _{MAX}	200.38	199.85	1.00	88.73	111.80
LAUCT	2343.61	2463.91	0.95	87.61	103.26
LAUCI	3154.46	3290.90	0.96	82.46	111.42
LC _{MAX}	167.67	159.80	1.05	93.83	117.33

Table 13: Additional Study Information for Balsalazide

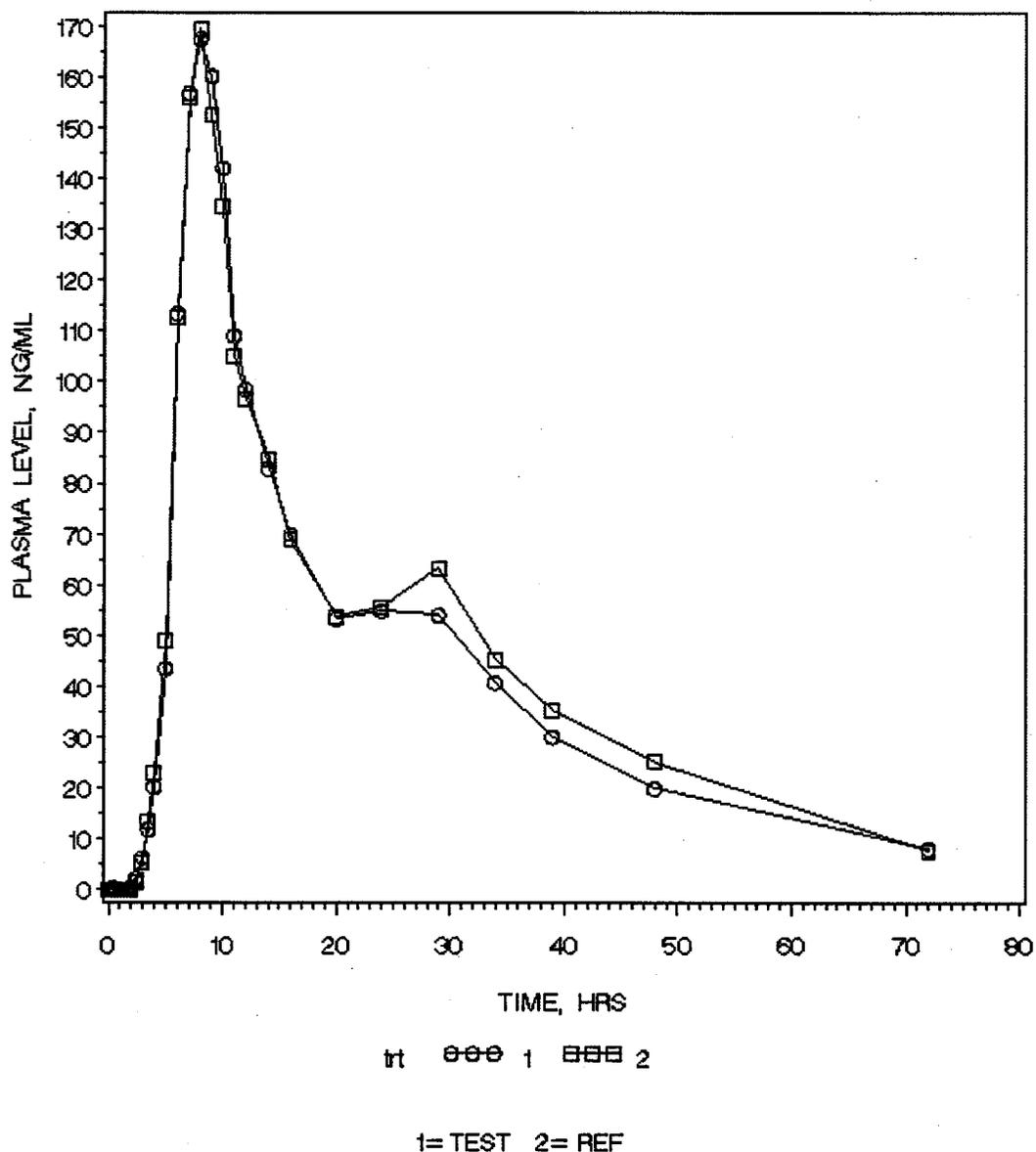
Root mean square error, AUC	0.3060
Root mean square error, C _{max}	0.4162
Ke and AUC _i determined for how many subjects?	77
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C _{max}	None
Were the subjects dosed as more than one group?	No

Table 14: Mean Plasma Mesalamine Concentrations, Single-Dose Fasting Bioequivalence Study

Time	Test (n=77)		Reference (n=77)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.17	0.00	.	0.00	.	.
0.33	0.33	877.50	0.16	877.50	2.08
0.5	0.00	.	0.00	.	.
0.75	0.00	.	0.00	.	.
1	0.00	.	0.00	.	.
1.25	0.00	.	0.00	.	.
1.5	0.00	.	0.00	.	.
1.75	0.18	877.50	0.21	877.50	0.87
2	0.47	618.51	0.15	871.78	3.26
2.5	2.23	467.20	1.65	335.68	1.35
3	6.25	310.68	5.39	229.77	1.16
3.5	11.70	242.57	13.22	196.42	0.89
4	19.98	191.14	22.67	174.42	0.88
5	42.98	133.87	48.45	118.96	0.89
6	113.39	91.19	112.68	100.85	1.01
7	155.91	83.72	155.92	91.08	1.00
8	166.28	74.09	168.74	81.14	0.99
9	158.97	71.17	151.68	76.60	1.05
10	140.94	71.85	133.74	75.79	1.05
11	108.54	74.50	104.46	79.23	1.04
12	98.42	78.50	96.05	77.71	1.02
14	83.11	85.49	84.42	89.71	0.98
16	70.90	91.95	68.75	91.83	1.03
20	54.23	84.86	54.13	70.62	1.00
24	55.37	78.03	55.97	68.33	0.99
29	54.24	81.17	63.12	78.05	0.86
34	40.70	92.90	45.07	87.92	0.90
39	29.90	106.51	34.93	108.66	0.86
48	19.91	129.44	24.89	114.98	0.80
72	8.03	299.41	7.74	233.74	1.04

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

PLASMA BALSALAZIDE Metabolite MESALAMINE LEVELS
 BALSALAZIDE Metabolite MESALAMINE CAPSULE, 750 MG, Dose 3x750 mg (2250 mg) ANDA # 77807
 UNDER FAST CONDITIONS
 DOSE= 3x750 mg



Comments on Chromatograms: For both the analyte and internal standard, there were no interfering peaks. Peak shapes and baseline formation were satisfactory for the internal standard and the analyte.

Comments on Pharmacokinetic Analysis:

- The fasting BE study was conducted in 77 healthy adult male and female subjects. Subject #36 vomited three times between the 10.75 to 11 hours post-dose. Since the median T_{max} for mesalamine in this study is 8 hr, and the T_{max} for this subject was 16 hr, the statistical analyses were performed with and without data from this subject. Results indicate exactly similar values for all relevant PK parameters in terms of point estimates and confidence intervals.
- The results for balsalazide from the study BALS- 0431 (point estimate, 90% CI) of the study are: LAUC_t of 0.96, 89%-105%; LAUC_i of 0.96, 88%-104% and LC_{max} of 0.89, 82%-96%. Study results for mesalamine (point estimate, 90% CI) of the study are: LAUC_t of 0.95, 88%-103%; LAUC_i of 0.96, 82%-112% and LC_{max} of 1.05, 94%-117%. The statistical results demonstrate that the test product meets the BE criteria compared to the reference drug.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for ln-transformed AUC_t, AUC_{inf}, and C_{max} are within the acceptable limits of 80-125%.

Summary/Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose fasting bioequivalence study is acceptable.

B. Formulation Data

Ingredient	Amount (mg)/Capsule	Amount (%) Capsule
	750mg	750mg
Balsalazide	750.0	94.7
Sodium Starch Glycolate, NF	(b) (4)	(b) (4)
Colloidal Silicon Dioxide, NF		
Magnesium Stearate, NF		
Total	792.0	100.0

The empty gelatin capsule used is a #00 Orange Opaque (b) (4) cap/Orange Opaque (b) (4) body imprinted MYLAN in black ink on cap and body.

The following table lists the ingredients and ingredient amounts found in the capsule shell:

Ingredient	mg/capsule
D&C Red #28	(b) (4)
D&C Yellow #10	
FD&C #40	
Titanium Dioxide	
Gelatin	
Black Imprinting Ink	
Total	118 mg (b) (4)

Sodium Lauryl Sulfate is also added (b) (4).

The Black Imprinting Ink is (b) (4) and contains: Shellac Glaze – (b) (4) Black Iron Oxide, FD&C Blue #2 Lake, FD&C Red #40 Lake, FD&C Blue #1 Lake, D&C Yellow #10 Lake, (b) (4), Propylene Glycol (b) (4) (b) (4) and (b) (4). Qualitative formulas are provided on pages 6867 and 6868.

C. Dissolution Data

The firm has submitted comparative dissolution profile under the following pH conditions using USP apparatus 1 (basket) at 100 rpm and 900 mL of each of the dissolution media. The comparative dissolution profiles in the 4 media have been recommended to establish the bioequivalency of the test product in conjunction with the in vivo BE study.

0.1N HCl
pH 4.5 buffer
pH 6.8 buffer
pH 7.4 buffer

The firm has also provided dissolution testing results in water using the above conditions. The results of dissolution profiles in the above media are summarized in the Table below.

Summary of In Vitro Dissolution Testing in different pH media and water are provided in the Table 15 below.

For the stability and quality control program, FDA currently recommends the following dissolution method for Balsalazide:

Medium: Potassium Phosphate Buffer, pH 6.8
Volume: 900 mL
Apparatus: USP II (Paddle) with sinkers
Rotational speed: 50 rpm
Sampling Times: 5, 10, 15, 20, 30, 45, 60 and 80 minutes
FDA Specification: NLT $\frac{(b)}{(4)}$ % (Q) in 30 minutes

In response to DBE's dissolution deficiency review response dated Jan 10, 2006, the firm has sent its acceptance dated Jan 19, 2006 to the following method, and adopted the FDA-recommended dissolution method and specification. The dissolution testing results under these conditions are summarized in Table 16 below.

Table 15. Summary of Comparative Dissolution Profiles of Mylan's Balsalazide Disodium and RLD Colazal in Different Media (900 mL each) Using USP Apparatus 1 (Basket) at 100 rpm

	Medium	5 min	10 min	15 min	20 min	30 min	45 min	60 min
Mylan Lot R1M0787 No of Units 12 Mean Range RSD	0.1 NHCl	0% 0%-1% 43.6%	1% 0%-1% 32.5%	0% 0%-1% 16.6%	1% 0%-1% 26.2%	0% 0%-1% 14.3%	0% 0%-1% 18.6%	1% 0%-1% 23.3%
Colazal® Lot 308512 No of Units 12 Mean Range RSD		0% 0%-1% 78.9%	0% 0%-1% 18.2%	1% 1%-1% 13.4%	1% 0%-1% 14.7%	1% 0%-1% 14.4%	1% 1%-2% 21.1%	1% 1%-1% 17.3%
Mylan Lot R1M0787 No of Units 12 Mean Range RSD	pH 4.5 Acetate Buffer	24% 13%-46% 41.1%	70% 53%-77% 9.7%	94% 85%-99% 4.6%	101% 99%-104% 1.7%	102% 99%-104% 1.8%	102% 99%-104% 1.7%	102% 99%-105% 1.8%
Colazal® Lot 308512 No of Units 12 Mean Range RSD		32% 25%-41% 16.9%	62% 53%-71% 9.0%	84% 75%-95% 6.6%	98% 92%-101% 1.1%	102% 100%-104% 1.1%	102% 100%-105% 1.1%	103% 100%-105% 1.1%
Mylan Lot R1M0787 No of Units 12 Mean Range RSD	pH 6.8 Phosphate Buffer	23% 14%-32% 26.8%	71% 61%-85% 9.8%	93% 85%-101% 5.2%	100% 96%-103% 2.2%	101% 96%-103% 2.2%	101% 96%-103% 2.2%	101% 96%-104% 2.2%
Colazal® Lot 308512 No of Units 12 Mean Range RSD		33% 22%-47% 20.2%	65% 54%-74% 10.6%	85% 72%-97% 8.6%	99% 92%-102% 3.7%	102% 98%-105% 1.7%	102% 98%-105% 1.7%	102% 98%-105% 1.7%

Table 15 Contd.

	Medium	5 min	10 min	15 min	20 min	30 min	45 min	60 min
Mylan Lot R1M0787 No of Units 12 Mean Range RSD	pH 7.4 Phosphate Buffer	27% 17%-39% 24.4%	61% 49%-73% 11.8%	86% 69%-102% 11.6%	98% 88%-103% 4.9%	101% 98%-104% 1.7%	101% 98%-104% 1.7%	101% 98%-104% 1.7%
Colazal® Lot 308512 No of Units 12 Mean Range RSD		16% 11%-30% 37.8%	64% 43%-76% 18.6%	94% 88%-103% 4.3%	101% 98%-106% 2.4%	101% 98%-106% 2.4%	101% 98%-106% 2.4%	101% 99%-106% 2.4%
Mylan Lot R1M0787 No of Units 12 Mean Range RSD	Deionized Water	35% 8%-32% 38.2%	61% 36%-83% 27.6%	93% 81%-100% 7.2%	102% 96%-106% 2.5%	103% 100%-108% 1.9%	104% 100%-109% 2.0%	104% 100%-110% 2.4
Colazal® Lot 308512 No of Units 12 Mean Range RSD		35% 22%-48% 25.2%	65% 49%-76% 12.9%	87% 77%-101% 7.9%	101% 95%-106% 3.3%	104% 101%-108% 1.9%	104% 101%-109% 2.2%	104% 101%-109% 2.2%

Table 17: Summary of In Vitro Dissolution Testing using FDA Recommended Method

Apparatus: USP II (Paddle) with sinker Medium: Potassium Phosphate Buffer, pH 6.8, 900 mL, 37 °C Rotational Speed: 50 RPM						
Results of In Vitro Dissolution Testing (% dissolved)						
Sampling Times (Min)	Test Product: Balsalazide Disodium Capsules Lot No.: R1M0787 Strength: 750 mg No of Dosage Units: 12			Reference Product: Colazal® Capsules Lot No.: 308512 Strength: 750 mg No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
5	26	18%-38%	26	40	32%-52%	14.4
10	75	60%-90%	12	69	64%-75%	5.1
15	92	80%-101%	6.4	85	76%-95%	6.2
20	99	95%-101%	1.8	95	85%-100%	4.6
30	100	96%-103%	2.0	101	98%-103%	1.8
45	100	97%-103%	1.9	101	98%-103%	1.4
60	100	96%-103%	2.0	101	98%-103%	1.6
80	100	97%-103%	2.0	102	99%-104%	1.8

Comments on Dissolution:

- Based on the available dissolution testing results in each of the pH media (i.e., acetate buffer pH 4.5, phosphate buffers pH 6.8 and pH 7.4) the f2-similarity test is invalid. Measurements at the 5-min time point for the test and reference products in each of these media exhibit a CV of >20%. In the case of phosphate buffer 7.4 the CV of > 10% at the subsequent 10- min time point (test and reference) is observed. . Per the Guidance for Industry on Dissolution Testing of IR products, these mean values should be excluded from f2 calculations. Furthermore, for both the test and the reference products, the mean dissolution release is ~85% or more at 15 min and each of the subsequent time points indicating a plateau condition. Because the dissolution profile comparison is most suitable when at least three dissolution time points are available before an asymptote is reached, the f2-similarity test cannot be appropriately applied here.
- Based on the dissolution testing profiles in different pH media, both test and reference products are equally acid resistant and would be expected to remain intact through the stomach (for at least 1 hour). Despite the discrepancies in the dissolution rate between the test and reference products at the early time points (i.e., 5 min and 10 min), the extent of drug dissolution after 15 min is nearly identical across all three buffer (pH 4.5, 6.8, and 7.4) and water. Because the transit time through the small intestine is three hours (irrespective of the fed or fasted state) at a pH of 5.0-7.0, these data suggest that both test and reference formulations would be equally dissolved by the time balsalazide reaches the lumen of the colon, the site of action for this drug. Thus, BE dissolution data are acceptable.

- The firm has adopted the FDA recommended dissolution conditions. Based on the submitted data, the firm's dissolution results meet the FDA recommended specification of NLT ^(b)₍₄₎ % (Q) in 30 minutes at the S1 level. The firm's dissolution testing using FDA method is acceptable.

D. Consult Reviews: None**E. SAS Output**

STUDY	DATA	SAS PROGRAM	SAS OUTPUT
<p>Study BALS-0431 Under Fasting Condition</p>	<p> ANDA 77807 Balsal conc.txt</p> <p> ANDA 77807 Balsal pk.txt</p> <p>  ANDA 77807 Mesal ANDA 77807Mesal conc.txt pk.txt</p>	<p> ANDA77807 Balsalazide SAS PRG.1</p> <p> ANDA77807 Mesal All Sub SAS PRG.txt</p>	<p> ANDA 77807 Balsalazide.txt</p> <p> ANDA77807 Mesalamine All Sub.tx</p> <p> ANDA77807 Mesal Ex Sub 36 .txt</p>

F. Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-807

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT:

Balsalazide Disodium Capsules
750 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

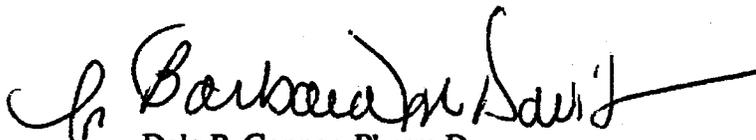
We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 900 mL of potassium phosphate buffer, pH 6.8 at 37 °C using apparatus II (paddle) with sinker at 50 rpm. The test products should meet the following specification:

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



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

CC: ANDA 77-807
 ANDA DUPLICATE
 DIVISION FILE
 HFD-650/ Bio Drug File
 HFD-650/ Reviewer C. Chaurasia
 HFD-650/ Project manager A. Sigler
 HFD-650/ Team Leader M. Makary

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Endorsements: (Final with Dates) finalized on June 9, 2006

HFD-650/C. Chaurasia

HFD-650/M. Makary

HFD-650/D.P. Conner

Clara S. Conner 6/12/2006

mm 6/12/06

BMD 6/12/06

rh

BIOEQUIVALENCE -- ACCEPTABLE

Submission date(s): July 18,
 2005, January 19, 2006

1. Fasting Bioequivalent STUDY (STF)
 Clinical: PRACS Institute, Ltd.
 4801 Amber Valley Parkway
 Fargo, ND 58104

Strengths: 750 mg
 Outcome: AC

Analytical: Mylan Pharmaceuticals Inc.
 3711 Collins Ferry Road, WV 26504

Outcome Decisions: AC – Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-807
Drug Product Name	Balsalazide Disodium Capsules
Strength	750mg
Applicant Name	Mylan Pharmaceuticals, Inc.
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Contact Information	S. Wayne Talton
Telephone	(304) 599 -2595
Fax	(304) 285-6407
Submission Date(s)	July 18, 2005
Amendment Date(s)	December 15, 2005 (Dissolution Amendment), January 19, 2006
Reviewer	Chandra S. Chaurasia, Ph.D.
First Generic	No

1 Executive Summary

This is a review of an addendum.

In the original review the firm performed an acceptable fasted bioequivalence (BE) study on the test product, Balsalazide Disodium Capsules, 750 mg, with the reference listed drug (RLD), Colazal® (balsalazide disodium) capsules, 750 mg from Salix Pharmaceuticals. The dissolution was found acceptable in the original review. The application was found acceptable.

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.

The firm should be notified that they should perform a fed BE study on their test product.

2 Table of Contents

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3 Submission Summary

3.1 Drug Product Information

Test Product	Balsalazide Disodium Capsules, 750 mg
RLD	Colazal® (balsalazide disodium) Capsules, 750 mg ¹
RLD Manufacturer	Salix Pharms
NDA No.	20-610
NDA Approval Date	18 Jul 2000
Indication	Ulcerative Colitis
Contraindication	Patients with hypersensitivity to salicylates
Most Frequent Side Effects	Headache (8%), abdominal pain (6%), nausea (5%), diarrhea (5%), vomiting (4%)
Recommended Daily Dosage	6.75 g/day
Warnings	Caution should be exercised for patients with known renal dysfunction
Mechanism of action	Thought to act by inhibiting production of inflammatory mediators (e.g., prostanooids, leukotrienes) which are highly active in inflammatory bowel disease/disorders; appears to have a topical rather than systemic action

¹ Colazal® capsules, PDR (electronic edition)

3.2 Addendum Information

3.2.1 Background

The RLD labeling has been amended to include the following statements that pertain to a food effect when taking the capsule product:

CLINICAL PHARMACOLOGY:

The plasma pharmacokinetics of balsalazide and its key metabolites from a crossover study in healthy volunteers are summarized in Table 1. In this study, a single oral dose of COLAZAL 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.

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_{max} and AUC_{last} were lower, while t_{max} was markedly prolonged, under fed (high-fat meal) compared to fasted conditions. Moreover, the data suggest that dosing 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.

DOSING AND ADMINISTRATION:

COLAZAL 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 COLAZAL are NOT coated beads/granules. Do not store drug/applesauce mixture for future use.

As per the CDER Guidance for Industry: Food-Effect Bioavailability and Fed **Bioequivalence Studies (“Food Guidance”)**, a generic product must demonstrate equivalence by including a fed BE study if the RLD label has statements about the effect of food on absorption or administration.

For modified-release capsule products containing beads, the Division of Bioequivalence generally requests an in vivo BE study in which the test and reference products are opened and the component beads sprinkled in applesauce and administered to the study

subjects (“sprinkle BE study”). The coating of beads used to fill modified-release capsules generally contains excipients which control the rate of drug release; thus, applesauce may disrupt the mechanism of release for such products. Therefore, as per the Food Guidance, the Division of Bioequivalence asks applicants to conduct sprinkle BE studies for modified-release capsule products when the FDA-approved labeling recommends that the capsule be opened and contents sprinkled on applesauce. For a generic version of Colazal®, it is not necessary that the applicant conduct a sprinkle BE study, because the Colazal® immediate-release capsule does not contain release-controlling excipients.

3.2.2 Deficiencies

1. Due to the changes in the RLD labeling mentioned above, the firm should submit a single dose, two-way crossover fed in-vivo bioequivalence study comparing Balsalazide Disodium Capsules, 750mg to the reference listed drug, Colazal® Capsules, 750mg.
2. The firm should measure both parent compound balsalazide and metabolite mesalamine using an appropriate assay.

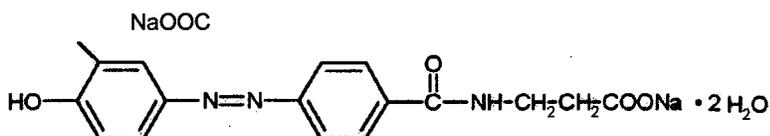
3.3 Recommendations

1. The single-dose fasted bioequivalence study conducted by Mylan Pharmaceuticals, Inc. on the test product, Balsalazide Disodium Capsules, 750mg, Lot # R1M0787, comparing it with the reference product, Colazal® Capsules 750mg, Lot # 308512, is acceptable
2. The dissolution testing conducted by Mylan Pharmaceuticals, Inc. on the test product, Balsalazide Disodium Capsules, 750mg, is acceptable.
3. The DBE recommends that the firm 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.
4. The firm should measure both parent compound balsalazide and metabolite mesalamine using an appropriate assay. For an acceptable 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.

Attachments

COLAZAL[®] (balsalazide disodium) Capsules (kôl a zal)

DESCRIPTION: Each *COLAZAL* capsule contains 750 mg of balsalazide disodium, a prodrug that is enzymatically cleaved in the colon to produce mesalamine (5-aminosalicylic acid or 5-ASA), an anti-inflammatory drug. Each daily dose of *COLAZAL* (6.75 grams) is equivalent to 2.4 grams of mesalamine. Balsalazide disodium has the chemical name (E)-5-[[4-[[[(2-carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate. Its structural formula is:



Molecular Weight: 437.32 Molecular Formula: $C_{17}H_{13}N_3O_6Na_2 \cdot 2H_2O$

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 and magnesium stearate. The sodium content of each capsule is approximately 86 mg.

CLINICAL PHARMACOLOGY: Balsalazide disodium 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- β -alanine. The recommended dose of 6.75 grams/day, for the treatment of active disease, provides 2.4 grams of free 5-ASA to the colon.

The 4-aminobenzoyl- β -alanine carrier moiety released when balsalazide disodium is cleaved is only minimally absorbed and largely inert. The mechanism of action of 5-ASA is unknown, but appears to be local to the colonic mucosa rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, 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.

Pharmacokinetics: *COLAZAL* 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. 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 1. In this study, a single oral dose of *COLAZAL* 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 1: Plasma Pharmacokinetics for Balsalazide and Key Metabolites (5-ASA and N-Ac-5ASA) with Administration of COLAZAL Following a Fast, a High-Fat Meal, and Drug Contents Sprinkled on Applesauce (Mean \pm SD)

Fasting n = 17		High-fat Meal n = 17	Sprinkled n = 17
C_{max} ($\mu\text{g/mL}$)			
Balsalazide	0.51 \pm 0.32	0.45 \pm 0.39	0.21 \pm 0.12
5-ASA	0.22 \pm 0.12	0.11 \pm 0.136	0.29 \pm 0.17
N-Ac-5-ASA	0.88 \pm 0.39	0.64 \pm 0.534	1.04 \pm 0.57
AUC_{last} ($\mu\text{g}\cdot\text{hr/mL}$)			
Balsalazide	1.35 \pm 0.73	1.52 \pm 1.01	0.87 \pm 0.48
5-ASA	2.59 \pm 1.46	2.10 \pm 2.58	2.99 \pm 1.70
N-Ac-5-ASA	17.8 \pm 8.14	17.7 \pm 13.7	20.0 \pm 11.4
T_{max} (h)			
Balsalazide	0.8 \pm 0.85	1.2 \pm 1.11	1.6 \pm 0.44
5-ASA	8.2 \pm 1.98	22.0 \pm 8.23	8.7 \pm 1.99
N-Ac-5-ASA	9.9 \pm 2.49	20.2 \pm 8.94	10.8 \pm 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_{max} and AUC_{last} were lower, while t_{max} was markedly prolonged, under fed (high-fat meal) compared to fasted conditions. Moreover, the data suggest that dosing 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 study of patients with mild-to-moderate active ulcerative colitis receiving three 750-mg COLAZAL capsules 3 times daily (6.75 g/day) for 8 weeks, steady state was reached within 2 weeks.

In a separate study of ulcerative colitis, patients received balsalazide, 1.5 grams twice daily, for over 1 year. Systemic drug exposure, based on mean AUC values, was up to 60 times greater (8 ng*hr/mL to 480 ng*hr/mL) after equivalent multiple doses of 1.5 grams twice daily when compared to healthy subjects who received the same dose.

Distribution: The binding of balsalazide to human plasma proteins was \geq 99%.

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

Elimination: 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.

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.

In a study with 10 healthy volunteers, 65% of a single 2.25 gram dose of *COLAZAL* 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 3-6 grams of *COLAZAL* daily for more than one 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 COLAZAL 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.

Special Populations

Geriatric: No information is available for the geriatric population.

Pediatric: The safety and effectiveness of balsalazide in the pediatric population have not been established.

Gender: No adequate and well-controlled studies which examine balsalazide in males versus females are available.

Renal Insufficiency: No adequate and well-controlled studies which examine balsalazide disposition in patients with mild, moderate, and severe renal impairment are available.

Hepatic Insufficiency: No information is available for patients with hepatic impairment.

Race: No information is available which examines balsalazide in different races.

Pharmacodynamic/Pharmacokinetic Relationship: No information is available.

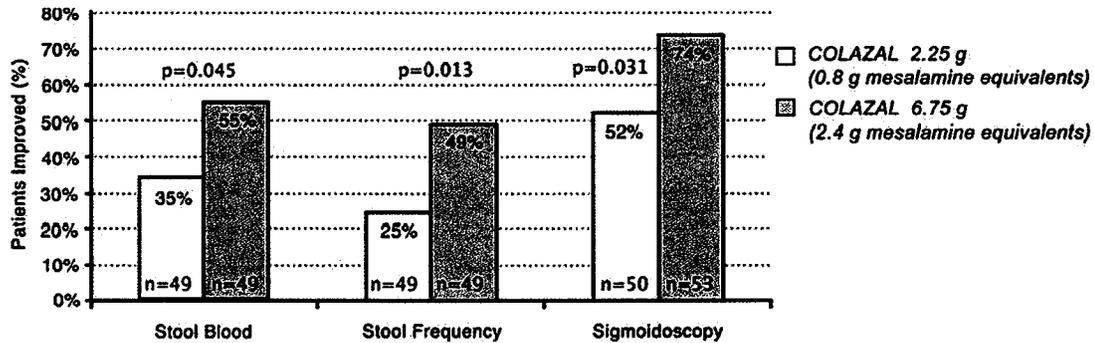
Drug-Drug Interactions: Neither in vitro nor in vivo drug-drug interaction studies have been performed with balsalazide.

CLINICAL TRIALS: Two randomized, double-blind studies were conducted.

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 grams/day or balsalazide 2.25 grams/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 doses of

COLAZAL (Figure 1).

Figure 1: Percentage of Patients Improved at 8 weeks



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

INDICATIONS AND USAGE: *COLAZAL* is indicated for the treatment of mildly to moderately active ulcerative colitis. Safety and effectiveness of *COLAZAL* beyond 12 weeks has not been established.

CONTRAINDICATIONS: *COLAZAL* is contraindicated in patients with hypersensitivity to salicylates or to any of the components of *COLAZAL* capsules or balsalazide metabolites.

PRECAUTIONS: Of the 259 patients treated with *COLAZAL* 6.75 grams/day in controlled clinical trials of active disease, exacerbation of the symptoms of colitis, possibly related to drug use, has been reported by 3 patients.

General: Patients with pyloric stenosis may have prolonged gastric retention of *COLAZAL* capsules.

Renal: At doses up to 2000 mg/kg (approximately 21 times the recommended 6.75 grams/day dose on a mg/kg basis for a 70 kg person), *COLAZAL* had no nephrotoxic effects in rats or dogs. Renal toxicity has been observed in animals and patients given other mesalamine products. Therefore, caution should be exercised when administering *COLAZAL* to patients with known renal dysfunction or a history of renal disease.

Drug Interactions: No drug interaction studies have been conducted for *COLAZAL*, however, the use of orally administered antibiotics could, theoretically, interfere with the release of mesalamine in the colon.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month rat (Sprague Dawley) carcinogenicity study, oral (dietary) balsalazide disodium at doses up to 2 grams/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+/-) forward mutation test, or mouse micronucleus test. However, it was genotoxic in the in vitro Chinese hamster lung cell (CH V79/HGPRT) 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+/-) 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+/-) forward mutation test, or the human lymphocyte chromosomal aberration test. Balsalazide disodium at oral doses up to 2 grams/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.

Pregnancy - Teratogenic Effects: Pregnancy Category B. Reproduction studies were performed in rats and rabbits at oral doses up to 2 grams/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 fetus 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.

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 *COLAZAL* is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of *COLAZAL* in pediatric patients have not been established.

ADVERSE REACTIONS: Over 1000 patients received treatment with *COLAZAL* in domestic and foreign clinical trials. In four controlled clinical trials patients receiving a *COLAZAL* dose of 6.75 grams/day most frequently reported the following events (reporting frequency $\geq 3\%$), headache (8%), abdominal pain (6%), diarrhea (5%), nausea (5%), vomiting (4%), respiratory infection (4%), and arthralgia (4%). Withdrawal from therapy due to adverse events was comparable among patients on *COLAZAL* and placebo. Adverse events reported by 1% or more of patients who participated in the four well-controlled, Phase 3 trials are presented by treatment group (Table 2).

Table 2: Adverse Events Occurring in at Least 1% of *COLAZAL* and Ulcerative Colitis Patients in Controlled Trials

<i>COLAZAL</i> 6.75 grams/day		Placebo
Adverse Event	[N=259]	[N=35]
Headache	22 (8%)	3 (9%)
Abdominal pain	16 (6%)	1 (3%)
Nausea	14 (5%)	2 (6%)
Diarrhea	14 (5%)	1 (3%)
Vomiting	11 (4%)	2 (6%)
Respiratory infection	9 (4%)	5 (14%)
Arthralgia	9 (4%)	
Rhinitis	6 (2%)	
Insomnia	6 (2%)	
Fatigue	6 (2%)	
Rectal bleeding	5 (2%)	1 (3%)
Flatulence	5 (2%)	
Fever	5 (2%)	

Dyspepsia	5 (2%)	
Pharyngitis	4 (2%)	
Pain	4 (2%)	1 (3%)
Coughing	4 (2%)	
Back pain	4 (2%)	1 (3%)
Anorexia	4 (2%)	
Urinary tract infection	3 (1%)	
Sinusitis	3 (1%)	1 (3%)
Myalgia	3 (1%)	
Frequent stools	3 (1%)	1 (3%)
Flu-like disorder	3 (1%)	
Dry mouth	3 (1%)	
Dizziness	3 (1%)	2 (6%)
Cramps	3 (1%)	
Constipation	3 (1%)	

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

The following adverse events, presented by body system, have also been infrequently reported by patients taking *COLAZAL* during clinical trials (N = 513) for the treatment of active acute ulcerative colitis or from foreign post-marketing reports. In most cases no relationship to *COLAZAL* has been established.

Body as a Whole: abdomen enlarged, asthenia, chest pain, chills, edema, hot flushes, malaise

Cardiovascular and vascular: bradycardia, deep venous thrombosis, hypertension, leg ulcer, palpitations, pericarditis
 Gastrointestinal: amylase increased, bowel irregularity, ulcerative colitis aggravated, diarrhea with blood, diverticulosis, epigastric pain, eructation, fecal incontinence, feces abnormal, gastroenteritis, giardiasis, glossitis, hemorrhoids, melena, neoplasm benign, pancreatitis, ulcerative stomatitis, stools frequent, tenesmus, tongue discoloration

Hematologic: anemia, epistaxis, fibrinogen plasma increase, hemorrhage, prothrombin decrease, prothrombin increase, thrombocythemia

Liver and biliary: bilirubin increase, hepatic function abnormal, SGOT increase, SGPT increase

Lymphatic: eosinophilia, granulocytopenia, leukocytosis, leukopenia, lymphadenopathy, lymphoma-like disorder, lymphopenia

Metabolic and nutritional: creatine phosphokinase increased, hypocalcemia, hypokalemia, hypoproteinemia, LDH increase, weight decrease, weight increase

Musculoskeletal: arthritis, arthropathy, stiffness in legs

Nervous: aphasia, dysphonia, gait abnormal, hypertonia, hypoesthesia, paresis, spasm generalized, tremor

Psychiatric: anxiety, depression, nervousness, somnolence

Reproductive: menstrual disorder

Resistance Mechanism: abscess, immunoglobulins decrease, infection, moniliasis, viral infection

Respiratory: bronchospasm, dyspnea, hemoptysis

Skin: alopecia, angioedema, dermatitis, dry skin, erythema nodosum, erythematous rash, pruritus, pruritus ani, psoriasis, skin ulceration

Special Senses: conjunctivitis, earache, ear infection, iritis, parosmia, taste perversion, tinnitus, vision abnormal

Urinary: hematuria, interstitial nephritis, micturition frequency, polyuria, pyuria

Post Marketing Reports:

The following events have been identified during post-approval use in clinical practice, of products which contain (or are metabolized to) mesalamine. Because they are reported voluntarily from a population of unknown size estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine.

Gastrointestinal: Reports of hepatotoxicity, including elevated liver function tests (**SGOT/AST, SGPT/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 events were reported in *COLAZAL* clinical trials. One case of Kawasaki-like syndrome which included hepatic function changes was also reported, however, this event was not reported in *COLAZAL* clinical trials.

DRUG ABUSE AND DEPENDENCY:

Abuse: None reported

Dependency: Drug dependence has not been reported with chronic administration of mesalamine.

OVERDOSAGE: No case of overdose has occurred with *COLAZAL*. A 3-year-old boy is reported to have ingested 2 grams of another mesalamine product. He was treated with ipecac and activated charcoal with no adverse reactions.

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

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

DOSAGE AND ADMINISTRATION: For Treatment of Active Ulcerative Colitis the usual dose in adults is three 750 mg *COLAZAL* capsules to be taken three times a day for a total daily dose of 6.75 grams for a duration of 8 weeks. Some patients in the clinical trials required treatment for up to 12 weeks.

COLAZAL 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 *COLAZAL* are NOT coated beads/granules. Do not store drug/applesauce mixture for future use.

HOW SUPPLIED: *COLAZAL* is available as beige capsules containing 750 mg balsalazide disodium and CZ imprinted in black.

NDC 65649-101-02 Bottles of
280 capsules. NDC 65649-
101-50 Bottles of 500
capsules.

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.

Rx only

Manufactured for Salix Pharmaceuticals, Inc., Morrisville, NC 27560

* *COLAZAL*[®] is a registered trademark of Salix Pharmaceuticals, Inc.

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6075.06/Feb. 2006

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-807

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Balsalazide Disodium Capsules, 750mg

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

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 C_{max} 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: ANDA 77-807

BIOEQUIVALENCY	INCOMPLETE
Original Submission date:	18 July, 2005
Amendment date(s):	15 December, 2005 19 January, 2006 (Addendum)

1. Study Addendum	Strengths: 750mg Capsule
(WC)	Outcome: IC
Clinical Site:	Clinical: PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104
Analytical Site:	Mylan Pharmaceuticals Inc. 3711 Collins Ferry Road, WV 26504

Outcome Decisions: IC - Incomplete

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/s/

Chandra S. Chaurasia
11/16/2006 10:36:49 AM
BIOPHARMACEUTICS

Moheb H. Makary
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BIOPHARMACEUTICS

Barbara Davit
11/17/2006 10:50:24 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-807
Drug Product Name	Balsalazide Disodium Capsules
Strength(s)	750 mg
Applicant Name	Mylan Pharmaceuticals, Inc.
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Applicant's Point of Contact	S. Wayne Talton
Contact's Telephone Number	(304) 599-2595, ext. 6551
Contact's Fax Number	(304) 285-6407
Original Submission Date(s)	July 18, 2005, January 19, 2006 & December 15, 2005
Submission Date(s) of Amendment(s) Under Review	April 16, 2007
Reviewer	Hoainhon Nguyen

1 EXECUTIVE SUMMARY

The current amendment contains one nonfasting bioequivalence (BE) study comparing the test product, Balsalazide Disodium Capsules, 750 mg (Mylan Pharmaceuticals), to the reference listed drug (RLD), Colazal[®] Capsules, 750 mg (Salix Pharmaceuticals).

The nonfasting BE study is **acceptable**. The study results are summarized below:

Nonfasting Bioequivalence Study - Balsalazide (N=60)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (ng.hr/mL)	800.2	841.1	0.95	89.84 – 100.7
AUC _∞ (ng.hr/mL)	853.8	898.0	0.95	89.86 – 100.6
C _{max} (ng/mL)	198.8	216.0	0.92	80.63 – 105.0

Nonfasting Bioequivalence Study - Mesalamine (N=60)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (ng.hr/mL)	1353	1215	1.11	100.0 – 123.9
AUC _∞ (ng.hr/mL)	2094	2045	1.02	87.01 – 120.5
C _{max} (ng/mL)	64.54	58.51	1.10	99.88 – 121.8

The fasting BE study and dissolution data have previously been found **acceptable** (See v:\firmsam\mylan\77807n0705.doc).

The application is **complete**.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Balsalazide Disodium Capsules, 750 mg
Reference Product	Colazal® Capsules, 750 mg
RLD Manufacturer	Salix Pharmaceuticals
NDA No.	20-610
RLD Approval Date	July 18, 2000
Indication	Balsalazide disodium is an oral prodrug that results in the in vivo formation of mesalamine (5-aminosalicylic acid), and indicated for the treatment of mild to moderately active ulcerative colitis.

3.2 PK/PD Information

Bioavailability	According to the Colazal® label, systemic absorption of intact balsalazide is low and variable, although its absolute bioavailability is unknown. Both balsalazide and mesalamine are measurable in plasma following an oral dose of Colazal®.
Food Effect	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 _{max} and AUC _{last} were lower, while t _{max} was markedly prolonged, under fed (high-fat meal) compared to fasted conditions. Moreover, the data suggest that dosing 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.
T_{max}	Peak plasma concentrations of balsalazide occur from 1 to 2 hours post-dosing, whereas peak plasma concentrations of mesalamine occurs at about 10 hours post-dosing.
Metabolism	Extensive colorectal metabolism (bacterial) of balsalazide; Metabolites: Mesalamine (5-aminosalicylic acid; 5-ASA) = active 4-aminobenzoyl-beta-alanine (4-ABA) = inactive 5-acetylaminosalicylic acid (Ac-5-ASA) = activity uncertain
Excretion	Renal: <1% of parent, ≤ 25% as metabolites Fecal: <1% of parent; > 65% excreted as metabolites
Half-life	Balsalazide: cannot be determined, large intersubject variability Mesalamine: ~1 hour

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed
---------------------------------------	--------------------

1.	Type of study:	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	750 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	Type of study:	Fed ¹
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	750 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in appropriate biological fluid):	Parent drug, balsalazice, and active metabolite, mesalamine
Bioequivalence based on (90% CI):	Both balsalazide and mesalamine
Waiver request of in-vivo testing (appropriate strengths):	None
Source of most recent recommendations:	Review and review addendum of the current ANDA 77-807 (v:\firmsam\mylan\ltrs&rev\77807n0705.doc, and DFS, respectively)
Summary of OGD or DBE History	The firm has previously submitted the fasting study and dissolution data for the test product. The fasting study and dissolution data are acceptable . See the review v:\firmsam\mylan\ltrs&rev\77807n0705.doc.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	

¹ The labeling for the reference listed drug (RLD), Colazal[®] (balsalazide disodium) capsules, 750 mg has *recently* 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.

BCS Waivers	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Balsalazide (BALS) Bioanalytical Method Validation Report
Analyte	Balsalazide (BALS)
Internal Standard (IS)	(b) (4)
Method Description	Protein Precipitation and On-line Extraction; Positive Ion ESI LC/MS/MS
Limit of Quantitation (ng/mL)	6.0
Average Recovery of Drug (%)	60.30 ^[a]
Average Recovery of IS (%)	84.55 ^[d]
Standard Curve Concentrations (ng/mL)	6.0, 12, 18, 30, 60, 120, 240, 360, 480 and 600
QC Concentrations (ng/mL)	6.0, 18, 60 and 400
QC Intra-batch Precision Range (%)	1.46% to 5.60%
QC Intra-batch Accuracy Range (%)	-5.32% to 9.48%
QC Inter-batch Precision Range (%)	1.97% to 4.44%
QC Inter-batch Accuracy Range (%)	-3.97% to 7.72%
Bench-Top Stability (hrs)	20 hours @ room temperature ^[d]
Stock Stability (days)	BALS SS 28 days @ 4°C ^[b] BALS WS 28 days @ 4°C ^[b] (b) (4) SS 28 days @ 4°C ^[d] WS 8 days @ 4°C ^[d]
Processed Stability (hrs)	123.5 hours @ room temperature ^[d]
Freeze-Thaw Stability (cycles)	5 cycles ^[c]
Long-Term Storage Stability (days)	141 days @ -70°C ^[c]
Dilution Integrity	Concentration diluted 2-fold
Selectivity	No interfering peaks noted in blank plasma samples

[a] Generated in BALS VALI ADD1

[b] Generated in BALS VALI

[c] Generated in BALS VALI ADD2

[d] Generated in BALS VALI ADD3

Information Requested	Data
Bioanalytical method validation report location	Mesalamine (MESA) Bioanalytical Method Validation Report, Volume X, Pages XX-XX
Analyte	Mesalamine (MESA)
Internal Standard (IS)	(b) (4)
Method Description	Derivatization with solid phase extraction, Reversed-phase HPLC with Fluorescence detection
Limit of Quantitation (ng/mL)	5 ^[c]
Average Recovery of Drug (%)	Low Control: 67.20% ^[a] Mid Control: 71.43% ^[a] High Control: 73.33% ^[a]
Average Recovery of IS (%)	55.50% ^[a]
Standard Curve Concentrations (ng/mL)	5, 10, 15, 25, 40, 80, 160, 240, 400, and 500 ^[c]
QC Concentrations (ng/mL)	15, 40, and 300 ^[c]
QC Intra-batch Precision Range (%)	1.45% to 7.63% ^[c]
QC Intra-batch Accuracy Range (%)	-2.87% to 6.74% ^[c]
QC Inter-batch Precision Range (%)	1.70% to 6.69% ^[c]
QC Inter-batch Accuracy Range (%)	-1.80 to 2.48% ^[c]
Bench-Top Stability (hrs)	21.5 hours @ room temperature ^[c]
Stock Stability (days)	MESA SS 28 days @ 4°C ^[a] MESA WS 28 days @ 4°C ^[a] (b) (4) SS 20 days @ 4°C ^[a] WS 20 days @ 4°C ^[a] SS 20 days @ 4°C ^[a]
Processed Stability (hrs)	117 hours @ room temperature ^[a]
Freeze-Thaw Stability (cycles)	3 cycles ^[a]
Long-Term Storage Stability (days)	382 days @ -70°C ^[b]
Dilution Integrity	Concentration diluted 2-fold
Selectivity	No interfering peaks noted in blank plasma samples

^[a] Generated during MESA-VALI

^[b] Generated during MESA-VALI-ADD1

^[c] Generated during MESA-VALI-ADD2

Comment: The data from the summary tables above were verified against data given in the analytical method validation reports. The pre-study validation data are acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs), Mean (Range)	Mean Parameters (\pm SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC _{0-t} (ng/mL·hr)	AUC _{∞} (ng/mL·hr)	$T_{1/2}$ (hr)	K_{el} (hr ⁻¹)	
BALS-06128	Single-Dose Fed Bioequivalence Study of Balsalazide disodium Capsules (750 mg; Mylan) and Colazal [®] Capsules (750 mg; Salix) in Healthy Volunteers	Open-label, Single-dose, Randomized, Two-period, Two-treatment Crossover	A=Balsalazide Disodium 750 mg Capsule 3 x 750 mg oral route, Lot# R1M0787	60 Dosed 60 Completed (M: 48; F: 12) Healthy Subjects Mean Age: 25.8 (Range: 18 to 59)	Balsalazide						Bio Amendment Volume 1, Attachment E
			243.8 \pm 200.3		1.125 (0.3-5)	872.7 \pm 384.4	930.1 \pm 381.1	2.245 \pm 0.738	0.3365 \pm 0.0947		
			B = Colazal [®] 750 mg Capsule 3 x 750 mg oral route, Lot# 318996		276.9 \pm 241.2	1.000 (0.3-5)	939.0 \pm 492.4	989.2 \pm 484.8	2.332 \pm 0.756	0.3254 \pm 0.0962	
			Mesalamine								
			A=Balsalazide Disodium 750 mg Capsule 3 x 750 mg oral route, Lot# R1M0787		78.56 \pm 48.67	28.00 (8-72)	1750 \pm 1149	2550 \pm 1518	17.64 \pm 11.43	0.0643 \pm 0.0610	
			B = Colazal [®] 750 mg Capsule 3 x 750 mg oral route, Lot# 318996		69.38 \pm 38.73	28.00 (5-60)	1626 \pm 1096	2439 \pm 1129	13.90 \pm 7.122	0.0628 \pm 0.0291	

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

Nonfasting Bioequivalence Study – Rabeprazole (N=60)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t} (ng.hr/mL)	800.2	841.1	0.95	89.84 – 100.7
AUC_∞ (ng.hr/mL)	853.8	898.0	0.95	89.86 – 100.6
C_{max} (ng/mL)	198.8	216.0	0.92	80.63 – 105.0

Nonfasting Bioequivalence Study – Mesolaminc (N=60)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t} (ng.hr/mL)	1353	1215	1.11	100.0 – 123.9
AUC_∞ (ng.hr/mL)	2094	2045	1.02	87.01 – 120.5
C_{max} (ng/mL)	64.54	58.51	1.10	99.88 – 121.8

Table 3. Reanalysis of Study Samples

BALS-06128 – Fed Study								
Repeat Analysis Results for balsalazide								
Additional Information in Section 5.3.1.4.1								
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	0.0	0.0	0.0%	0.0%	0.0	0.0	0.0%	0.0%
Reason A ¹	9	14	0.38%	0.58%	9	14	0.38%	0.58%
Reason B ¹	1	2	0.04%	0.08%	1	2	0.04%	0.08%
Total	10	16	0.42%	0.67%	10	16	0.42%	0.67%

¹Reason A = Sample Outside Limits of Curve Range (ALQ)

Reason B = Abnormal Internal Standard (IS) Response

BALS-06128 – Fed Study								
Repeat Analysis Results for mesalamine								
Additional Information in Section 5.3.1.4.1								
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	0.0	0.0	0.0%	0.0%	0.0	0.0	0.0%	0.0%
Reason A ¹	1	0	0.04%	0.0%	1	0	0.04%	0.0%
Reason B ¹	1	0	0.04%	0.0%	1	0	0.04%	0.0%
Total	2	0	0.08%	0.0%	2	0	0.8%	0.0%

¹Reason A = Sample Lost During Assay Procedure

Reason B = Poor Chromatography

Comments from the Reviewer: The nonfasting studies is acceptable.

ANDA 77-807
Single-Dose Nonfasting Bioequivalence Study Review
Study Number BALS-06128

3.7 Formulation

Location in appendix	See the review of the original submission, v:\firmsam\mylan\ltrs&rev\77807n0705.doc
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	Acceptable
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	See the review of the original submission, v:\firmsam\mylan\ltrs&rev\77807n0705.doc
Source of Method (USP, FDA or Firm)	FDA
Medium	Potassium Phosphate Buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50
DBE-recommended specifications	NLT ^(b) ₍₄₎ % (Q) in 30 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Fast dissolving
Is method acceptable?	Acceptable
If not then why?	

Firm acknowledged the FDA-recommended dissolution method and specification in the January 19, 2006 amendment.

3.9 Waiver Request(s)

Strengths for which waivers are requested	None
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	

3.10 Comments

None

3.11 Recommendations

1. The single-dose nonfasting bioequivalence study conducted by Mylan Pharmaceuticals on its Balsalazide Disodium Capsules, 750 mg, lot # R1M0787, comparing it to Colazal[®] Capsules (Salix Pharmaceuticals), 750 mg, lot #318996, is **acceptable**.

The fasting BE study and dissolution data have previously been found **acceptable** (See v:\firmsam\mylan\77807n0705.doc).

The application is **complete**.

3.12 Comments for Other OGD Disciplines

None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Nonfasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	BALS-06128
Study Title	Single-Dose Fed Bioequivalence Study of Balsalazide disodium Capsules (750 mg; Mylan) and Colazal [®] Capsules (750 mg; Salix) in Healthy Volunteers
Clinical Site (Name & Address)	PRACS Institute, Ltd. 625 DeMers Avenue East Grand Forks, MN 56721 218-773-5560
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period 1: 27-Jan-2007 Period 2: 03-Feb-2007
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Road Morgantown, WV 26505 304-599-5430
Analytical Director	(b) (6) Ph.D.
Analysis Dates	Balsalazide: 09-Feb-2007 – 13-Mar-2007 Mesalamine: 14-Feb-2007 – 13-Mar-2007
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	45 (balsalazide) 45 (mesalamine)

Table 5. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	Balsalazide disodium	Colazal [®]
Manufacturer	Mylan Pharmaceuticals Inc.	Salix Pharmaceuticals, Inc.
Batch/Lot No.	R1M0787	318996
Manufacture Date	03/31/2004*	
Expiration Date		04/2009

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Strength	750 mg	750 mg
Dosage Form	Capsule	Capsule
Bio-Batch Size	(b) (4)	
Potency (Assay)		N/A
Content Uniformity (mean, %CV)	99.8%	
Dose Administered	99.9% (2.4%)	99.9% (2.8%)
Route of Administration	3 x 750 mg	3 x 750 mg

*NOTE: The expiration date for the test product has not been determined. The above up-to-date potency assay and content uniformity data were obtained on January 15, 2007 just prior to the start of the nonfasting study. In addition, the firm has also submitted dissolution data conducted on the same date to show that the test product still met the FDA-recommended specification of NLT $\frac{(b)}{(4)}\%Q$ in 30 minutes (Submission dated April 16, 2007, Bioequivalence Amendment, Attachment C, pages 10 and 12).

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

Number of Subjects	60 participated; 60 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 3, 4, 5, 9, 11, 12, 13, 15, 17, 19, 21, 24, 25, 27, 29, 32, 33, 35, 37, 39, 42, 43, 45, 46, 51, 52, 53, 55, 56, 59 BA: remaining subjects
Blood Sampling Times	Balsalazide: Predose, 0.167, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12, 16 and 24 hours postdose. Mesalamine: Predose, 2.0, 5.0, 8.0, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 36, 42, 48, 60 and 72 hours postdose.
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	Blood samples were collected in Vacutainer® containing K ₃ -EDTA, centrifuged at 3000 rpm for 10 minutes at 4°C, harvested for plasma which was stored at -70°C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	10 hours predose
Length of Confinement	10 hours predose until 48 hours postdose
Safety Monitoring	Vital signs were evaluated prior to each dose administration, at 2, 24 and 48 hours postdose.
Standard FDA Meal Used?	Yes

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

MYLAN FED BIOEQUIVALENCE STUDY BALS-06128			
		TREATMENT GROUPS	
		Test Product N=60¹	Reference Product N=60¹
Age (years)	Mean ± SD	25.80 ± 8.79	25.80 ± 8.79
	Range	18 - 59	18 - 59
Age Groups	< 18	-	-
	18 - 39	54 (90.00%)	54 (90.00%)
	40 - 64	6 (10.00%)	6 (10.00%)
	65 - 75	-	-
	> 75	-	-
Sex	Male	48 (80.00%)	48 (80.00%)
	Female	12 (20.00%)	12 (20.00%)
Hispanic or Latino Race	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	1 (1.67%)	1 (1.67%)
Not Hispanic or Latino Race	N	-	-
	A	-	-
	B	1 (1.67%)	1 (1.67%)
	I	-	-
	W	57 (95.00%)	57 (95.00%)
	WA	1 (1.67%)	1 (1.67%)
BMI	Mean ± SD	25.06 ± 2.82	25.06 ± 2.82
	Range	19.1 - 29.8	19.1 - 29.8
Other Factors		n/a	n/a

¹Subjects completing clinical study

RACE:	
American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W
White and Asian	WA

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
None	N/A	N/A	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event ¹	Reported Incidence by Treatment Groups	
	Mylan Fed Bioequivalence Study BALS-06128	
	Test N=60 ²	Reference N=60 ²
	n (%) ³	n (%) ³
Gastrointestinal disorders		
Hypoaesthesia oral	-	1 (1.67%)
Toothache	-	1 (1.67%)
General disorders and administration site conditions		
Vessel puncture site reaction	-	1 (1.67%)
Nervous system disorders		
Dizziness	2 (3.33%)	-
Headache	-	2 (3.33%)
Syncope	1 (1.67%)	-
Respiratory, thoracic and mediastinal disorders		
Dry throat	1 (1.67%)	-
Nasal congestion	2 (3.33%)	-
Pharyngolaryngeal pain	2 (3.33%)	-
Sinus congestion	1 (1.67%)	-
Vascular disorders		
Epistaxis	-	3 (5.00%)
Total Subjects Reporting at Least One Adverse Event	7 (11.67%)	8 (13.33%)

1 MedDRA Version 8.0

2 N = Number of subjects dosed for each treatment

3 n =Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100% (n/N%))

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Mylan Fed Bioequivalence Study BALS-06128		
Type	Subject #s (Test)	Subject #s (Ref.)
Other – Subjects 27, 32, and 59 reported medication use over the course of the study.	27, 32, 59	N/A
Other – The Period II 24 hour query was not obtained for all subjects	N/A	N/A
Other – Subjects 04, 05, 23, 29, and 50 had temperatures below 96.0 at Period I pre-dose	N/A	N/A
Missed Blood Sample Collections	02, 29, 32, 54	N/A
Blood Sample Collection Time Deviations	02, 06, 09, 12, 13, 16, 18, 19, 29, 32, 37, 42, 45, 52	02, 08, 18, 34, 35, 37, 42, 45, 48, 54

Note: Protocol deviations, with the exception of individual blood sample collection time deviations and vital signs collection time deviations are presented herein.

Comments on Dropouts/Adverse Events/Protocol Deviations: There was no serious adverse effect reported. Sampling time deviations were corrected by using the actual sampling times.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. BALS-06128 Analyte Name Balsalazide										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	6.000	12.00	18.00	30.00	60.00	120.0	240.0	360.0	480.0	600.0
Inter day Precision (%CV)	1.56	3.14	2.79	3.11	2.64	3.15	3.45	2.69	2.12	2.51
Inter day Accuracy (%Actual)	100.45	100.33	99.06	100.27	96.23	98.5	102.17	101.42	103.54	98.05
Linearity	0.9927 – 0.9993									
Linearity Range (ng/mL)	6.000 – 600.0									
Sensitivity/LOQ (ng/mL)	6.000									

Bioequivalence Study No. BALS-06128 Analyte Name Balsalazide			
Parameter	Quality Control Samples		
Concentration (ng/mL)	18.00 ng/mL	60.00 ng/mL	400.0 ng/mL
Inter day Precision (%CV)	4.27	3.98	4.86
Inter day Accuracy (%Actual)	98.67	98.77	102.25

Bioequivalence Study No. BALS-06128 Analyte Name Mesalamine										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	5.000	10.00	15.00	25.00	40.00	80.00	160.0	240.0	400.0	500.0
Inter day Precision (%CV)	0.90	1.99	1.47	1.35	1.30	1.36	1.05	1.30	1.28	1.28
Inter day Accuracy (%Actual)	100.04	99.86	100.60	100.36	98.77	98.8	98.81	100.54	101.40	100.84
Linearity	0.9993 – 0.9999									
Linearity Range (ng/mL)	5.000 – 500.0									
Sensitivity/LOQ (ng/mL)	5.000									

Bioequivalence Study No. BALS-06128			
Analyte Name mesalamine			
Parameter	Quality Control Samples		
Concentration (ng/mL)	15.00 ng/mL	40.00 ng/mL	300.0 ng/mL
Inter day Precision (%CV)	3.63	1.67	1.57
Inter day Accuracy (%Actual)	101.40	99.25	101.53

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	None
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

SOP No.	Effective Date of SOP	SOP Title
D-400-07	10/19/2006	Reassay or Reinjection of Clinical Samples
D-416-05	10/19/2006	Reassay of Whole Subjects

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A. There was no PK repeat.
Does the reviewer agree with the outcome of the repeat assays?	Yes

Summary/Conclusions, Study Assays: Acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Test Treatment

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Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	60	0.000	.	0.000	0.000
Hour0.167	60	11.396	254.845	0.000	191.700
Hour0.33	60	85.643	167.371	0.000	846.200
Hour0.50	60	141.212	121.932	6.039	1167.000
Hour0.75	60	172.756	85.348	10.050	875.700
Hour1	60	185.519	78.004	19.500	824.200
Hour1.25	60	180.616	81.054	37.380	1036.000
Hour1.50	60	154.503	63.702	43.500	693.200
Hour1.75	60	132.335	61.104	46.600	612.800
Hour2	60	130.257	66.575	39.660	695.500
Hour2.50	60	118.425	41.814	46.280	397.700
Hour3	60	112.742	32.342	43.730	264.000
Hour3.50	60	109.060	30.331	52.770	198.300
Hour4	60	107.666	35.011	42.640	180.000
Hour5	60	93.920	41.589	32.690	178.500
Hour6	60	71.708	42.826	23.510	151.100
Hour8	60	35.455	50.362	0.000	78.010
Hour12	60	8.262	106.792	0.000	35.190
Hour16	60	1.469	261.725	0.000	20.090
Hour24	60	0.000	.	0.000	0.000

Reference Treatment

Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	60	0.000	.	0.000	0.000
Hour0.167	60	11.939	130.955	0.000	72.720
Hour0.33	60	133.824	113.969	0.000	598.400
Hour0.50	60	184.029	93.502	0.000	756.600
Hour0.75	60	189.550	82.622	29.450	915.500
Hour1	60	182.630	76.643	54.950	775.300
Hour1.25	60	200.063	106.581	55.880	1350.000
Hour1.50	60	175.629	98.035	56.790	1073.000
Hour1.75	60	153.051	96.015	60.160	1105.000
Hour2	60	140.136	85.658	61.060	937.500
Hour2.50	60	120.894	54.449	61.160	517.100
Hour3	60	115.861	40.745	57.200	326.900
Hour3.50	60	112.548	37.555	46.650	233.700
Hour4	60	108.793	39.103	45.970	228.200
Hour5	60	93.567	46.596	23.610	210.300
Hour6	60	73.730	52.247	12.650	215.400
Hour8	60	40.783	63.127	0.000	151.500
Hour12	60	8.819	108.957	0.000	42.270
Hour16	60	2.046	297.310	0.000	38.230
Hour24	60	0.165	774.597	0.000	9.902

Figure 1

Balsalazide									
Dose=3x750 mg									
Fasting Bioequivalence Study No. BALS-06128									
Parameter	Test				Reference				Mean T/R
	Mean	Coeff of Variation	Minimum	Maximum	Mean	Coeff of Variation	Minimum	Maximum	
AUCT (ng.hr/mL)	868.54	42.50	396.33	2097.70	939.02	52.43	355.82	2933.73	0.98
AUCI (ng.hr/mL)	917.55	39.96	412.38	2115.13	988.41	49.26	445.55	2965.38	0.98
CPEAK (ng/mL)	243.82	82.13	73.21	1167.00	276.94	87.09	71.47	1350.00	1.10
TPEAK (hrs)	1.58	76.27	0.33	5.00	1.39	80.46	0.33	5.00	1.66
THALF (hrs)	2.22	41.15	0.88	5.57	2.28	39.26	1.01	5.65	1.01
KEL (hrs ⁻¹)	0.36	36.83	0.12	0.79	0.35	36.79	0.12	0.69	1.07

Mesalamine									
Dose=3x750 mg									
Fasting Bioequivalence Study No. BALS-06128									
Parameter	Test				Reference				Mean T/R
	Mean	Coeff of Variation	Minimum	Maximum	Mean	Coeff of Variation	Minimum	Maximum	
AUCT (ng.hr/mL)	1743.14	65.39	62.19	5564.23	1625.98	67.40	21.17	4564.77	1.28
AUCI (ng.hr/mL)	2706.87	56.35	876.64	7226.53	2630.22	71.59	504.89	10902.85	1.23
CPEAK (ng/mL)	78.56	61.95	14.26	257.40	69.37	55.83	9.99	177.00	1.23
TPEAK (hrs)	28.50	46.97	8.00	72.00	26.25	45.47	5.00	60.00	1.23
THALF (hrs)	19.41	66.95	2.29	54.31	16.83	73.46	1.36	60.17	1.95
KEL (hrs ⁻¹)	0.06	98.25	0.01	0.30	0.07	115.71	0.01	0.51	1.18

Table 15. Geometric Means and 90% Confidence Intervals Calculated by the Firm

BALSALAZIDE DISODIUM CAPSULES, 750 MG (3 X 750 MG)				
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Balsalazide Fed (BALS-06128)				
balsalazide				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUC _{0-t}	801.8	841.1	0.95	90% – 101%
AUC _∞	864.8	900.3	0.95	90% – 101%
C _{max}	198.8	216.0	0.92	81% – 105%
Balsalazide Fed (BALS-06128)				
mesalamine				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUC _{0-t}	1360	1215	1.12	100% – 124%
AUC _∞	2213	2158	1.05	92% – 121%
C _{max}	64.54	58.51	1.10	100% – 122%

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*Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB]

**Used Natural Log Transformed Parameter

Table 16. Geometric Means and 90% Confidence Intervals Calculated by the Reviewer

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Nonfasting Bioequivalence Study - Balsalazide				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (ng.hr/mL)	800.2	841.1	0.95	89.84 – 100.7
AUC _∞ (ng.hr/mL)	853.8	898.0	0.95	89.86 – 100.6
C _{max} (ng/mL)	198.8	216.0	0.92	80.63 – 105.0

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Nonfasting Bioequivalence Study - Mesalamine				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (ng.hr/mL)	1353	1215	1.11	100.0 – 123.9
AUC _∞ (ng.hr/mL)	2094	2045	1.02	87.01 – 120.5
C _{max} (ng/mL)	64.54	58.51	1.10	99.88 – 121.8

Table 17. Additional Study Information (Balsalazide)

Root mean square error, AUC _{0-t}	0.187741	
Root mean square error, AUC _∞	0.185026	
Root mean square error, C _{max}	0.432610	
	Test	Reference
Ratio of AUC _{0-t} /AUC _∞ - Mean (Range)	0.94 (0.63-0.99)	0.94 (0.73-0.99)
Kel and AUC _∞ determined for how many subjects?	All	All
Do you agree or disagree with firm's decision?	Disagree; however, the study outcome was the same.	Disagree; however, the study outcome was the same.
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?	No	No

Table 18. Additional Study Information (Mesalamine)

Root mean square error, AUC _{0-t}	0.350420	
Root mean square error, AUC _∞	0.356378	
Root mean square error, C _{max}	0.325325	
	Test	Reference
Ratio of AUC _{0-t} /AUC _∞ : Mean (Range)	0.77 (0.37-0.99)*	0.80 (0.36-0.99)*
Kel and AUC _∞ determined for how many subjects?	38	40
Do you agree or disagree with firm's decision?	Disagree; however, the study outcome was the same.	Disagree; however, the study outcome was the same.
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?	No	No

*NOTE: Mesalamine has a long and variable half-life (ranged from 2.29-54.31 hours for Test treatment and 1.36-60.17 hours for Reference treatment) and the sampling time was truncated at 72 hours. The ratio values of AUC_{0-t}/AUC_∞, therefore, are mostly less than 80%. It should be noted that the mean and range of mesalamine half-life were similar to those found in the fasting study of the current ANDA as well as in the fasting study of another ANDA (# (b) (4)).

Comments on Pharmacokinetic and Statistical Analysis:

The study results met the confidence interval acceptance criteria.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The nonfasting study is acceptable.

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Table 19. Balsalamine Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Test Treatment

Time	N	Mean	Control Variation	Minimum	Maximum
Hour0	60	0.000	.	0.000	0.000
Hour0.167	60	11.396	254.845	0.000	191.700
Hour0.33	60	85.643	167.371	0.000	846.200
Hour0.50	60	141.212	121.932	6.039	1167.000
Hour0.75	60	172.756	85.348	10.050	875.700
Hour1	60	185.519	78.004	19.500	824.200
Hour1.25	60	180.616	81.054	37.380	1036.000
Hour1.50	60	154.503	63.702	43.500	693.200
Hour1.75	60	132.335	61.104	46.600	612.800
Hour2	60	130.257	66.575	39.660	695.500
Hour2.50	60	118.425	41.814	46.280	397.700
Hour3	60	112.742	32.342	43.730	264.000
Hour3.50	60	109.060	30.331	52.770	198.300
Hour4	60	107.666	35.011	42.640	180.000
Hour5	60	93.920	41.589	32.690	178.500
Hour6	60	71.708	42.826	23.510	151.100
Hour8	60	35.455	50.362	0.000	78.010
Hour12	60	8.262	106.792	0.000	35.190
Hour16	60	1.469	261.725	0.000	20.090
Hour24	60	0.000	.	0.000	0.000

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Reference Treatment

Time	N	Mean	Coefficient of Variation	Minimum	Maximum
Hour0	60	0.000	.	0.000	0.000
Hour0.167	60	11.939	130.955	0.000	72.720
Hour0.33	60	133.824	113.969	0.000	598.400
Hour0.50	60	184.029	93.502	0.000	756.600
Hour0.75	60	189.550	82.622	29.450	915.500
Hour1	60	182.630	76.643	54.950	775.300
Hour1.25	60	200.063	106.581	55.880	1350.000
Hour1.50	60	175.629	98.035	56.790	1073.000
Hour1.75	60	153.051	96.015	60.160	1105.000
Hour2	60	140.136	85.658	61.060	937.500
Hour2.50	60	120.894	54.449	61.160	517.100
Hour3	60	115.861	40.745	57.200	326.900
Hour3.50	60	112.548	37.555	46.650	233.700
Hour4	60	108.793	39.103	45.970	228.200
Hour5	60	93.567	46.596	23.610	210.300
Hour6	60	73.730	52.247	12.650	215.400
Hour8	60	40.783	63.127	0.000	151.500
Hour12	60	8.819	108.957	0.000	42.270
Hour16	60	2.046	297.310	0.000	38.230
Hour24	60	0.165	774.597	0.000	9.902

Figure 1

**Balsalazide Mean Plasma Concentrations
Single Dose Nonfasting Study**

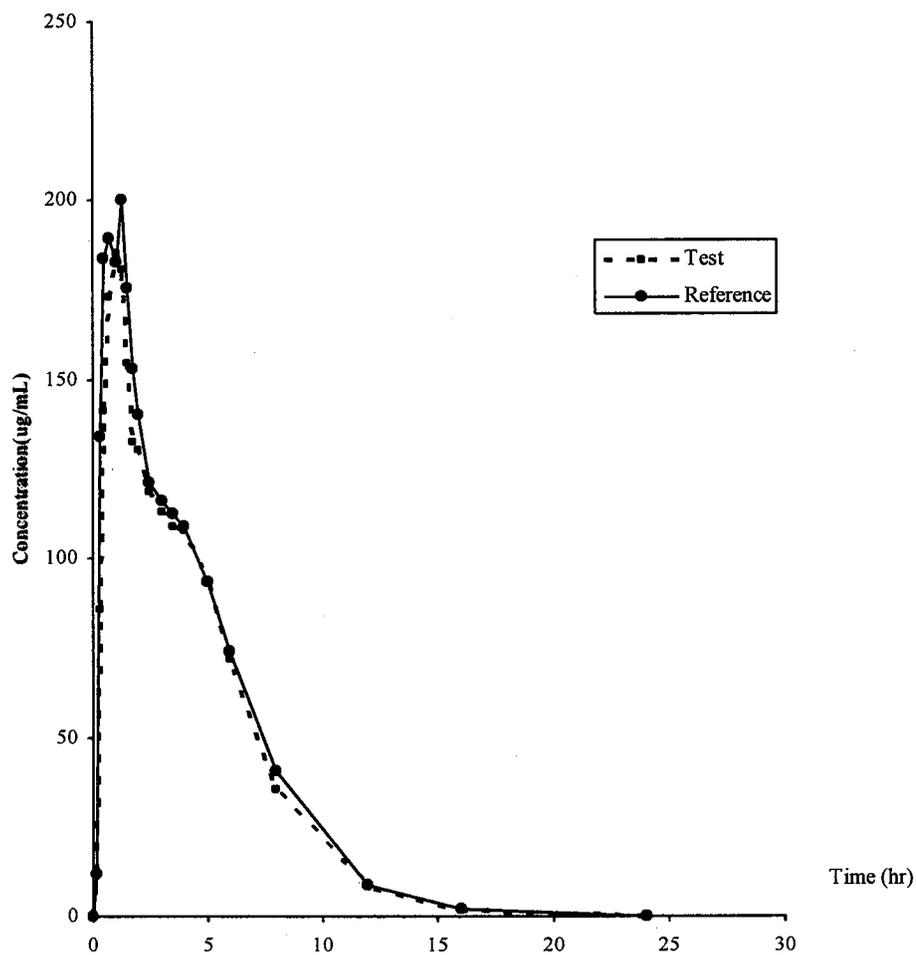


Table 20. Mesalamine Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Test Treatment

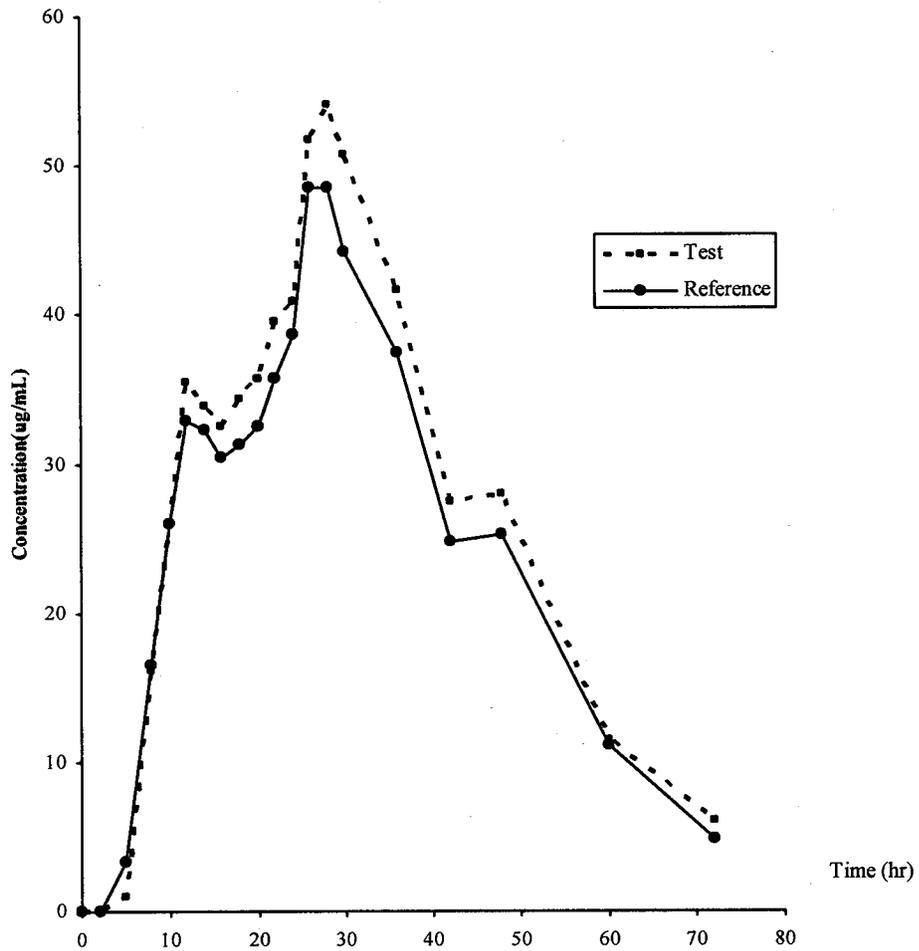
Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	60	0.000	.	0.000	0.000
Hour2	60	0.000	.	0.000	0.000
Hour5	60	1.036	439.536	0.000	25.430
Hour8	60	16.131	212.098	0.000	205.500
Hour10	60	26.012	123.604	0.000	138.800
Hour12	60	35.463	90.466	0.000	145.600
Hour14	60	33.892	104.154	0.000	240.000
Hour16	60	32.479	103.191	0.000	216.700
Hour18	60	34.347	101.862	0.000	226.300
Hour20	60	35.744	102.547	0.000	256.800
Hour22	60	39.546	93.411	0.000	257.400
Hour24	60	40.907	75.495	0.000	181.200
Hour26	60	51.711	72.021	0.000	222.900
Hour28	60	54.036	71.360	0.000	203.200
Hour30	60	50.718	67.891	0.000	153.600
Hour36	60	41.633	90.698	0.000	175.800
Hour42	60	27.444	99.867	0.000	137.900
Hour48	60	27.986	92.883	0.000	109.100
Hour60	60	11.450	184.262	0.000	103.800
Hour72	60	6.078	209.021	0.000	51.850

Reference Treatment

Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	60	0.000	.	0.000	0.000
Hour2	60	0.000	.	0.000	0.000
Hour5	60	3.348	603.993	0.000	156.100
Hour8	60	16.499	219.429	0.000	177.000
Hour10	60	26.044	115.293	0.000	126.600
Hour12	60	32.840	95.423	0.000	132.900
Hour14	60	32.218	92.046	0.000	143.100
Hour16	60	30.432	98.695	0.000	137.400
Hour18	60	31.310	89.404	0.000	127.100
Hour20	60	32.561	82.016	0.000	121.800
Hour22	60	35.719	76.608	0.000	132.400
Hour24	60	38.643	71.181	0.000	131.500
Hour26	60	48.595	60.420	0.000	143.900
Hour28	60	48.542	64.987	0.000	135.000
Hour30	60	44.274	69.788	0.000	128.600
Hour36	60	37.450	79.079	0.000	105.900
Hour42	60	24.740	93.890	0.000	88.290
Hour48	60	25.302	92.950	0.000	101.100
Hour60	60	11.043	175.923	0.000	82.350
Hour72	60	4.851	259.627	0.000	76.680

Figure 2

Mesalamine Mean Plasma Concentrations
Single Dose Nonfasting Study



5

Following this page, 26 pages withheld in full (b)(4)- SAS Output

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-807

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Balsalazide Disodium Capsules, 750 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you have conducted the dissolution testing using the following FDA-recommended dissolution method and specification:

The dissolution testing should be conducted in 900 mL of pH 6.8 phosphate buffer at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ using USP Apparatus II @ 50 rpm.

The test product should meet the following specification:

NLT ^(b)₍₄₎ % (Q) of the labeled amount of the drug 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

ANDA: 77-807

1.	Fed Study	Strength:	750 mg
	(STP)	Outcome:	AC
	Submission Date(s)	April 16, 2007	
	Clinical Site:	PRACS Institute, Ltd. East Grand Forks, MN	
	Analytical Site:	Mylan Pharmaceuticals Inc. Bioanalytical Department Morgantown, WV	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit
--	--

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

/s/

Hoainhon T. Nguyen
5/1/2007 03:12:33 PM
BIOPHARMACEUTICS

Moheb H. Makary
5/2/2007 06:42:57 AM
BIOPHARMACEUTICS

Barbara Davit
5/2/2007 09:49:35 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-807

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 18, 2005

ORIGINAL ABBREVIATED NEW DRUG APPLICATION (ELECTRONIC DATA AND BIOEQUIVALENCE DATA ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

77-807
N-000

Handwritten signatures and dates:
5/25/05
13 Sept 2005

RE: BALSALAZIDE DISODIUM CAPSULES, 750MG

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.92 and §314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None

Established Name: Balsalazide Disodium Capsules

Reference Listed Drug: Colazal® Capsules, NDA 20-610

This application consists of a total of 30 volumes.

Archival Copy - 14 volumes.

Review Copy - 14 volumes.

Technical Section For Chemistry - 2 volumes.

Technical Section For Pharmacokinetics - 12 volumes.

Analytical Methods - 2 extra copies; 1 volume each.

CD-Rom – eCover Letter, e356h, eTOC, eLabeling Components, Bioequivalence Summary
Tables and data listings for the bioequivalence studies conducted in support of
this application.

This application provides for the manufacture of Balsalazide Disodium Capsules, 750mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

RECEIVED

JUL 18 2005

OGD / CDER

G:\Project\ANDA\Balsalazide Disodium Caps\SECTIONS-01THRU07.doc

Department—Fax Numbers

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Business Development (304) 598-5419
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Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
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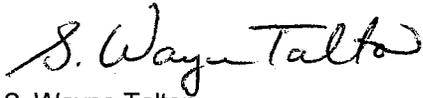
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Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

Gary J. Buehler
Page 2 of 2

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,



S. Wayne Talton
Vice President
Regulatory Affairs

SWT/nk

ANDA 77-807

SEP 14 2005

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Balsalazide Disodium Capsules, 750 mg

DATE OF APPLICATION: July 18, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 18, 2005

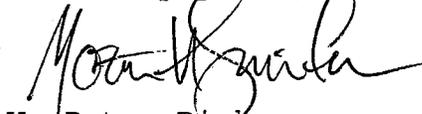
We will correspond with you further after we have had the opportunity to review the application.

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
301-827-5848

Sincerely yours,



Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-807

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/
HFD-143/OIM/DRM

Endorsement:

HFD-615/M.Shimer, Chief, RSB

HFD-615/S.Shepperson, CSO

Moran
9-13-2005

date

MSep 2005

date

Word File v:\CDSNAS\OGDS11\FIRMSAM\MYLAN\LTRS&REV\77807.ACK.DOC

F/T ss 9-13-05

ANDA Acknowledgment Letter!



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 19, 2006

MINOR AMENDMENT (CMC INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A

RE: BALSALAZIDE DISODIUM CAPSULES, 750MG
ANDA 77-807
RESPONSE TO AGENCY CORRESPONDENCES DATED DECEMBER 22, 2005
AND JANUARY 10, 2006

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the CMC comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated December 22, 2005 (provided in Attachment F). Reference is also made to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated January 10, 2006 (provided in Attachment G).

In response to the Agency's comments of December 22nd, Mylan wishes to amend this application as follows.

A. The deficiencies presented below represent MINOR deficiencies.

FDA COMMENT 1:

(b) (4)

MYLAN RESPONSE:

(b) (4)

FDA COMMENT 2:

(b) (4)

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Following this page, 2 pages withheld in full-(b)(4)

JAN 20 2006

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OGD / CDER

Please note that the following dissolution method and specification recommended by the Division of Bioequivalence have been incorporated into Mylan's stability and quality control programs.

Apparatus:	2 (paddle) with sinkers
Speed:	50 rpm
Volume:	900 mL
Medium:	Potassium Phosphate Buffer, pH 6.8
Temperature:	37°C
Sampling Times:	5, 10, 15, 20, 30, 45, 60 and 80 minutes
Limits:	NLT ^(b) / ₍₄₎ (Q) in 30 minutes

The following are provided: (1) revised finished product specifications in Attachment B; (2) revised dissolution procedure (FP-BALSAL-DS-M) and corresponding method validation in Attachment E; and (3) eighteen (18) months of updated room temperature stability data as well as dissolution data on retain samples from our three month accelerated stability program in Attachment D. Please note that the stability data tables have been updated to reflect the Agency's recommended dissolution specification so that the 24 month room temperature stability samples will be tested and reported in accordance with the revised dissolution specification.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

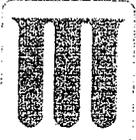


S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Yoon Kong, Project Manager
Division of Chemistry II, Team 7



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 19, 2006

ORIGINAL
N/A/B

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT (CMC INFORMATION ENCLOSED)

RE: BALSALAZIDE DISODIUM CAPSULES, 750MG
ANDA 77-807
RESPONSE TO AGENCY CORRESPONDENCE DATED JANUARY 10, 2006

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated January 10, 2006 (refer to Attachment D). In response to the January 10th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

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.

FDA COMMENT 1: We acknowledge that the dissolution testing is conducted using the following FDA-recommended method:

Apparatus: 2 (paddle) with sinkers
Speed: 50 rpm
Volume: 900 mL
Medium: Potassium Phosphate Buffer, pH 6.8
Temperature: 37°C
Sampling Times: 5, 10, 15, 20, 30, 45, 60 and 80 minutes

We recommend that the test product should meet the following specification:

Not less than ^(b)₍₄₎ % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

With your acceptance to the above deficiency, please indicate if you accept the above dissolution specification.

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JAN 20 2006

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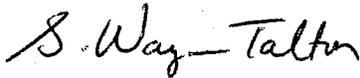
MYLAN RESPONSE: As requested, Mylan acknowledges our acceptance of the following dissolution method and specification for incorporation into our stability and quality control programs:

Apparatus:	2 (paddle) with sinkers
Speed:	50 rpm
Volume:	900 mL
Medium:	Potassium Phosphate Buffer, pH 6.8
Temperature:	37°C
Sampling Times:	5, 10, 15, 20, 30, 45, 60 and 80 minutes
Limits:	NLT ^(b) (4) % (Q) in 30 minutes

Revised finished product specifications, dissolution procedure (FP-BALSAL-DS-M) and Post-Approval Stability Protocols are provided in Attachments A, B and C, respectively. Please note that a Minor Chemistry Amendment is also being submitted concurrently with this Bioequivalence Amendment under separate cover.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,



S. Wayne Talton
Vice President
Regulatory Affairs

Desk Copy: Beth Fabian-Fritsch, Project Manager
Division of Bioequivalence



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 6, 2006

TELEPHONE AMENDMENT (CMC INFORMATION ENCLOSED)

N/AM

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: BALSALAZIDE DISODIUM CAPSULES, 750MG
ANDA 77-807
RESPONSE TO AGENCY TELEPHONE CALL RECEIVED MARCH 27, 2006

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the chemistry comments pertaining to this application which were provided to Mylan in a telephone call received on March 27, 2006 from Ms. Shahnaz Read, of your Office. In response to the Agency's comments of March 27th, Mylan wishes to amend our application as follows:

FDA COMMENT 1:

(b) (4)

MYLAN RESPONSE:

FDA COMMENT 2:

MYLAN RESPONSE:

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APR 07 2006

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(304) 285-6411

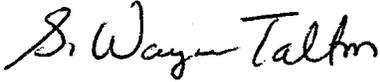
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(304) 598-3232

Gary J. Buehler
Page 2 of 2

This amendment is submitted in duplicate. Should you require additional information, please contact the undersigned at (304) 599-2595, ext. 6551 via facsimile at (304) 285-6407.

Sincerely,

A handwritten signature in cursive script that reads "S. Wayne Talton".

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Ms. Shahnaz Read, Review Chemist
Division of Chemistry II

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 9, 2006

LABELING AMENDMENT (ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NAR

RE: BALSALAZIDE DISODIUM CAPSULES, 750 mg
ANDA 77-807
(RESPONSE TO THE AGENCY CORRESPONDENCE DATED MAY 25, 2006)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the labeling comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated May 25, 2006. A copy of the Agency's May 25th correspondence is provided on the enclosed CD-Rom as Letter.pdf.

In response to the Agency's May 25th correspondence, we wish to amend this application with final printed labeling which has been revised as follows:

CONTAINER:

FDA COMMENT 1.a: Please ensure your labels comply with the bar code requirements prior to full approval.

MYLAN RESPONSE: The enclosed final printed container labels contain the standard bar code requirements per CFR§201.25 and are in compliance with the Final Rule published in the Federal Register on February 26, 2004 (Volume 69, Number 38).

FDA COMMENT 1.b: Please revise "Each tablet contains..." to "Each capsule contains..." ✓

MYLAN RESPONSE: Mylan's left panel on each container label has been revised to read 'Each capsule contains...'

INSERT:

FDA COMMENT 2.a: DESCRIPTION, Inactive Ingredients: Add "gelatin". ✓

MYLAN RESPONSE: Mylan's revised final printed outsert contains 'gelatin' in the list of inactive ingredients in the 'DESCRIPTION' section.

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JUN 12 2006
OGD / CDER

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Information Systems (304) 285-6404
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Maintenance & Engineering (304) 598-5408
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(304) 285-6411

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Gary J. Buehler

Page 2 of 2

FDA COMMENT 2.b: OVERDOSAGE: Second paragraph, first sentence, revise “duse” to “use”.

MYLAN RESPONSE: Mylan’s revised final printed outsert contains the corrected word ‘use’ in the second paragraph of the ‘OVERDOSAGE’ section.

FDA COMMENT 2.c: HOW SUPPLIED: Please add your storage conditions (temperature storage).

MYLAN RESPONSE: Mylan’s revised final printed outsert contains Mylan’s current standard storage statement in the ‘HOW SUPPLIED’ section.

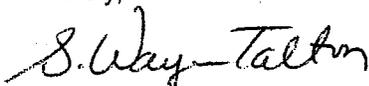
In accordance with the Agency’s *Guidances Providing Regulatory Submissions in Electronic Format – ANDAs and Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Balsalazide Disodium Capsules, as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word versions of all proposed labeling components. To access these Word files, bookmarks are provided within the pdf versions.

Should a Structured Product Labeling (SPL) version of the Reference Listed Drug’s labeling become available post approval, Mylan commits to submit a SPL version of our generic product labeling in a Changes Being Effected Supplement, the next Annual report, or in a Post-Marketing Special Report as applicable.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA’s website for any approved labeling changes.

Should you have any questions regarding this supplement, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,



S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dmy

Enclosure

Desk Copy Ms. Ann Vu, Labeling Reviewer
Division of Labeling and Program Support

BIOEQUIVALENCY AMENDMENT

ANDA 77-807

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: Mylan Pharmaceuticals Inc.

TEL: 304-599-2595 x 6551

ATTN: S. Wayne Talton

FAX: 304-285-6407

FROM: Aaron Sigler

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on July 18, 2005, 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 1 page. 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.

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-807

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Balsalazide Disodium Capsules, 750mg

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

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
11/20/2006 03:52:38 PM
Signing for Dale P Conner

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 16, 2007

ORIG AMENDMENT
N/A

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT (CHEMISTRY INFORMATION ENCLOSED)

RE: BALSALAZIDE DISODIUM CAPSULES, 750MG
ANDA 77-807
RESPONSE TO AGENCY CORRESPONDENCE DATED NOVEMBER 20, 2006

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated November 20, 2006 (refer to Attachment A). In response to the November 20th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

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

FDA COMMENT 1:

The labeling for the reference listed drug (RLD), Colazal® (balsalazide disodium) capsules, 750mg 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 C_{max} of both balsalazide and mesalamine should fall within the range of 0.8 to 1.25.

RECEIVED

APR 17 2007

OGD / CDER

Department—Fax Numbers
Accounting (304) 285-4003
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406

(304) 285-4003
(304) 599-7284
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(304) 598-5411
(304) 598-5445
(304) 285-6411

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Quality Control
Regulatory Affairs
Research & Development
Sales & Marketing

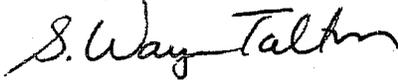
(304) 598-5401
(304) 598-5407
(304) 598-5409
(304) 285-6407
(304) 285-6419
(304) 598-3232

MYLAN RESPONSE: As requested by the Agency, Mylan has conducted a Single-Dose Fed Bioequivalence Study comparing Balsalazide Disodium Capsules (750 mg; Mylan) to the reference listed drug, Colazal® Capsules (750 mg; Salix) in Healthy Volunteers. The bioequivalence study report (BALS-06128) is provided in Attachment E. Bioequivalence Summary Tables in support of study BALS-06128 are provided in Attachment D for the reviewer's reference.

With respect to the chemistry portion of this application, Certificates of Analysis and dissolution profiles for Balsalazide Disodium Capsules, 750mg, Lot R1M0787 and for Colazal® Capsules, 750mg, Lot 318996, the test and reference products used in the fed bioequivalence study, are provided in Attachment B. Please note that these data were generated just prior to the start of the bioequivalence study. Mylan would also like to take this opportunity to provide twenty four (24) months of cumulative room temperature stability data for Balsalazide Disodium Capsules, 750mg, Lot R1M0787 to support the stability of the exhibit batch (refer to Attachment C).

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,



S. Wayne Talton
Vice President
Regulatory Affairs

Desk Copy: Aaron Sigler, Project Manager
Division of Bioequivalence

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

UAF
Exclusivity
amendment
Ad
4/24/07

April 18, 2007

LABELING AND PATENT AMENDMENT (PATENT AND ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NAF
NXP

RE: BALSALAZIDE DISODIUM CAPSULES, 750 MG
ANDA 77-807
(Labeling Revisions In Accordance with the CDER Internet Posting
Dated December 20, 2006)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which is currently under review. Mylan wishes to amend our ANDA with draft labeling in PLR format (Outsert code BALZ:RX1; Revised April 2007) that has been revised in accordance with the CDER Internet Posting dated December 20, 2006 which contained approved labeling revisions for the Reference Listed Drug, Colazal® (Salix Pharmaceuticals). A copy of the Reference Listed Drug labeling from the December 20, 2006 posting is provided herein as RLD.pdf for the reviewer's reference. Please note that Mylan's container labels remain the same as those previously submitted on October 16, 2006.

A Patent Amendment is provided in Attachment A which addresses exclusivity listings (New Patient Population and associated Pediatric exclusivity) which have been listed in the FDA's "Orange Book" subsequent to our previous submissions. Refer to Attachment A.pdf on the enclosed CD-Rom for details.

In accordance with the Agency's Guidance *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Balsalazide Disodium Capsules as described in the electronic Table of Contents. As a review aid, Mylan has also included a Microsoft Word version of our proposed labeling component. To access this Word file, a bookmark is provided within the pdf version.

Mylan intends to submit a Structured Product Labeling (SPL) version of our generic product labeling in an amendment to this application at the time we submit Final Printed Labeling.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval consistent with the Best Pharmaceuticals for Children Act. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

RECEIVED
APR 19 2007
OGD / CDER

Department—Fax Numbers

Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
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Medical Unit
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(304) 598-5411
(304) 598-5445
(304) 285-6411

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Quality Control
Regulatory Affairs
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Sales & Marketing

(304) 598-5401

(304) 598-5407
(304) 598-5409
(304) 285-6407
(304) 285-6419
(304) 598-3232

Project\ANDA\Balsalazide Disodium Caps\Labeling Amendment - Patent Amendment - Internet post, Dated 12-20-2006 (BALZ-RX1).doc

Gary J. Buehler

Page 2 of 2

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

A handwritten signature in black ink that reads "S. Wayne Talton". The signature is written in a cursive, flowing style.

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dmy

Enclosure

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

ORIG AMENDMENT
N/AE

September 14, 2007

LABELING AMENDMENT (ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: BALSALAZIDE DISODIUM CAPSULES, 750 MG
ANDA 77-807
RESPONSE TO AGENCY CORRESPONDENCE RECEIVED SEPTEMBER 13, 2007

Dear Mr. Buehler:

Mylan wishes to amend the above referenced Abbreviated New Drug Application (ANDA) to provide final printed labeling (Outsert code BALZ:R3; Revised September 2007) that has been revised in accordance with the labeling template provided in the Agency's email correspondence dated September 13, 2007. A copy of the Agency's correspondence dated September 13th is provided herein as Letter1.pdf for the reviewer's reference. All changes to our proposed labeling are fully described in the side-by-side comparison provided herein as Comp.pdf. Please note that Mylan's proposed final printed labeling (BALZ:R3, Revised September 2007) has been compared to our previously submitted draft outsert (BALZ:RX1, Revised April 2007) since this version was submitted in the PLR format. Also note that Mylan's final printed container labels remain the same as those previously submitted in our Labeling Amendment dated June 9, 2006. For the convenience of the reviewer, copies of the final printed container labels are included on the enclosed CD-Rom.

In accordance with the Agency's Guidance *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Balsalazide Disodium Capsules as described in the electronic Table of Contents. As a review aid, Mylan has also included a Microsoft Word version of our proposed outsert. To access this Word file, a bookmark is provided within the pdf version.

Mylan commits to submit a SPL version of our generic product labeling post approval in the first Annual Report, as a Special Post-Marketing Report or upon Agency request.

RECEIVED

SEP 17 2007

OGD

Department—Fax Numbers	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	Legal Services	(304) 598-5408	Quality Assurance	(304) 598-5407
Administration	Maintenance & Engineering	(304) 598-5411	Quality Control	(304) 598-5409
Business Development	Medical Unit	(304) 598-5445	Regulatory Affairs	(304) 285-6407
Corporate Services	Product Development	(304) 285-6411	Research & Development	(304) 285-6419
Human Resources			Sales & Marketing	(304) 598-3232

Gary J. Buehler

Page 2 of 2

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,



S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dmy

Enclosure

Desk Copy: Ann Vu, Labeling Reviewer
Division of Labeling and Program Support

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

November 9, 2007

LABELING AMENDMENT (ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED

NOV 13 2007

OGD

ORIGINAL AMENDMENT

N/A

RE: BALSALAZIDE DISODIUM CAPSULES, 750 MG
ANDA 77-807
RESPONSE TO AGENCY CORRESPONDENCES RECEIVED
NOVEMBER 7 and 8, 2007

Dear Mr. Buehler:

Mylan wishes to amend the above referenced Abbreviated New Drug Application (ANDA) to provide final printed labeling (Outsert code BALZ:R5; Revised November 2007) that has been revised in response to Agency e-mail correspondences dated November 7 and 8, 2007 which are provided on the enclosed CD-Rom as Letter 1.pdf and Letter 2.pdf, respectively, for the reviewer's reference. The Agency's correspondence dated November 7th contained labeling revisions approved for the Reference Listed Drug on November 2, 2007. All changes to our proposed labeling including Mylan's calculation of sodium content are fully described in the side-by-side comparison provided herein as Comp.pdf. Please note that Mylan's proposed final printed labeling (BALZ:R5, Revised November 2007) has been compared to our previously submitted final printed outsert (BALZ:R3, Revised September 2007) since this version was submitted in the PLR format. Also note that Mylan's final printed container labels remain the same as those previously submitted in our Labeling Amendment dated June 9, 2006.

In accordance with the Agency's Guidance *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Balsalazide Disodium Capsules as described in the electronic Table of Contents. As a review aid, Mylan has also included a Microsoft Word version of our proposed outsert. To access this Word file, a bookmark is provided within the pdf version.

Mylan commits to submit a SPL version of our generic product labeling within 14 days post approval as a Special Post-Marketing Report.

Department – Fax Numbers	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	Legal Services	(304) 598-5408	Quality Assurance	(304) 598-5407
Administration	Maintenance & Engineering	(304) 598-5411	Quality Control	(304) 598-5409
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Corporate Services	Product Development	(304) 285-6411	Research & Development	(304) 285-6419
Human Resources			Sales & Marketing	(304) 598-3232

Project ANDA Balsalazide Disodium Caps Labeling Amendment Agency Correspondence Dated 11/07/07 BALZ:R5.doc

Gary J. Buehler

Page 2 of 2

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

A handwritten signature in cursive script that reads "S. Wayne Talton".

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dmy

Enclosure

Desk Copy: Ann Vu, Labeling Reviewer
Division of Labeling and Program Support

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

November 21, 2007

Mr. Jeffrey Senger
Acting Chief Counsel
Office of the Chief Counsel
Food and Drug Administration
Department of Health and Human Services
Room 605 (GCF-1)
5600 Fishers Lane
Rockville, Maryland 20857

RECEIVED

NOV 23 2007

OGD

N/MC

Re: Mylan Pharmaceuticals Inc.
ANDA No. 77-807
Balsalazide Disodium Capsules, 750mg

Dear Sir or Madam:

The purpose of this letter is to express Mylan Pharmaceuticals Inc. ("Mylan")'s concern and disappointment with the delay caused in approving the above referenced ANDA as a result of the Citizen Petition and corresponding Supplements submitted by Salix Pharmaceuticals, Inc. ("Salix") in connection with Docket No. 05P-0146/CP 1.

The continued delay created by the Citizen Petition and Supplements filed by Salix undermines the very purposes of the recently enacted FDA Amendments Act of 2007, which specifically prohibit the Agency from delaying the approval of a pending ANDA as a result of a citizen petition unless the Agency determines that "a delay is necessary to protect the public health." FDC Act § 505(q)(1)(A), as amended by FDAAA. With an aim of increasing transparency, the FDA Amendments Act of 2007 also requires FDA to provide an applicant with a summary of the specific substantive issues raised in a petition within 30 days of FDA's determination that a delay is necessary to protect public health. FDC Act § 505(q)(1)(B). To that end, Mylan has not been provided any information which would justify a delay in Mylan's approval. Moreover, the FDA Amendments Act of 2007 permit the Agency to deny a petition at any point if the petition (or its supplement) was submitted with the primary purpose of delaying the approval of an application and does not raise valid scientific or regulatory issues on its face. FDC Act § 505(q)(1)(E).

Further delaying the approval of Mylan's application is also counter to the Agency's GIVE initiative, which seeks to bring first generic products to consumers faster by providing an expedited review of applications when there are no blocking patents or exclusivity protections for the reference listed drug.¹ More than ten months have passed since Salix' pediatric exclusivity expired on Jan. 8, 2007.

¹ See FDA Press Release, "FDA Announces Initiative to Bolster Generic Drug Program" dated Oct. 4, 2007 available at <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01719.html>. "As part of the GIVE efforts, FDA is

Department—Fax Numbers

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Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

As you are aware, Mylan is the holder of the above-referenced ANDA, filed July 18, 2005 for Balsalazide Disodium Capsules, 750mg. On August 20, 2004 and January 10, 2005, Mylan submitted controlled correspondence to its application requesting comments on the determination of bioequivalence of Balsalazide Disodium Capsules, 750mg ("Balsalazide"). Specifically, Mylan requested confirmation that no clinical endpoint study should be required for this drug product. On April 7, 2005, Mylan received correspondence from the Office of Generic Drugs (OGD) providing bioequivalence recommendations for Balsalazide, which did not include a requirement for a clinical endpoint study. Mylan followed the Agency's recommendations, and Mylan's Balsalazide Disodium 750 mg capsules are bioequivalent to Salix's Colazal® 750 mg capsules.

On April 13, 2005, Salix filed a "Citizen Petition to Establish Appropriate Bioequivalence Standards for Generic Locally-Acting Gastrointestinal (GI) Drug Products" (Docket No.: 05P-0146/CP 1). In that petition, Salix urged the Agency to require specific bioequivalence requirements, *i.e.*, comparative clinical trials, as a condition of approval for oral drug products containing balsalazide disodium.²

As discussed in Mylan's controlled correspondence, Mylan does not believe that clinical trials are necessary for the approval of generic Balsalazide. No basis exists for the Agency to deviate from its bioequivalence recommendations in the January 10, 2005 correspondence to Mylan. Salix has failed to provide any credible reason for deviating from such recommendation for this product and amounts essentially for a request that FDA reconsider the specific guidance the Agency has already given.

Mylan has satisfied all conditions necessary for approval, including several recent labeling changes, the last of which was submitted on Nov. 9, 2007. In keeping with the requirements of the FDA Amendments Act and the policy of FDA's GIVE Initiative, Mylan urges the Agency to move forward in approving Mylan's pending ANDA No. 77-807 and avoid further delay created by the Citizen Petition and Supplements filed by Salix. Should the Agency have any additional questions or comments, I can be reached at (724)514-1844.

Respectfully submitted,

Brian S. Roman 

Brian S. Roman
Vice President and General Counsel

CC: Gary Buehler, Office of Generic Drugs, FDA
Elizabeth Dickinson, Office of the Chief Counsel, FDA

revising the review order for certain drug applications. For example, first generic products, for which there are no blocking patents or exclusivity protections on the reference listed drug, are identified at the time of submission for expedited review. This will mean that these products, for which there are currently no generic products on the market, may reach the consumer much faster."

² On July 14, 2006, Salix filed a Supplement to its Citizen Petition to renew its request that comparative trials be required as a condition of approval for oral drug products containing balsalazide disodium. Additional Supplements were also filed on November 14, 2006, June 14, 2007 and Sept. 27, 2007. Like Salix's initial Citizen Petition, these supplements lack sufficient merit to warrant further delay in approving Mylan's ANDA.

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-807 Applicant Mylan
 Drug butylacetylcholine Disodium Capsules Strength(s) 750mg

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer
 Chief, Reg. Support Branch
 Date 12 July Date _____
 Initials MS 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 Date Checked 7/20/06
 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

Type of Letter: Pre-IV
 Comments: Pre-IV to 192 extend 7/10/06 but exclusivities were submitted. we will assume pre exclusivity will be granted until we hear otherwise MS

2. Project Manager, Y Kong Team 7 Date 4-25-06 Date _____
 Review Support Branch Initials YK Initials _____

Original Rec'd date 7-18-05 EER Status Pending Acceptable OAI

Date Acceptable for Filing 7-18-05 Date of EER Status 9-14-05 (filed)

Patent Certification (type) II Date of Office Bio Review 6-12-06 (holder)

Date Patent/Exclus. expires 9-27-06 (7/10/06) Date of Labeling Approv. Sum 6-20-06 (v. 1)

Citizens' Petition/Legal Case Yes No Date of Sterility Assur. App. N/A.

(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes No

First Generic Yes No MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No Modified-release dosage form: Yes No

Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved Date _____

Previously reviewed and CGMP def. /NA Minor issued Date _____

Comments:

3. David Read (PP IVs Only) Pre-MMA Language included Date _____
 OGD Regulatory Counsel, Post-MMA Language Included Initials _____

Comments:

4. Div. Dir./Deputy Dir. Date 7/20/06
 Chemistry Div. I II OR III Initials JL
 Comments:

CMC OK

REVIEWER:

FINAL ACTION

5. Frank Holcombe First Generics Only
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

For Frank

Date 8/29/06
Initials PH

CAC OK - Radhika Rajivopalam

6. Vacant
Deputy Dir., DLPS

Date _____
Initials _____

7. Peter Rickman
Director, DLPS

Date _____
Initials _____

Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments:

OR

8. Robert L. West
Deputy Director, OGD

Date _____
Initials _____

Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments:

9. Gary Buehler
Director, OGD

Date _____
Initials _____

Comments:

First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue

10. Project Manager, Team _____
Review Support Branch

Date _____
Initials _____

_____ Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

_____ Time notified of approval by phone _____ Time approval letter faxed

FDA Notification:

_____ Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

_____ Date Approval letter copied to \\CDS014\DRUGAPP\ directory. File

V:/division/dlps/approvrou8.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-807 Applicant Mylan
Drug Balsalazide Disodium Capsules Strength(s) 750 mg

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. **Martin Shimer** Date 2 OCT 07 Date _____
 Chief, Reg. Support Branch Initials MHS Initials _____
 Contains GDEA certification: Yes No Determ. of Involvement? Yes No
 (required if sub after 6/1/92) Pediatric Exclusivity System
 RLD = _____ NDA# _____
 Patent/Exclusivity Certification: Yes No 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: No remaining patents protecting the RLD Colazal. On 4/19/07 Mylan
 communicated their intent to omit claims related to ODE and NPP from their labeling.

ANDA is eligible for Full Approval once outstanding CP is answered.

2. **Project Manager, Theresa Liu Team 7** Date 10/1/07 Date _____
 Review Support Branch Initials stcl Initials _____
 Original Rec'd date 7/18/05 EER Status Pending Acceptable OAI
 Date Acceptable for Filing 7/18/05 Date of EER Status 9/5/07
 Patent Certification (type) pIII Date of Office Bio Review 5/2/07
 Date Patent/Exclus. expires 6/20/2014 Date of Labeling Approv. Sum 9/28/07
 Citizens' Petition/Legal Case Yes No Labeling Acceptable Email Rec'd Yes No
 (If YES, attach email from PM to CP coord) 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 MV Commitment Rcd. from Firm Yes No
 it to Cecelia Parise)
 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 10/4/07 Date 10/4/07
 Name/Initials sav Name/Initials slg
 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 the OB, Drugs@Fda and DSS. One thing I noticed on the AP letter is that the '992 patent already expired so I'm not sure if you should tweak the language or let Bob do it.

Thanks
Ann

4. David Read **(PP IVs Only)** Pre-MMA Language included Date _____
OGD Regulatory Counsel, Post-MMA Language Included Initials _____
Comments:

5. Div. Dir./Deputy Dir. Date 10/16/07
Chemistry Div. II Initials RCA

Comments: CMC OK, no issues see attached spreadsheet. First generic audit 7/06 when
TAed

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 10/29/07
Director, DLPS Initials swpr
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: no remaining patents protecting the RLD; exclusivity ODE and NPP have been
carved-out of labeling; Bio acceptable 5/2/07; Labeling acceptable 9/28/07; EER
acceptable 9/5/07

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.**

/s/

Theresa Liu
12/28/2007 11:00:30 AM