CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-830 SUPPL # N/A HFD # 180

Trade Name tradename (mesalamine) Delayed Release Tablets

Generic Name mesalamine

Applicant Name Procter & Gamble

Approval Date, If Known PDUFA goal date: April 22,2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	19-651	Asacol (mesalamine) Delayed Release Tablets
NDA#	22-000	Lialda (mesalamine) Delayed Release Tablets
NDA#	19-618	Rowasa (mesalamine) Rectal Suspension Enema
	21-252	Canasa (mesalamine) Rectal Suppository
	20-049	Pentasa (mesalamine) Controlled Release Capsules

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 2000082: A DOUBLE-BLIND, RANDOMIZED, 6-WEEK, PARALLEL-GROUP DESIGN CLINICAL TRIAL TO ASSESS SAFETY AND EFFICACY OF ASACOL 4.8 G/DAY (800 MG TABLET) VERSUS ASACOL 2.4 G/DAY (400 MG TABLET) FOR THE TREATMENT OF MODERATELY ACTIVE ULCERATIVE COLITIS

Study 2006444: Assessing the Safety and Clinical Efficacy of a New Dose (Asacol 800 mg tablets/4.8g/day) A double-blind, randomized, 6-week, parallel-group clinical trial to assess the safety and efficacy of Asacol® 4.8g/day (800 mg mesalamine tablet) versus Asacol 2.4g/day (400 mg mesalamine tablet) for the treatment of moderately active ulcerative colitis.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation

and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 2000082: A DOUBLE-BLIND, RANDOMIZED, 6-WEEK, PARALLEL-GROUP DESIGN CLINICAL TRIAL TO ASSESS SAFETY AND EFFICACY OF ASACOL 4.8 G/DAY (800 MG TABLET) VERSUS ASACOL 2.4 G/DAY (400 MG TABLET) FOR THE TREATMENT OF MODERATELY ACTIVE ULCERATIVE COLITIS

Study 2006444: Assessing the Safety and Clinical Efficacy of a New Dose (Asacol 800 mg tablets/4.8g/day) A double-blind, randomized, 6-week, parallel-group clinical trial to assess the safety and efficacy of Asacol® 4.8g/day (800 mg mesalamine tablet) versus Asacol 2.4g/day (400 mg mesalamine tablet) for the treatment of moderately active ulcerative colitis.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 26,093	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 26,093	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Kristen Everett
Title: Regulatory Project Manager
Date: 11 APR 2008

Name of Office/Division Director signing form: Donna Griebel
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Appears This Way
On Original

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

/s/

Heather G Buck
4/30/2008 02:20:04 PM

Donna Griebel
5/29/2008 05:40:10 PM

Exclusivity Statement
Requesting Three Years of Exclusivity

As part of this New Drug Application submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act, Procter & Gamble Pharmaceuticals (P&GP) is requesting three years exclusivity for the use of 800 mg ASACOL (mesalamine) delayed-release tablets at 4.8 gram/day dosing for the treatment of moderately active ulcerative colitis. P&GP is the sole developer of this drug product and owns the patent rights.

Pursuant to 21 CFR 314.50(j) and 314.108(b)(4) support for this exclusivity request is based on the following:

Previous Approval of the Drug Product

1. P&GP has previously received marketing approval under 505 (b) for the use of 400 mg ASACOL at 2.4 g/day for the treatment of mildly to moderately active ulcerative colitis. Approval was granted by FDA on 31 January 1992.

2. P&GP has previously received marketing approval under 505 (b) for the use of 400 mg ASACOL at 1.6 g/day for the maintenance of remission of ulcerative colitis. Approval was granted by FDA on 19 August 1997.

New Clinical Investigations Essential to the Approval

Procter & Gamble Pharmaceuticals, Inc. is the sponsor named in Form FDA-1571 for the new clinical investigations conducted in support of this indication, under IND 26,093. These new clinical investigations are essential to approval of this application for ASACOL as a new dosing regimen (4.8 g/day) with a higher strength tablet (800 mg).

Report Title	Location (Vol/Page)
Study 2000082: A double-blind, randomized, 6 week, parallel-group design clinical trial to assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) versus Asacol 2.4 g/day (400 mg tablet) for the treatment of moderately active ulcerative colitis. (as amended 19 February 2003)	[See Section 5.3.5.1.1]
Study 2000083:A double-blind, randomized, 6 week, parallel-group design clinical trial in patients with mildly to moderately active ulcerative colitis to assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) versus Asacol 2.4 g/day (400 mg tablet).	[See Section 5.3.5.1.2]

Certification: Studies not part of the basis of a finding of substantial evidence of effectiveness for a previously approved application

P&GP certifies that each of the clinical investigations in humans included in the application have not been relied upon by FDA to demonstrate:

1. substantial evidence of effectiveness of a previously approved drug product for any indication or,
2. safety for a new patient population and,
3. do not duplicate the results of another investigation that was relied upon by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

Certification: Scientific Literature Search

P&GP certifies that a thorough literature search has been conducted to evaluate the relevance of published mesalamine safety and effectiveness studies to support dosing at 4.8 g/day for the treatment of moderately active ulcerative colitis. To the best of our knowledge, this search was complete and accurate and, in our opinion, the published studies do not provide a sufficient basis for the approval of a new indication for treatment with 4.8 g/day mesalamine of patients with moderately active UC without reference to the new clinical investigations in this application. The output of this search is appended to this request.

The published studies are insufficient to provide a basis for approval because they have at least one or more of the following deficiencies:

- None of the published studies evaluated safety and efficacy using an 800 mg mesalamine delayed-release tablet.
- With the exception of reference #14 which is the Mayo Clinic study sponsored by P&GP and previously submitted to the Division (see below), no other published reports included safety or efficacy analyses of dosing with 4.8 g/day mesalamine.

Certification: Previously available information, not sufficient for approval

P&GP included a Mayo Clinic study (see ref # 14) in which patients dosed at 4.8 g/day exhibited significantly greater improvement in overall symptoms compared to patients on placebo as one of two adequate and well controlled trials supporting approval of ASACOL 400 mg tablets for treatment of patients with mildly to moderately active ulcerative colitis in NDA 19-651.

On 30 October 1987, the Division indicated that the data from C.3 was sufficient to demonstrate efficacy at the higher dose but that additional information to assess the safety profile of the higher dose was needed. P&GP subsequently provided data two open-label compassionate use studies in which the subset of patients exposed to Asacol doses of 4.8 g/day showed no clinically meaningful differences in adverse event profiles when compared to patients exposed to 2.4 g/day

However, as reflected in P&GP minutes (submitted to IND 26,093 serial submission #137) from a pre-NDA meeting held 19 September 1994, the Division's perspective was that 4.8 g/day dosing was not substantiated by adequate and well controlled clinical trials. In addition the Division

advised that the therapeutic benefit of 4.8 g/day dosing be distinguished from the 2.4 g/d dose. This was confirmed in subsequent meetings with the Division.

Table I: Summary of Literature Results

ref no	Title	Authors, address	Literature source
1	Balsalazide Is More Effective and Better Tolerated Than Mesalazine in Acute Ulcerative Colitis (Uc)	Green JRB;Holdsworth CD;Lobo AJ;Leicester R;Gibson JA;Kerr GD;Hodgson H;Parkins KJ;Taylor MD;Richardson PDI;Abacus Investigator Group;, Stoke, Sheffield, London, Stafford, Shrewsbury and Kings Langley, UK	Gut (London), Abstracts, Autumn Meet British Soc Gastroenterology, Manchester, UK, Sept 18-20, 1996, 39, Suppl 1, A17- (1996)
2	Balsalazide Is More Effective and Better Tolerated Than Mesalazine in Acute Ulcerative Colitis (Uc)	Green JRB;Holdsworth CD;Lobo AJ;Leicester R;Gibson JA;Kerr GD;Hodgson H;Parkins KJ;Taylor MD;Pdi RICH;Abacus Investigator Group;, Stoke, Sheffield, London, Stafford, Shrewsbury, and Astra Pharmaceuticals, Kings Langley, UK	Gastroenterology, Abstracts, Digestive Disease Week and 97th Ann Meet Amer Gastroenterol Assoc, Washington, DC, May 11-14, 1997 Gastroenterology 112(4, Suppl):A984 (April) (1997)
3	Clinical Trials. Comparison of Delayed Release 5 Aminosalicylic Acid (Mesalazine) and Sulphasalazine in the Treatment of Mild to Moderate Ulcerative Colitis Relapse	Riley SA;Mani V;Goodman MJ;Herd ME;Dutt S;Turnberg LA;,	Gut (London), 29, 5, 669-674 (1988)
4	Delayed-Release 5-Aminosalicylic Acid (5-ASA) and Sulphasalazine (Ssz) in the Treatment of Mild to Moderate Ulcerative Colitis (Uc) Relapse	Riley SA;Mani V;Goodman MJ;Turnberg LA;,	Gut (London), Abstracts, British Soc. Gastroenterol., London, Sept. 15-18, 1987, 28, 10, A1329- (1987)
5	Dose Finding Study of the Efficacy and Safety of Newly Developed 5-ASA Containing Pellets in Patients with Active Ulcerative Colitis	Kruis W;Meir SB;Feher J;Stolte M;, Koeln and Bayreuth, Germany, Tel Hashomer, Israel, and Budapest, Hungary	Gastroenterology, Abstracts, Digestive Disease Week and 101st Ann Meet Amer Gastroenterol Assoc, San Diego, CA, May 21-24, 2000, 118, 4, Suppl 2, A780- (2000)
6	Improvement with Delayed Release Oral Mesalamine (5-ASA) in Ulcerative Colitis Should be Evident Within Three Weeks	Schroeder KW;Tremaine WJ;Ilstrup D;,	Gastroenterology, Abstracts, 89th Ann. Meet. Amer. Gastroenterol. Assoc., New Orleans, LA, May 14-20, 1988, 94, 5, Part 2, A412- (1988)

7	Improvement with Delayed Release Oral Mesalamine (5-ASA) in Ulcerative Colitis Occurs Within Three Weeks	Schroeder KW;Tremaine WJ;Ilstrup D;,	Amer J Gastroent, Abstracts, 53rd Ann. Sci. Meet., American Coll. Gastroenterology, Oct. 17-19, 1988, New York, NY,, 83, 9, 1058- (1988)
8	Oral Delayed-Release Mesalazine in the Treatment of Mild Ulcerative Colitis: A Dose Ranging Study	Miglioli M;Bianchi PG;Brunetti G;Sturniolo GC;Italian Ibd Group;, Milano, Padova, Bologna, Roma, Italy	Europ J Gastroenterol Hepatol, 2, 3, 229-234 (1990)
9	Sulphasalazine Associated Seminal Abnormalities: Results of Asacol (Delayed Release 5-Amino Salicylic Acid) Substitution	Riley S;Mani V;Mandal B;Turnberg L;,	Dig Diseases Sci, Abstracts, World Congresses, 8th Gastroenterology, 6th Digestive Endoscopy, 3rd Colo-Proctology, Sao Paulo, Brazil, Sept. 7-12, 1986, 31, 10, Suppl., 319S- (1986)
10	Comparison of delayed release 5 aminosalicylic acid (mesalazine) and sulphasalazine in the treatment of mild to moderate ulcerative colitis relapse	Riley SA;Mani V;Goodman MJ;Herd ME;Dutt S;Turnberg LA;, Department of Medicine, University of Manchester Medical School, Hope Hospital, Salford	Gut, 29, 5, 669-674 (1988 May
11	Mesalazine 4 g daily given as prolonged-release granules twice daily and four times daily is at least as effective as prolonged-release tablets four times daily in patients with ulcerative colitis	Farup PG;Hinterleitner TA;Lukas M;Hebuterne X;Rachmilewitz D;Campieri M;Meier R;Keller R;Rathbone B;Oddsson E;, Dr. P.G. Farup, Unit for Applied Clinical Res.- NTNU, Regionssykehuset I, 7006 Trondheim, Norway	Inflammatory Bowel Diseases, 7/3, 237-242, Refs-0998 (2001)
12	The optimal dose of 5-aminosalicylic acid in active ulcerative colitis: A dose-finding study with newly developed mesalamine	Kruis W;Bar-Meir S;Feher J;Mickisch O;Mlitz H;Faszczyk M;Chowers Y;Lengyele G;Kovacs A;Lakatos L;Stolte M;Vieth M;Greinwald R;, Dr. W. Kruis, Evangelisches Krankenhaus Kalk, Buchforststrasse 2, 51103 Cologne, Germany. Ansorg@evkk.de	Clinical Gastroenterology and Hepatology, 1/1, 36-43, Refs-3565 (2003 Jan 1)
13	Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis. A multicenter study	Sninsky, C. A.; Cort, D. H.; Shanahan, F.; Powers, B. J.; Sessions, J. T.; Pruitt, R. E.; Jacobs, W. H.; Lo, S. K.; Targan, S. R.; Cerda, J. J.;	Annals of internal medicine, 115 (5) PAGES- 350-355 (1991 Jan 9)
14	Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study	Schroeder, K. W.; Tremaine, W. J.; Ilstrup, D. M.	New England Journal of Medicine, 317 (26) PAGES- 1625-1629 (1987 Dec 24)

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-830 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: October 29, 2004 Action Date: August 29, 2005

HFD 180 Trade and generic names/dosage form: Asacol 800 (mesalamine) tablets

Applicant: Procter & Gamble Pharmaceuticals, Inc. Therapeutic Class: Ulcerative colitis

Indication(s) previously approved: mildly to moderately active ulcerative colitis

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: moderately active ulcerative colitis

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: X Partial Waiver X Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Sponsor has requested a partial waiver for patients < 5 years of age and a deferral for pediatric patients age 5 to 17 years of age until December 2010

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr. < 5	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other: Studies are impossible or highly impractical because the number of patients is so small and geographically dispersed.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr. 5 ____ Tanner Stage____
Max____ kg____ mo.____ yr. 17 Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: Studies will be conducted sequentially to identify appropriate doses. Deferral date is based on estimated time to recruit patients, particularly in the 5 to 8 year old range, for both pediatric studies. Pediatric drug development plans have been submitted to the Agency (May 9, 2005, protocol 2005018 submitted to IND 26,093, ss # 232). PREA pediatric plan is submitted to NDA 21-830 concurrent with this amendment.

Date studies are due (mm/dd/yy): December 31, 2010

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-830

HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Kristen Everett
8/29/2005 11:52:44 AM

10/22/07 Submission

Debarment Certification

Certification Pursuant to the Generic Drug Enforcement Act of 1992

Procter & Gamble Pharmaceuticals hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Respectfully submitted,

Stephen Marcello, M.D.
Director
Global Clinical Development and Clinical Operations
Procter & Gamble Pharmaceuticals

Appears This Way
On Original

MEMORANDUM OF TELECON

DATE: Wednesday May 14, 2008

APPLICATION NUMBER: NDA 21-830

BETWEEN:

PROCTER & GAMBLE PHARMACEUTICALS (P&GP)
Funmi Ajayi, Ph.D., Senior Director, Experimental Medicine
Guhan Balan, Ph.D., M.B.A., Associate Director, Pharmacokinetics
Chris Bernhardt, Ph.D., Director, GI Category Regulatory Affairs
Terri Gaffney, B.Sc, Project Leader
Mark Hosterman, PharmD, Clinical Pharmacovigilence
Vicki Ireland, Regulatory Affairs Manager
Eileen King, Ph.D., Senior Director, Biometrics and Statistical Sciences
David Lacy, Marketing Director, GI Category
Matt Malloy, Associate General Counsel
Lynne Tracey, Vice President, GI Category, Research & Development
Marie Hershberger, Consumer/Professional & Marketing Knowledge
Wendy Sauber, Senior Director of Regulatory Affairs

AND

FDA
Donna Griebel, M.D., Division Director, Division of Gastroenterology Products (DGP)
John Hyde, Ph.D., M.D., Medical Team Leader, Division of Gastroenterology Products
Anil Rajpal, M.D., Medical Officer, Division of Gastroenterology Products
Milton Fan, Ph.D., Statistical Reviewer, Division of Biometrics 3
Sue-Chih Lee, Ph.D., Clinical Pharmacology Leader, Division of Clinical Pharmacology 3
Insook Kim, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Denise Toyer, Pharm.D., Deputy Director, Division of Medical Error Prevention (DMEP)
Linda Kim-Jung, Pharm.D., Team Leader, Division of Medical Error Prevention
Walter Fava, R.Ph., Safety Evaluator, Division of Medical Error Prevention
Kristen Everett, R.N., Regulatory Project Manager, Division of Gastroenterology Products
Heather Buck, M.S., M.B.A., Regulatory Project Manager, Division of Gastroenterology Products

SUBJECT: Discussion of proposed trade name Asacol 800 and labeling negotiations

BACKGROUND:
February 24, 2005, P&GP submitted new information to support their proposed Asacol 800 trade name

August 1, 2005, the Division informed P&GP that the trade name Asacol 800 was found to be acceptable

October 22, 2007, P&GP submitted a complete response to the approvable letter issued by the Division on August 29, 2005

April 2008, the Division issues a Discipline Review letter stating that upon further review, the trade name was unacceptable

May 14, 2008, P&GP submitted background information for the trade name discussion

DISCUSSION:
Note: The first fifteen minutes were devoted to the trade name discussion; the remaining time was spent negotiating the label. The latter part of the meeting is not captured in these minutes as the label itself typically serves as the documentation of the meeting. The minutes below are focused on the trade name discussion of the meeting only.

DMEP asked P&GP whether the participants in the survey conducted in May 2008 were provided with bioequivalence information for Asacol and Asacol 800. P&GP responded that participants were provided with the bioequivalence information for the two products.

DMEP explained that in the usual pharmacy practice setting, pharmacists will substitute lower strengths for higher strengths of the same product without checking references to determine whether the two strengths are bioequivalent. In the survey conducted by P&GP however, participants were provided with the information that Asacol and Asacol 800 are not bioequivalent and therefore the survey was biased. DMEP suggested that data collection should be conducted in a study where participants are not informed of the bioequivalence differences between the two products.

P&GP agrees with DMEP that prevention of avoidable events (i.e., drug substitution) is key. DMEP expressed their feeling that no modifier will truly prevent substitution.

P&GP will continue to research modifiers, and gather data they have from past surveys and research. DMEP agreed to review any data they wish to send.

ACTION ITEMS:
P&GP will submit supporting data as they feel necessary, as we continue our review of their application.

ATTACHMENTS:
Background Package submitted by PG&P on May 14, 2008

Heather Buck
Regulatory Project Manager (HFD-180)

Procter & Gamble Pharmaceuticals, Inc.
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9760
www.pg.com

May 13, 2008

Donna Griebel, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale road
Beltsville, MD 20705-1266

Re: NDA 21-830, 800 mg (mesalamine) Delayed-Release Tablets
Background Information for Teleconference
Amendment 29

Dear Dr. Griebel:

This provides background information for the trade name discussion this Wednesday, May 14th at 3 pm.

Our objectives are a) to focus on the potential acceptability of three proposed options to address the concerns identified by DMEP in the Discipline Review of the Asacol® 800 trade name and b) to determine the timing and process to enable review of a trade name to continue as part of the NDA review.

The package contains:

- **Overview** – a summary describing the overall benefit risk assessment of the use of a trade name containing the Asacol root compared to a new trade name and the three options proposed by P&GP for FDA to consider.
- **Education, Monitoring, Packaging and Advertising** – an outline of the plan that would be implemented as an immediate post-marketing commitment to address the concerns associated with the use of the Asacol root name for the 800 mg product. Also provided is an example of the packaging art and text that could be used to further differentiate the Asacol and Asacol 800 (or Asacol root name) products.
- **Bioequivalence** – a summary of the relevance of BE in assessing clinical efficacy and safety of delayed-release mesalamine products. This includes an FDA background summary prepared for an October, 2004 GI Advisory Committee that evaluated the challenges associated with the use of BE data for locally active GI drugs.
- **Safety** – a summary comparing the safety of the Asacol and the 800 mg product at the doses of 2.4 and 4.8 g/day, respectively.
- **References** - copies of all cited references.

Please let us know if there is any additional information that would be helpful. We would be happy to courier color copies of the examples of artwork if that would aid the reviewers.

In closing, we would like to thank the Division for helping us address these issues so promptly.

Sincerely,

Christian A. Bernhardt, PhD
Director, Regulatory Affairs for GI
Procter & Gamble Pharmaceuticals
Bernhardt.CA@pg.com
Phone (513) 622.4965/FAX (513) 622.3191

Table of Contents

1. Overview

Procter and Gamble Pharmaceuticals (P&GP) respectfully disagrees with the Agency's conclusion that marketing the 800 mg product under a different trade name offers less opportunity for errors compared to marketing it under an Asacol-associated trade name, such as "Asacol 800". We believe that use of dual trademarks for 2 products marketed by the same manufacturer with the same active ingredient does not eliminate the potential for medication errors and in this case carries with it greater potential safety risks from the unintended use of doses of greater than 4.8 g/day.

We believe it will be more effective to educate the health care system with respect to the important differences between the products with the retention of the Asacol root in the tradename. Gastroenterologists have a 16-year history of prescribing knowledge with Asacol. Introducing the product with a different trade name would require communicating a new name for a delayed-release mesalamine product and conveying differences compared to Asacol. This differentiation will be challenging as both products have the same active ingredient and delayed-release technology with a similar mechanism of action. We believe that a different name would put physicians and pharmacists at a disadvantage in understanding the nature of the 800 mg product, in addition to the potential for double-prescribing.

This has been confirmed in a recent survey (May 2008) conducted to understand the issues associated with communicating the proper use of the 800 mg product. A product profile of the 800 mg product that included a discussion of the differences with Asacol (lack of demonstrated bioequivalence) was shared with 50 gastroenterologists and 75 pharmacists. They were then asked to indicate which name option (including a new trade name) would be best to use for the product. Only 3 felt that a new trade name would be preferable to the use of a name containing the Asacol root.

We believe that the package insert labeling being considered in conjunction with the proposed education, monitoring, packaging and advertising program outlined in this package below would be most effective in the context of a name containing the Asacol root. We believe this approach substantially reduces the risk for medication error of consequence compared to the use of 2 different trade names. We are committed to working with the Division and DMEP to maximize the effectiveness of the program outlined in this package.

Options Being Considered for Response

Since we believe the optimal benefit-risk profile supports approval of the product with "Asacol" as a component of the proprietary name, we would ask the Division to consider 3 options that may address the concerns identified in the DMEP comments and Discipline Review Letter.

These options are:

1. Retain the Asacol 800 name and obtain Division agreement to the components of a comprehensive education program to physicians, nurses, pharmacists, and patients that describe how Asacol and Asacol 800 are different. Reports of all medication errors would be monitored and reported every 3 months for the first 2 years of marketing. The differences between the Asacol and Asacol 800 mg products would be additionally distinguished with more differentiated package art. b(4)

b(4)

(Note: this statement is pending final agreement with the Division to the package insert.) Non-reminder advertising for the 800 mg product (and any co-advertising with Asacol) would also include this statement.

2. Augment the approach described in Option 1 with a post-approval commitment to promptly submit a labeling supplement for Asacol (NDA 19-651) to change the trade name to "Asacol 400." (We expressly request Division agreement to expedite this supplement as a CBE 30.) This approach would prompt pharmacists to seek clarification from prescribers if an Asacol prescription was not specified as either the 400 mg or 800 mg products.
3. Use the Asacol root name in conjunction with a suitable modifier (other than "800") that relates to an aspect of the 800 mg product that distinguishes it from the 400 mg product. The communication objectives of the modifiers being considered is summarized in the table below.

Modifier Communication Objective
Non specific Strength
Dual-Coat as Distinguishing Characteristic
Moderate Patient Usage

Research is being conducted testing 7 different modifiers and results will be available in advance of May 29th.

3 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Administrative-*_____

3. Bioequivalence

FDA cited lack of demonstrated bioequivalence (BE) as one of the factors considered in the evaluation of the trade name. We believe the potential consequence of this concern to be overstated for the following reasons:

- Mesalamine (5-ASA) is a topically active locally acting GI drug. In this context the relevance of BE to assess clinical consequence of error is not definitive compared to the value of clinical results (Attachment 3)
- In 1999 and 2000, FDA agreed with P&GP that it would not be feasible to demonstrate bioequivalence between one tablet of Asacol 800 mg and 2 Asacol 400 mg tablets largely due to the high degree of intersubject variation in the absorption of mesalamine (5-ASA) (see Question 1 and response from attached correspondence from FDA on Dec 15th 2000; Attachment 4).
- As a result, P&GP proposed, and FDA concurred, that sparse blood samples be collected in UC patients enrolled in clinical trials and compared between both regimens as a way of assessing relative systemic exposures.
- The population PK data are supportive of a dose proportional response when comparing the systemic exposures to 5-ASA and N-Ac-5-ASA from the 400 mg product at 2.4 g/day, to the 800 mg product at 4.8 g/day. Further, there is similarity in systemic exposures in patients with mild or moderate UC (see CP-Tables 3 and 6 extracted from the October 2004 submission).
- These findings reflect exposure at steady-state in the target patient population. This is believed to be most relevant for the assessment of the clinical consequences of error associated with the use of a chronically administered therapy such as Asacol 800. This is also consistent with the conclusions from the FDA's background information for the 2004 Advisory Committee on bioequivalence for locally active GI drugs (Attachment 3).

CP-Table 3
Summary of 5-ASA and N-Ac-5-ASA Plasma Concentrations (ng/mL) at Weeks 3 and 6 Visits in Patients with Mild or Moderate Ulcerative Colitis
(Studies 2000082 and 2000083)

5-ASA

	2.4 gram/day (400 mg tablet)[a]			4.8 gram/day (800 mg tablet)[b]				
	Baseline	Week 3	Week 6	Baseline	Week 3	Week 3 Ratio[a]	Week 6	Week 6 Ratio[a]
N	339	285	275	330	289		273	
Arithmetic Mean	181.18	975.04	966.80	196.09	1959.16	2.01	1931.21	2.00
Geometric Mean	194.19	548.43	462.56	251.75	1139.76	2.08	1057.25	2.29
SD	827.16	1292.25	1414.72	940.72	2346.46		2310.75	
Median	0.00	509.00	427.00	0.00	1230.00	2.42	1200.00	2.81
CV%	456.54	132.53	146.33	479.75	119.77		119.65	
Minimum	0.0	0.0	0.0	0.0	0.0		0.0	
Maximum	9300.0	9890.0	8680.0	12900.0	19400.0		19100.0	

N-AC-5-ASA

	2.4 gram/day (400 mg tablet)[a]			4.8 gram/day (800 mg tablet)[b]				
	Baseline	Week 3	Week 6	Baseline	Week 3	Week 3 Ratio[a]	Week 6	Week 6 Ratio[a]
N	339	286	275	330	290		273	
Arithmetic Mean	333.09	1871.85	1789.20	408.53	2904.02	1.55	2951.32	1.65
Geometric Mean	484.57	1415.05	1262.99	733.86	2169.04	1.53	2130.55	1.69
SD	925.79	1561.33	1684.29	1474.04	2291.74		2626.87	
Median	0.00	1485.00	1330.00	0.00	2355.00	1.59	2160.00	1.62
CV%	277.94	83.41	94.14	360.82	78.92		89.01	
Minimum	0.0	0.0	0.0	0.0	0.0		0.0	
Maximum	6700.0	9940.0	9820.0	18700.0	14000.0		14900.0	

Includes patients whose concentration values were available and the elapsed time since last dose for a given visit was positive and within 24 hours.

[a] 4.8 g per day with the 800 mg tablet/2.4 g per day with the 400 mg tablet.

Adapted from 2000082 and 2000083 Final Study Reports [See Section 5.3.5.1.1, 2000082, EoT Table 25] [See Section 5.3.5.1.2, 2000083, EoT Table 19]

CP-Table 6
Exposure Ratio (Mild / Moderate) of 5-ASA & N-AC-5-ASA Plasma Concentrations (ng/mL) at Week 3 and 6 Visits (Studies 2000082 and 2000083)

	5-ASA			
	2.4 Ratio		4.8 Ratio	
	Week 3	Week 6	Week 3	Week 6
Arithmetic Mean	0.82	0.77	0.88	0.82
Geometric Mean	0.78	0.93	0.94	0.78
Median	0.93	0.94	0.87	0.91

	N-AC-5-ASA			
	2.4 Ratio		4.8 Ratio	
	Week 3	Week 6	Week 3	Week 6
Arithmetic Mean	0.93	0.81	0.95	0.94
Geometric Mean	0.94	0.92	0.87	0.97
Median	0.93	0.84	0.94	0.95

Includes patients whose concentration values were available and the elapsed time since last dose for a given visit was positive and within 24 hours. Ratios were calculated using the indicated (mean or median) plasma concentration value for patients with mildly active ulcerative colitis divided by the indicated concentration value for patients with moderately active ulcerative colitis within each Asacol dose group (2.4 g/day or 4.8 g/day).
Adapted from 2000082 and 2000083 Final Study Reports [See Section 5.3.5.1.1, 2000082] [See Section 5.3.5.1.2, 2000083]

4. Safety

Because of the known and well-documented dose-related AE profiles associated with sulfasalazine (Azulfidine) and olsalazine sodium (Dipentum), these agents are not included in this summary.

Asacol (mesalamine) has an excellent safety profile at all clinically studied doses. The most recent clinical studies, ASCEND I, II, and III (2000083, 2000082, and 2006444), included dosing arms of 2.4 (using the 400 mg tablet) and 4.8 (using the 800 mg tablet) grams per day. AEs in these studies were similar to those in the current label and similar for both dosing groups. A comparison of the safety of these 2 doses in patients with mild ulcerative colitis and in patients with moderate ulcerative colitis to determine if there were any dose-related differences was consistent with data previously provided in the complete response submission. Table 1 is a summary of AEs by disease severity (mild and moderate) for patients from the 3 ASCEND studies.

Table 1
Summary of Adverse Events by Disease Severity
Studies 2000082, 2000083 and 2006444 Combined
(Intent-to-treat)

	Mild		Moderate	
Category	2.4g/day Asacol (400 mg Tablet) (N=113) n (%) nAE	4.8g/day Asacol (800 mg Tablet) (N=125) n (%) nAE	2.4g/day Asacol (400 mg Tablet) (N=618) n (%) nAE	4.8g/day Asacol (800 mg Tablet) (N=602) n (%) nAE
AEs	46 (40.7%) 88	45 (36.0%) 85	165 (26.7%) 321	164 (27.2%) 309
Serious AEs	2 (1.8%) 6	0 (0.0%) 0	11 (1.8%) 16	6 (1.0%) 8
Withdrawn due to AEs	4 (3.5%) 11	4 (3.2%) 9	27 (4.4%) 38	24 (4.0%) 42
Deaths	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Mean number of AEs per enrolled patient	0.8	0.7	0.5	0.5
Mean number of AEs per patient with AEs	1.9	1.9	1.9	1.9

N = number of patients within specified Baseline Disease Severity and Randomized treatment
n(%) = number and percent of patients who reported adverse events within specified Baseline Disease Severity and Randomized treatment
nAE = number of adverse events within specified Baseline Disease Severity and Randomized treatment
One 2.4 g/day patient with an unknown disease severity was included in the overall category.
/ASACOL/CSS/ADHOC/aesum2.sas; SAS 8.2 HP 800 28APR08 14:21 t20jul07 TY1006.

Mild patients show similar results for all AEs, serious AEs, and withdrawals due to AEs for both doses. The result for moderate patients is also similar for both dose groups. The mean number of AEs per patients with AEs is identical for both severity groups and dose groups (1.9).

Attachment 5 provides a summary of MedDRA Preferred Terms for AEs reported by 2% or more of any patient population, by disease severity and dose group. As observed in the overall summary in Table 1, the AE table in Attachment 5 demonstrates that the nature and frequencies of AEs are similar between dose groups in mild and moderate patients and show no dose-related AE relationship.

A recent meta-analysis by the Cochrane Collaboration (Attachment 6) reviewed the use of 5-ASA for induction of remission in ulcerative colitis. They reviewed clinical studies of 5-ASA vs. placebo published within the last 25 years with regard to development of any side effects for three dose ranges: < 2 grams, 2-2.9 grams, and 3 grams or greater per day (Sutherland 2006).

Analysis was provided in a whisker plot (Attachment 6; page 26) and results are very similar for all 3 dose ranges indicating no dose-related increase in AEs. Additionally they also provided a meta-analysis for placebo-controlled clinical studies and the rate of withdrawals due to AEs. Again, the results were provided in a whisker plot (Attachment 6; page 27) and showed similar results indicating no dose-related increase in withdrawals due to AEs. The authors concluded that the AEs seen with 5-ASA formulations did not significantly differ from that seen with placebo. Both of these examples are consistent with our own data presented in Table 1 and provide confidence that increasing dose does not increase AEs.

Canadian labeling has carried the 4.8 g/day dosing using the 400 mg tablet since approval in 1991, and use of the Asacol 800 tablet was approved in Canada in April 2005. In periodic safety reviews of Asacol post-marketing experience, the AE profile observed from Canadian report sources has remained consistent with the safety profile described in the current Asacol 400 mg tablet US PI. Additionally, none of the post-marketing events subsequent to the 800 mg tablet approval have been due to confusion of the 2 dose formulations. Prescribing information and pivotal clinical trials of other 5-ASA therapies further support the excellent safety profile and lack of dose related AEs associated with 5-ASAs (Pentasa 2007, Hanauer 1993, Colazal 2007, Levine 2002, Lialda 2007, Sandborn 2007).

Additionally, an in depth search was conducted to determine the number of medication errors that have occurred confusing the root name Asacol with another drug (such as OsCal, Visicol, etc.). Relevant databases were searched and no literature references were found citing any case of the Asacol brand name being confused with any other brand name drug. This provides confidence the proposed Asacol 800 name will not likely be confused with another brand name drug.

In summary, the lack of association between dose level and AEs observed in more than 1400 patients treated in the ASCEND trials is supported by published analyses, approved package inserts for other mesalamine products, and Asacol 800 North American post-marketing experience since 2005.

5. References

Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. The Chochrane Database of Systematic Reviews 2006:2. Art No.: CD000543.pub2. DOI: 10.1002/14651858.CD000543.pub2. 19 April 2006.

Colazal prescribing information, November 2007. http://www.salix.com/assets/pdf/prescribe_info/colazalpi.pdf

Hanauer S, Schwartz J, Robinson M, Roufail W, Arora S, Cello J, et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. Am J Gastroenterol 1993;88(8):1188-97.

Levine DS, Riff DS, Pruitt R, Wruble L, Koval G, Sales D, et al. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g) and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. Am J Gastroenterol 2002;97(6):1398-407.

Lialda prescribing information, January 2007. http://www.lialda.com/includes/prescribing.pdf

Pentasa prescribing information, January 2007. http://www.pentasaus.com/HCP/pentasa_pi.pdf

Sandborn WJ, Kamm MA, Lichtenstein GR, Lyne A, Butler T, Joseph RE. MMX Multi Matrix System mesalazine for the induction of remission in patients with mild-to-moderate ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. Aliment Pharmacol Ther 2007;26(2):205-15.

6. Attachments

Attachment 1: **Current and Proposed Asacol Package Art**

Attachment 2: **Proposed Asacol Label Statements**

Attachment 3: **FDA Advisory Committee background information from October 2004; http://www.fda.gov/OHRMS/DOCKETS/AC/04/briefing/2004-4078B1_07_Bioequivalence-Testing.pdf**

Attachment 4: **IND 26093, Correspondence from FDA to Procter & Gamble, Dec 15th, 2000**

Attachment 5: **Asacol Safety Table**

Attachment 6: **Cochrane review of oral 5-aminosalicylic acid for induction of remission in ulcerative colitis**

4 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

Attachment 3: FDA Advisory Committee background information from October 2004; http://www.fda.gov/OHRMS/DOCKETS/AC/04/briefing/2004-4078B1_07_Bioequivalence-Testing.pdf

6 Page(s) Removed.

See the Advisory Committee Meeting Information located on the FDA Website Below.

http://www.fda.gov/ohrms/dockets/ac/
[transcripts]

Attachment 4: IND 26093, Correspondence from FDA to Procter & Gamble, Dec 15th, 2000

Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

12/15/00

IND 26,093

Procter & Gamble Pharmaceuticals, Inc.
Attention: Lenore Faulhaber, Ph.D., M.B.A.
US Regulatory Affairs
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Faulhaber:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Asacol (mesalamine) Tablets.

We also refer to your amendment dated September 1, 2000 (serial # 167), in which you requested a meeting. The meeting's purpose was to discuss several specific questions concerning your proposed clinical development plan, which is designed to support an increased daily Asacol dose (4.8 gm/day) administered with a new dosage strength (800 mg).

In a September 12, 2000 letter, we indicated that instead of a meeting, we would review your September 1, 2000 correspondence and provide written responses to your specific questions. Note that we transmitted our comments from the biopharmaceutics review of your submission in a November 14, 2000 letter.

We have completed the clinical review of your submission and have the following comments and recommendations. (Your questions are reproduced below in regular print; our responses follow in bold print.)

1. PG&P believes that the data from the 2 pilot bioavailability studies (see Attachment 2) show that it will not be feasible to demonstrate bioequivalence between two 400 mg Asacol tablets and one 800 mg Asacol tablet. Consequently, we believe that further attempts to demonstrate bioequivalence are unwarranted. In meetings with the Division in February and October 1999, the Division agreed that demonstrating bioequivalence was not critical for approval of the 800 mg tablet, because the efficacy and safety of the 800 mg tablet will be qualified in the 4.8 g/day arm of the proposed safety and efficacy studies. We are proposing that if approved, the label will state that bioequivalence has not been established for these 2 dosage forms and that the 400 mg and 800 mg tablets cannot be used interchangeably. Does the Division concur with this proposal?

Agency Response: As noted in our November 14, 2000 letter, we concur that pharmacokinetic and pharmacodynamic studies will not allow demonstration of bioequivalence between the approved Asacol 400 mg tablet and the proposed Asacol 800 mg tablet, largely due to the degree of intersubject variation in the absorption and metabolism of mesalamine.

2. Does the Division agree that the proposed safety and efficacy studies, in conjunction with the proposed pharmacokinetic studies, provide sufficient support for approval of the 4.8 g/day dose, administered with the 800 mg tablet?

   Agency Response: We concur that safety and efficacy of the 4.8 gm/day dose should be based on the results of adequate and well-controlled clinical trials, in addition to biopharmaceutical information.

3. Does the Division agree that the proposed design of the clinical safety and efficacy studies will deliver appropriate data to support the proposed labeling changes?

   Agency Response: The following are comments related to the design of your proposed Phase III study:

   a. **There is no universal acceptance of a numerical score of PGA to assess improvement of ulcerative colitis. Please provide justification for your proposed PGA score to assess improvement of ulcerative colitis.**

   b. **A claim for symptomatic improvement of mildly to moderately active ulcerative colitis requires resolution (absence) of the cardinal symptom of ulcerative proctitis, namely rectal bleeding. Improvement in other concomitant symptoms may add to the improvement assessment, but does not obviate the need for improvement in the cardinal symptom of stool blood. See the "Guidelines for the Clinical Evaluation of Drugs for Ulcerative Colitis, third draft).**

   c. **The proposed study design may allow assessment of superiority of the 4.8 gm dose, compared to the currently approved 2.4 gm dose.**

   d. **It may be of interest to consider a clinical trial design which would encompass a range of Asacol doses (e.g., 2.4 gm/day, 3.2 gm/day or 4.0 gm/day, and 4.8 gm/day).**

4. Doses the Division agree that the proposed clinical development plan for the Asacol 4.8 g/day dose will provide sufficient safety and efficacy data to support the proposed labeling change?

   Agency Response: This is a review issue which will depend on the strength and consistency of the submitted data. We will defer answering this question until the safety and efficacy data have been submitted and reviewed.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Lilia Talarico
12/15/00 02:00:44 PM

Appears This Way
On Original

Attachment 5 Asacol Safety Table

Appears This Way
On Original

Adverse Events Occurring in >=2 % in Either Treatment Group by Disease Severity
Studies 2000082, 2000083 and 2006444 Combined (Intent-to-treat)
(Page 1 of 2)

MedDRA SOC MedDRA HLT MedDRA Preferred Term	Mild		Moderate		Overall	
	2.4g/day Asacol (400 mg Tablet) (N=113) n (%)	4.8g/day Asacol (800 mg Tablet) (N=125) n (%)	2.4g/day Asacol (400 mg Tablet) (N=618) n (%)	4.8g/day Asacol (800 mg Tablet) (N=602) n (%)	2.4g/day Asacol (400 mg Tablet) (N=732) n (%)	4.8g/day Asacol (800 mg Tablet) (N=727) n (%)
Gastrointestinal disorders	19 (16.8%)	15 (12.0%)	83 (13.4%)	85 (14.1%)	102 (13.9%)	100 (13.8%)
Nausea and vomiting symptoms	5 (4.4%)	6 (4.8%)	19 (3.1%)	18 (3.0%)	24 (3.3%)	24 (3.3%)
Nausea	5 (4.4%)	6 (4.8%)	16 (2.6%)	14 (2.3%)	21 (2.9%)	20 (2.8%)
Vomiting	4 (3.5%)	1 (0.8%)	8 (1.3%)	9 (1.5%)	12 (1.6%)	10 (1.4%)
Gastrointestinal and abdominal pains (excl oral and throat)	5 (4.4%)	2 (1.6%)	19 (3.1%)	21 (3.5%)	24 (3.3%)	23 (3.2%)
Abdominal pain	4 (3.5%)	2 (1.6%)	13 (2.1%)	15 (2.5%)	17 (2.3%)	17 (2.3%)
Colitis (excl infective)	3 (2.7%)	0 (0.0%)	19 (3.1%)	18 (3.0%)	22 (3.0%)	18 (2.5%)
Colitis ulcerative	2 (1.8%)	0 (0.0%)	18 (2.9%)	17 (2.8%)	20 (2.7%)	17 (2.3%)
Dyspeptic signs and symptoms	2 (1.8%)	1 (0.8%)	4 (0.6%)	13 (2.2%)	6 (0.8%)	14 (1.9%)
Flatulence, bloating and distension	2 (1.8%)	3 (2.4%)	10 (1.6%)	8 (1.3%)	12 (1.6%)	11 (1.5%)
Gastrointestinal atonic and hypomotility disorders NEC	3 (2.7%)	0 (0.0%)	2 (0.3%)	3 (0.5%)	5 (0.7%)	3 (0.4%)
Infections and infestations	11 (9.7%)	14 (11.2%)	36 (5.8%)	39 (6.5%)	47 (6.4%)	53 (7.3%)
Upper respiratory tract infections	7 (6.2%)	8 (6.4%)	16 (2.6%)	21 (3.5%)	23 (3.1%)	29 (4.0%)
Nasopharyngitis	2 (1.8%)	4 (3.2%)	8 (1.3%)	14 (2.3%)	10 (1.4%)	18 (2.5%)
Sinusitis	4 (3.5%)	2 (1.6%)	3 (0.5%)	3 (0.5%)	7 (1.0%)	5 (0.7%)
Nervous system disorders	12 (10.6%)	10 (8.0%)	36 (5.8%)	35 (5.8%)	48 (6.6%)	45 (6.2%)
Headaches NEC	10 (8.8%)	8 (6.4%)	27 (4.4%)	27 (4.5%)	37 (5.1%)	35 (4.8%)
Headache	9 (8.0%)	8 (6.4%)	27 (4.4%)	26 (4.3%)	36 (4.9%)	34 (4.7%)
Neurological signs and symptoms NEC	3 (2.7%)	1 (0.8%)	3 (0.5%)	4 (0.7%)	6 (0.8%)	5 (0.7%)
Dizziness	3 (2.7%)	1 (0.8%)	3 (0.5%)	3 (0.5%)	6 (0.8%)	4 (0.6%)

N = number of patients within specified treatment.
n = number of patients in category and treatment group.
% =percentage of patients in category and treatment group: (n/N)*100.
One 2.4 g/day patient with an unknown disease severity was included in the overall category.
/ASACOL/CSS/ADHOC/aesum3.sas; SAS 8.2 HP 800 28APR08 15:43 f20jul07 TY1006.

Adverse Events Occurring in >=2 % in Either Treatment Group by Disease Severity
Studies 2000082, 2000083 and 2006444 Combined (Intent-to-treat)
(Page 2 of 2)

MedDRA SOC MedDRA HLT MedDRA Preferred Term	Mild		Moderate		Overall	
	2.4g/day Asacol (400 mg Tablet) (N=113) n (%)	4.8g/day Asacol (800 mg Tablet) (N=125) n (%)	2.4g/day Asacol (400 mg Tablet) (N=618) n (%)	4.8g/day Asacol (800 mg Tablet) (N=602) n (%)	2.4g/day Asacol (400 mg Tablet) (N=732) n (%)	4.8g/day Asacol (800 mg Tablet) (N=727) n (%)
General disorders and administration site conditions	4 (3.5%)	9 (7.2%)	20 (3.2%)	15 (2.5%)	24 (3.3%)	24 (3.3%)
Asthenic conditions	1 (0.9%)	3 (2.4%)	3 (0.5%)	2 (0.3%)	4 (0.5%)	5 (0.7%)
Fatigue	1 (0.9%)	3 (2.4%)	3 (0.5%)	1 (0.2%)	4 (0.5%)	4 (0.6%)
Febrile disorders	1 (0.9%)	4 (3.2%)	8 (1.3%)	1 (0.2%)	9 (1.2%)	5 (0.7%)
Pyrexia	1 (0.9%)	4 (3.2%)	8 (1.3%)	1 (0.2%)	9 (1.2%)	5 (0.7%)
Musculoskeletal and connective tissue disorders	5 (4.4%)	5 (4.0%)	13 (2.1%)	16 (2.7%)	18 (2.5%)	21 (2.9%)
Musculoskeletal and connective tissue signs and symptoms NEC	4 (3.5%)	3 (2.4%)	9 (1.5%)	10 (1.7%)	13 (1.8%)	13 (1.8%)
Back pain	3 (2.7%)	1 (0.8%)	4 (0.6%)	6 (1.0%)	7 (1.0%)	7 (1.0%)
Respiratory, thoracic and mediastinal disorders	5 (4.4%)	4 (3.2%)	18 (2.9%)	11 (1.8%)	23 (3.1%)	15 (2.1%)
Skin and subcutaneous tissue disorders	4 (3.5%)	2 (1.6%)	14 (2.3%)	11 (1.8%)	18 (2.5%)	13 (1.8%)
Rashes, eruptions and exanthems NEC	3 (2.7%)	2 (1.6%)	6 (1.0%)	4 (0.7%)	9 (1.2%)	6 (0.8%)
Rash	3 (2.7%)	2 (1.6%)	4 (0.6%)	4 (0.7%)	7 (1.0%)	6 (0.8%)
Investigations	2 (1.8%)	3 (2.4%)	7 (1.1%)	7 (1.2%)	9 (1.2%)	10 (1.4%)
Psychiatric disorders	1 (0.9%)	3 (2.4%)	4 (0.6%)	5 (0.8%)	5 (0.7%)	8 (1.1%)

N = number of patients within specified treatment.
n = number of patients in category and treatment group.
% =percentage of patients in category and treatment group: (n/N)*100.
One 2.4 g/day patient with an unknown disease severity was included in the overall category.
/ASACOL/CSS/ADHOC/aesum3.sas; SAS 8.2 HP 800 28APR08 15:43 f20jul07 TY1006.

Attachment 6: Cochrane review of oral 5-aminosalicylic acid for induction of remission in ulcerative colitis

37 Page(s) of
Copyright Material
have been Withheld from this
Portion of the Review.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-830

Procter & Gamble Pharmaceuticals
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol 800 (mesalamine) Delayed-Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 17, 2008. The purpose of the meeting was for P&G to provide the history and background of the application in order to help facilitate review, and gather any additional analyses needed by the agency.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 496-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

Appears This Way
On Original

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 17, 2008
TIME: 12:00 PM EST
LOCATION: FDA/CDER White Oak, Room 1311
APPLICATION: NDA 21-830
DRUG NAME: Asacol 800 (mesalamine) Delayed-Release Tablets
TYPE OF MEETING: Type C

MEETING CHAIR: John Hyde, M.D., Medical Team Leader

MEETING RECORDER: Heather Buck, Regulatory Project Manager

FDA ATTENDEES:

Donna Griebel, M.D., Division Director, Division of Gastroenterology Products
John Hyde, Ph.D., M.D., Medical Team Leader, Division of Gastroenterology Products
Anil Rajpal, M.D., Medical Officer, Division of Gastroenterology Products
Mike Welch, Ph.D., Deputy Division Director, Division of Biometrics 3
Milton Fan, Ph.D., Statistical Reviewer, Division of Biometrics 3
Sue-Chih Lee, Ph.D., Clinical Pharmacology Leader, Division of Clinical Pharmacology 3
Insook Kim, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Heather Buck, Regulatory Project Manager, Division of Gastroenterology Products

PROCTER & GAMBLE PHARMACEUTICALS ATTENDEES:

Nora Zorich, M.D., Ph.D., Research & Development, Procter & Gamble Pharmaceuticals
Lynne Tracey, Gastroenterology R&D, Procter & Gamble Pharmaceuticals
Kevin Malloy, Ph.D., Gastroenterology Research/Associate Director, Procter & Gamble Pharmaceuticals
Eileen King, Ph.D., Senior Directory, Biometrics & Statistical Sciences, Procter & Gamble Pharmaceuticals
Christian Bernhardt, Ph.D., Regulatory Affairs Director, Procter & Gamble Pharmaceuticals
Lawrence Goldkind, M.D., Staff Gastroenterologist, National Naval Medical Center, Bethesda, MD

BACKGROUND:

- October 22, 2004 – FDA received original NDA 21-830
- August 25, 2005 – FDA sent approvable action letter to P&G
- October 22, 2007 – FDA received Complete Response to action letter (Class 2 Resubmission)
- January 29, 2008 – FDA received Type C Meeting Request

MEETING OBJECTIVES:

The main objective is for P&G to provide the history and background of the application in order to help facilitate review, and gather any additional analyses needed by the agency.

DISCUSSION POINTS:

The discussion was focused on the background and history of the application. No new information was presented in the background package; it was a representation of the Complete Response the Agency received October 22, 2007. Dr. Goldkind presented a discussion of practical considerations in the use of mesalamine for UC from the clinical practice perspective. P&G presented copies of tables showing the endpoints and studies for which the 4.8 g/d dose showed numerical superiority over the 2.4 g/d dose. P&G also presented histograms showing the overlap in distribution of creatinine change for the two doses. Because the application was still under review, the Division was not able to provide a definite response to questions about the regulatory conclusions to be drawn from the clinical data. The Division welcomed P&G's offer to provide additional analyses if needed. No formal agreements were reached.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

Four handouts were provided by P&G during the meeting; each of these had already been submitted in the Complete Response. These were the following: (1) a tabular summary of Week 6 efficacy results (moderate disease population of Studies 2000082, 2000083, and 2006444); (2) a tabular summary of Week 3 efficacy results (moderate disease population of Studies 2000082, 2000083, and 2006444); (3) a mountain plot showing percent change in creatinine from baseline to final value by treatment group (combined intent-to-treat populations of Studies 2000082, 2000083 and 2006444); (4) American College of Gastroenterology guidelines for the treatment of ulcerative colitis (*Kornbluth A, Sachar DB, "Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee." Am J Gastroenterol. 2004 Jul;99(7):1371-85).*

Table 2.7.3.1
Summary of Efficacy Endpoints at Week 6
Studies 2000082, 2000083 and 2006444
(Patients with Moderate Disease [PGA=2] at Baseline)

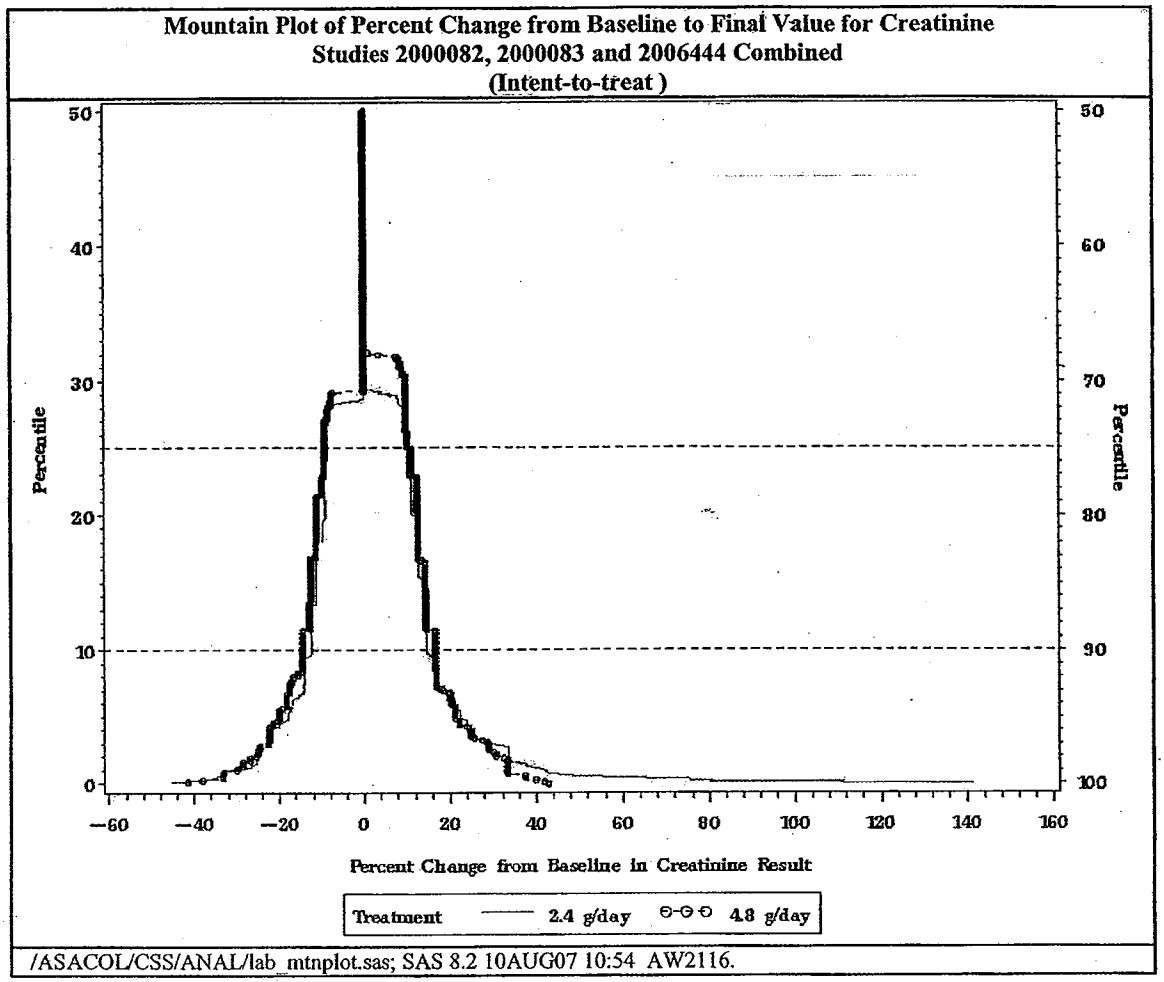
	Study 2000083		Study 2000082		Study 2006444	
Category	2.4 g/day	4.8 g/day	2.4 g/day	4.8 g/day	2.4 g/day	4.8 g/day
Randomized (Total) Moderate ITT (Total) Moderate ITT – analyzable (Total)	154 96 93	147 (301) 84 (180) 76 (169)	195 139 130	191 (386) 129 (268) 124 (254)	383 383 366	392 (775) 389 (772) 369 (735)
Treatment Success (Set to Failure Analysis)	57% (55%)	**72%* (65%)**	59% (55%)	**72%* (69%*)**	69% (66%)	**74% (70%)**
Complete Remission Partial Response	11% 46%	**20%** **53%**	18% 42%	**20%** **52%**	5% 63%	3% **71%**
Stool Frequency (SF) Improvement	70%	**78%**	71%	**74%**	74%	**79%**
Rectal Bleeding (RB) Improvement	75%	**87%**	77%	**79%**	80%	**84%**
Sigmoidoscopy Improvement	66%	**84%***	69%	**75%**	31%	30%
Physician's Global Assessment (PGA) Improvement	73%	**88%***	73%	**83%**	73%	**79%**
Patient's Functional Assessment (PFA) Improvement	70%	**76%**	71%	70%	72%	**76%**
Clinical Remission (SF AND RB = 0)	38%	**48%**	42%	40%	35%	**43%***
Change from Baseline in UCDAI – Last Observation Carried Forward Analysis	-2.8	**-3.8***	-3.1	**-3.6**	-3.1	**-3.3**
Treatment Success – Left-Sided Disease (Set to Failure Analysis)	58% (56%)	**74% (67%)**	60% (57%)	**71% (68%)**	70% (67%)	**75% (72%)**

*p<0.05; 4.8 g/day compared with 2.4 g/day.
Bold and Highlighted Text show where Asacol 800 (4.8 g/day) is numerically better than Asacol (2.4 g/day).
NA=not applicable.

Table 2.7.3.2
Summary of Efficacy Endpoints at Week 3
Studies 2000082, 2000083 and 2006444
(Patients with Moderate Disease [PGA=2] at Baseline)

	Study 2000083		Study 2000082		Study 2006444	
Category	2.4 g/day	4.8 g/day	2.4 g/day	4.8 g/day	2.4 g/day	4.8 g/day
Treatment Success (Set to failure)	54% (53%)	61% (55%)	52% (49%)	**61% (59%)**	NA	NA
Stool Frequency (SF) Improvement	58%	66%	61%	**64%**	66%	**76%***
Rectal Bleeding (RB) Improvement	68%	73%	64%	**75%**	77%	**78%**
Sigmoidoscopy Improvement	57%	60%	58%	**61%**	NA	NA
Physician's Global Assessment (PGA) Improvement	67%	73%	62%	**71%**	NA	NA
Patient's Functional Assessment (PFA) Improvement	67%	63%	58%	57%	64%	71%
Clinical Remission (SF AND RB = 0)	27%	32%	25%	**26%**	18%	**25%***
Treatment Success – Left-Sided Disease (Set to failure)	52% (51%)	62% (56%)	54% (51%)	**58% (55%)**	NA	NA

*p<0.05; 4.8 g/day compared with 2.4 g/day.
Bold and Highlighted text show where Asacol 800 (4.8 g/day) is numerically better than Asacol (2.4 g/day).
NA=not applicable; sigmoidoscopy was not assessed at Week 3 in Study 2006444



The percent change from baseline to final value (patients who withdrew and week six completers) are very similar for creatinine values.

Appears This Way
On Original

15 Page(s) of
Copyright Material
have been Withheld from this
Portion of the Review.

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

/s/

Heather G Buck
4/22/2008 12:53:16 PM

John Hyde
4/22/2008 01:59:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

DISCIPLINE REVIEW LETTER

Procter & Gamble Pharmaceuticals, Inc.
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs, GI Category
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-8462

Dear Dr. Bernhardt:

Please refer to your October 22, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol® 800 (mesalamine) Delayed-Release Tablets.

We also refer to your October 22, 2007, complete response to the August 29, 2005, action letter.

We further refer to our letter dated August 1, 2005, where we informed you that the proposed tradename, Asacol 800, was found to be acceptable. After further review of this tradename, we now find it unacceptable for the following reasons:

> The results of the Proprietary Name Risk Assessment and failure mode and effect analysis (FMEA) found that the proposed name, Asacol 800, has potential for confusion with the currently marketed Asacol product due to identical root names, overlapping frequency of administration (three times a day), and the possibility of an achievable strength, when two Asacol 400 mg tablets may be substituted for one Asacol 800. This is especially problematic as the two products are not bioequivalent and have different indications of use. Marketing this product under a separate name offers less opportunity for errors in comparison to marketing it under the same name.
>
> Therefore, we request that you submit an alternate name for this product. We recommend that you submit two alternate names for review, and indicate your primary and secondary choice.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we

may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Heather Buck, Regulatory Project Manager, at 301-796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Brian Strongin
4/18/2008 10:19:15 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 4/16/2008

TO: Kristen Everett, Regulatory Project Manager
Rajpal, Medical Officer

FROM: Khairy Malek, Medical Officer
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-830

APPLICANT: Procter & Gamble Pharmaceuticals, Inc.

DRUG: Asacol 800 (mesalamine) Delayed Release Tablets

NME: No

THERAPEUTIC CLASSIFICATION: Class 2 resubmission-6 month

INDICATIONS: 1. Treatment of patients with moderately active Ulcerative Colitis

CONSULTATION REQUEST DATE: November 28, 2007

DIVISION ACTION GOAL DATE: April 22, 2008

PDUFA DATE: April 22, 2008

1. BACKGROUND:

Asacol 400 mg tablet is an approved drug as a delayed-release dosage form. The new study is to evaluate a new tablet formulation containing 800 mg of mesalamine in comparison with the 400 mg tablets. The proposed indication is the treatment of moderately active ulcerative colitis.

The objective of this study is to confirm the clinical benefit of Asacol 4.8 g/day in comparison with Asacol 2.4 g/day for the treatment of moderately active ulcerative colitis. The comparison is to assess the non-inferiority of the 4.8 g/day dose with the 2.4 g/day dose and if confirmed, then to assess its superiority.

There was one protocol used in this study which is Protocol #2006444.

II. RESULTS:

Name of Clinical Investigator (CI)	Location	Inspection Date	Final Classification
Jeffrey Axler, M.D. Site # 103188	Toronto, ON, Canada	April 14 - 16, 2008	NAI (pending)
David Stanton, M.D. Site # 103208	Orange, CA	January 30 – February 13, 2008	VAI
Arthur Poch, M.D.	Shreveport, LA	February 11 - 13, 2008	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unacceptable.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. Jeffrey Axler, M.D.-Site 103188
2065 Finch Ave. West, Toronto, ON, Canada
The following information is based on personal discussion with the field investigator. If any violation is observed after receiving the EIR, it will be reported separately.

   a. What was inspected: At this site 13 subjects were enrolled, 10 completed the study and 3 had early termination: subject #4001 and #4002, due to lack of efficacy; and #4005 because of flatulence and abdominal pain. The field investigator reviewed the records of all subjects in the study. There were no limitations to the inspection.

   b. General Observation/Commentary:
   The inspection revealed no violations of the federal regulations.

   c. Assessment of data integrity:
   The data from this study can be used in support of the NDA.

2. David Stanton, M.D.-Site 103208
   505 S. Main St., Orange County, CA

   a. What was inspected: At this site 6 subjects were randomized, 5 completed the study and 1 withdrew. The field investigator reviewed the records of all subjects in the study. There were no limitations to the inspection.

   b. General observations/commentary:
   The inspection revealed one protocol violation in that subject #4001 was enrolled before the result of the serum creatinine was received. The CI responded that he received the result orally.

   One informed consent violation was that for subject #4008, the blood sample was drawn almost 4 weeks before signing the informed consent.
   Also, an inaccurate record was found in the number of tablets returned for subject #4003.

   c. Assessment of data integrity:
   These violations would not affect the integrity of the data. The data from this site can be used in support of the NDA.

3. Arthur Poch, M.D.-Site 103194
   3217 Mabel St., Shreveport, LA

   a What was inspected: At this site 5 subjects were enrolled and 4 completed the study. The field investigator reviewed the records of all subjects in the study. There were no limitations to the inspection.

   b. General observations/commentary:
   The inspection revealed one protocol violation in that subject #4008 was enrolled against an exclusion criterion as the subject was using fish oil as a nutritional supplement.

   c. Assessment of data integrity:
   The one violation noted above would not affect the validity of the data. The data from this site can be used in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from the study sites inspected are valid. The data from the 3 sites can be used in support of the NDA.

{See appended electronic signature page}
Khairy Malek, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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

/s/

Khairy Malek
4/16/2008 11:29:31 AM
MEDICAL OFFICER

Constance Lewin
4/16/2008 11:35:47 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

INFORMATION REQUEST LETTER

Procter & Gamble Pharmaceuticals
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

Please refer to your October 22, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol 800 (mesalamine) Delayed Release Tablets.

We also refer to your Revised Container and Carton Labels submission (Amendment 24) received on March 4, 2008.

We are reviewing your container and carton labels and have the following request regarding font:

- Use lower case letters for "Mesalamine"
- Revise "Delayed Release Tablets" to be the same size as "Mesalamine"

We request that you resubmit the revised container and carton labels by Monday April 7, 2008 in order for us to continue our evaluation of your NDA.

If you have any questions, call Heather Buck, Regulatory Project Manager, at 301-796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Julieann DuBeau
4/7/2008 04:18:14 PM
Signing for Brian Strongin

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

INFORMATION REQUEST LETTER

Procter & Gamble Pharmaceuticals
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

Please refer to your October 22, 2004 new drug application (NDA) submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol 800 (mesalamine) Delayed Release Tablets.

We also refer to your labeling submission (Amendment 22) received on February 13, 2008.

We are reviewing the statistical section of your submission and have the following request regarding analysis of one of your secondary efficacy endpoints:

- For Protocol 2006444, patient improvement at Week 3 is pre-specified as one of the secondary efficacy endpoints. However, you have failed to include results from your analysis of patient improvement at Week 3 in the clinical report. Please provide statistical analysis for patient improvement at Week 3 for protocol 2006444.

We are reviewing your proposed Asacol 800 package insert from your submission and have the following request:

- Section 6.2 includes a number of additional adverse events that are not in the corresponding section of the currently approved Asacol labeling. We request that you limit inclusion of adverse events in Section 6.2 of the proposed Asacol 800 labeling to those events for which there is some basis to believe that there is a causal relationship between occurrence of the event and use of the drug. Please propose labeling revisions to Section 6.2, and provide your rationale for including each adverse event that is not included in the corresponding section of the currently approved Asacol labeling. (See the guidance document *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* for a broader discussion of this issue.)

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Heather Buck, Regulatory Project Manager, at 301-796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Brian Strongin
4/4/2008 11:18:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

INFORMATION REQUEST LETTER

Procter & Gamble Pharmaceuticals
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

Please refer to your October 22, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol 800 (mesalamine) Delayed Release Tablets.

We also refer to your Amendment 023 dated February 22, 2008.

We are reviewing the statistical section of your submission and have the following requests regarding analysis of your primary efficacy endpoint:

According to your submission dated December 7, 2007, a total of 552 patients had enrolled in the study by March 2, 2007. This number is well over the 470 patients required by the protocol. You amended your protocol to add 300 more patients to increase the sample size to 770 patients. We understand this enrollment increase was planned to provide sufficient power to test the added non-inferiority hypothesis. However, we consider this to be a post-hoc change to your study design. In order to explore the sensitivity of your efficacy results to the sample size change, we recommend you perform additional computations of the 95% confidence interval of treatment difference as noted below:

1. Compute a 95% confidence interval for treatment difference using the Cochran-Mantel-Haenszel (CMH) method[1] adjusting for enrollment before and after the amendment.

2. Compute a 95% confidence interval for treatment difference using the adaptive adjustment method[2] adjusting for enrollment before and after amendment.

---

[1] Zhao, PL, Troxell, JK, Quan, H, Lee, M, and Bolognese, JA. (2001) "Confidence Interval for the Difference in Binomial Proportions from Stratified 2x2 Samples", *Proceeding of the Annual Meeting of the ASA, August 5-9, 2001.*

[2] Cui, L, Hung, HMJ, Wang, S (1999) "Modification of sample size in group sequential clinical trials", *Biometrics 55, 853-857.*

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Heather Buck, Regulatory Project Manager, at 301-796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Brian Strongin
3/21/2008 09:57:19 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

Procter & Gamble Pharmaceuticals Inc.
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol 800 (mesalamine) Delayed Release Tables.

We also refer to your January 28, 2008, correspondence received January 29, 2008, requesting a meeting to discuss the review of Complete Response [Amendment 20 (Asacol® 800 @ 4.8 g/day)].

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Monday March 17, 2008
Time: 12 PM – 1 PM EST
Location: FDA White Oak Campus, Conference Room 1311, Building 22, 10903 New Hampshire Avenue, Silver Spring, Maryland 20903

Tentative CDER Participants:

- Donna Griebel, M.D., Division Director, Division of Gastroenterology Products
- Joyce Korvick, M.D., M.P.H., Deputy Director, Division of Gastroenterology Products
- John Hyde, Ph.D., M.D., Medical Team Leader, Division of Gastroenterology Products
- Anil Rajpal, M.D., Medical Officer, Division of Gastroenterology Products
- Mike Welch, Ph.D., Acting Team Leader, Division of Biometrics 3
- Milton Fan, Ph.D., Statistical Reviewer, Division of Biometrics 3
- Marie Kowblansky, Ph.D., Pharmaceutical Assessment Leader, Office of New Drug Quality Assessment
- Maria Ysern, M.Sc., Chemistry Reviewer, Office of New Drug Quality Assessment
- Heather Buck, MS, MBA, Regulatory Project Manager, Division of Gastroenterology Products
- Kristen Everett, R.N., Regulatory Project Manager, Division of Gastroenterology Products

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at heather.buck@fda.hhs.gov so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Heather Buck at x 61413, or Doris Garrison (Division Secretary) at x 60896.

Please come prepared with a proposed agenda. You may submit this agenda via email or fax to heather.buck@fda.hhs.gov, (301) 796-9905.

If you have any questions, call me at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Heather G Buck
2/14/2008 01:44:19 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

INFORMATION REQUEST LETTER

Procter & Gamble Pharmaceuticals
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

Please refer to your October 22, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol 800 (mesalamine) Delayed Release Tables.

We also refer to your December 7 2007, submission containing the information requested in the Information Request Letter sent to you on December 4, 2007.

We are reviewing the Statistical section of your submission and have the following requests regarding analysis of your primary efficacy endpoint:

1. Please provide justification of the 10% non-inferiority margin
2. Please provide the 95% confidence interval adjusting for before and after amendment

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Heather Buck, Regulatory Project Manager, at 301-796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Appears This Way
On Original

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

/s/

Brian Strongin
2/11/2008 08:34:23 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

INFORMATION REQUEST LETTER

Procter & Gamble Pharmaceuticals, Inc.
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

Please refer to your October 22, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol (mesalamine) 800 mg Delayed-Release Tablets.

Please also refer to your October 22, 2007, submission containing a complete response to the August 29, 2005, approvable letter.

We are reviewing the Physician's Labeling Rule format of the package insert included in your submission and have the following comments and information requests. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential

1 Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Administrative-*_____

b(4)

Please address the identified deficiencies/issues and re-submit labeling by February 14, 2008. This updated version of labeling will be used for further labeling discussions.

If you have any questions, call Heather Buck, Regulatory Project Manager, at 301-796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Brian Strongin
1/17/2008 09:11:57 AM

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 21-830

Name of Drug: ASACOL®800 (mesalamine) delayed-release tablet for oral administration

Applicant: Proctor & Gamble Pharmaceuticals, Inc.

Material Reviewed:

Submission Date: October 22, 2007

Receipt Date: October 22, 2007

Submission Date of Structure Product Labeling (SPL): October 22, 2007

Type of Labeling Reviewed: WORD

Background and Summary

Procter & Gamble received an approvable action for NDA 21-830 on August 29, 2005. They have conducted an additional clinical trial and have now submitted a complete response to the approvable letter. The proposed indication for this NDA is the treatment of patients with moderately active ulcerative colitis. P&G has conducted a Phase 3 study entitled: ASCEND III: Assessing the Safety and Clinical Efficacy of a New Dose (Asacol 800 mg tablets/4.8g/day) A double-blind, randomized, 6-week, parallel-group clinical trial to assess the safety and efficacy of Asacol® 4.8g/day (800 mg mesalamine tablet) versus Asacol 2.4g/day (400 mg mesalamine tablet) for the treatment of moderately active ulcerative colitis.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

1 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

b(4)

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by February 14, 2008. This updated version of labeling will be used for further labeling discussions.

Heather Buck
Regulatory Project Manager
Division of Gastroenterology Products

Supervisory Comment/Concurrence:

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products

Drafted: HB 1/7/08
Revised/Initialed: BS 1/15/08, HB 1/15/08
Finalized: HB 1/15/08
Filename: CSO Labeling Review Template (updated 1-16-07).doc
RPM LABELING REVIEW

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

/s/

Heather G Buck
1/17/2008 07:57:49 AM
CSO

Brian Strongin
1/17/2008 09:12:37 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

INFORMATION REQUEST LETTER

Procter & Gamble Pharmaceuticals, Inc.
Attention: Christian Bernhardt, Ph. D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

Please refer to your October 22, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol 800 (mesalamine) Delayed Release Tablets.

Please also refer to your October 22, 2007, submission containing a complete response to the August 29, 2005, approvable letter.

We are reviewing the statistical section of your October 22, 2007 submission, and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide information on patient enrollment at the time that study protocol 2006444 titled "ASCEND III" was amended to increase the sample size to 770 patients and to add the test for non-inferiority to the primary efficacy endpoint.

2. Please provide demographic and baseline information by treatment group before and after the protocol amendment.

3. Please provide analyses of efficacy results before and after the protocol amendment.

4. Please provide analyses of efficacy results for the primary efficacy endpoint as defined in study protocol 2000082 [study title: "A double-blind, randomized, 6-week, parallel-group design clinical trial to assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) versus Asacol 2.4 g/day (400 mg tablet) for the treatment of moderately active ulcerative colitis"], and study protocol 2000083 [study title: "A double-blind, randomized 6 week, parallel-group design clinical trial in patients with mildly to moderately active ulcerative colitis to assess the safety and efficacy of Asacol 4.8 g/day (800 mg tablet) versus Asacol 2.4 g/day (400 mg tablet)"].

If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Julieann DuBeau
12/4/2007 04:18:57 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

Procter & Gamble Pharmaceuticals, Inc.
Attention: Christian A. Bernhardt, Ph.D.
Director, Regulatory Affairs for GI Category
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Bernhardt:

We acknowledge receipt on October 22, 2007 of your October 22, 2007 resubmission to your new drug application for Asacol 800 (mesalamine) Delayed Release Tablets.

We consider this a complete, class 2 response to our August 29, 2005, action letter. Therefore, the user fee goal date is April 22, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver for pediatric patients less than 5 years of age and the deferral for patients 5 to 17, granted on October 19, 2005, for the pediatric study requirement for this application.

If you have any questions, call me at (301) 796-0453.

Sincerely,

{See appended electronic signature page}

Kristen Everett, R.N.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Appears This Way
On Original

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

/s/

Kristen Everett
11/5/2007 11:27:50 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-830
IND 26,093

Procter & Gamble Pharmaceuticals, Inc.
Attention: Kevin T. Roll, Pharm.D.
Director, U.S. Regulatory Affairs
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Roll:

Please refer to your New Drug Application (NDA) submitted under section 505(b) and your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Asacol® 800 (mesalamine) Delayed-Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 3, 2006. The purpose of the meeting was to discuss your proposals to support registration of Asacol® 800 (mesalamine) delayed-release tablets at 4.8 g/day for the treatment of patients with moderately active ulcerative colitis.

b(4)

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0453.

Sincerely,

{See appended electronic signature page}

Kristen Everett, R.N.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Memorandum of Meeting Minutes

Meeting Date:	February 3, 2006
Meeting Time:	1:00 pm – 2:00 pm
Meeting Location:	FDA White Oak Campus, Conference Room 1313
Application Number:	NDA 21-830
Drug Name:	Asacol® 800 (mesalamine) Delayed-Release tablets
Type of Meeting:	Type B
Meeting Chair:	Ruyi He, M.D., Medical Team Leader.
Meeting Recorder:	Kristen Everett, R.N. Regulatory Project Manager

BETWEEN:

Procter and Gamble Pharmaceuticals, Inc.

Ms. Lynne M. Tracey, Vice President, Global Regulatory Affairs
Chris Bernhardt, Ph.D., Associate Director, Regulatory Affairs
Steven Jungerwirth, M.D., Vice President, Global Clinical Development & Operations
Bruce Yacyshyn, M.D., Director, North American Clinical Development
Eileen King, Ph.D., Senior Director, Biometrics and Statistical Sciences
Kevin Malloy, Ph.D., Project Leader and Senior Director, New Drug Development
Joan Meyer, Ph.D., Project Leader and Senior Director, New Drug Development

AND

Division of Gastroenterology Products (DGP)
Brian E. Harvey, M.D., Ph.D., Director
Joyce Korvick, M.D., M.P.H., Deputy Director
Ruyi He, M.D., Medical Team Leader
Fathia Gibril, M.D., Medical Reviewer
Kristen Everett, R.N., Regulatory Project Manager

Division of Biometrics II
Milton Fan, Ph.D., Biostatistics Reviewer

PURPOSE:

Type B meeting to discuss your proposals to support registration of Asacol® 800 (mesalamine) Delayed-Release Tablets at 4.8 g/day for the treatment of patients with moderately active ulcerative colitis

b(4)

BACKGROUND:

On December 9, 2005, Procter & Gamble Pharmaceuticals, Inc. submitted a Type B meeting request to discuss your proposals to support registration of Asacol® 800 (mesalamine)

Delayed-Release Tablets at 4.8 g/day for the treatment of patients with moderately active ulcerative colitis,

b(4)

On January 5, 2006, Procter & Gamble Pharmaceuticals, Inc. submitted a background package to the Agency.

On January 31, 2006, responses to the questions contained in the meeting package were faxed to Procter & Gamble Pharmaceuticals, Inc.

DISCUSSION:

Response to sponsor's questions and additional meeting discussion.

Questions from Procter & Gamble Pharmaceuticals for February 3rd, 2006 Meeting

IND 26,093 with cross reference to NDA #21-830
Asacol®800 (mesalamine) Delayed-Release Tablets

The objective of this meeting is to discuss 1) a proposal to support registration via NDA 21-830 for the Asacol 800 mg tablet at 4.8 g/day for the treatment of patients with moderately active ulcerative colitis

b(4)

studies will be conducted under IND 26,093.

Treatment of Moderately Active Ulcerative Colitis

1. The proposed primary efficacy measure in the planned study will be based on the Physician Global Assessment, sigmoidoscopy, rectal bleeding, and stool frequency as in studies 2000082 and 2000083 but will exclude the Patient Functional Assessment. Will this be a sufficient measure of effectiveness for the Division to make a decision regarding approvability in the context of Studies 2000082 and 2000083?

   Response:
   The proposed primary efficacy measure appears to be acceptable. However, we recommend that you collect and analyze PFA data as a secondary endpoint.

   Additional Discussion:
   We discussed other potential assessments for use as the primary endpoint and the sponsor will have internal discussions on potential benefits of using alternative scores (e.g., MAYO score)

2. The ITT study population defined in this study for the primary efficacy analysis will be those patients who are randomized and receive at least 1 dose of study drug and for whom the treatment outcome at week 6 can be determined. Those patients who are randomized but do not receive any study drug or whose treatment outcome cannot be determined will not be included in the primary efficacy analyses and will not be included in the ITT study population. Will this be acceptable to the Division?

Response:
No. The principal of ITT analysis is to include all randomized patients who received at least one dose of study drug regardless of their treatment outcome. However, you can use the proposed method as an additional analysis.

b(4)

b(4)

Response:
Approvability of your NDA will be based upon the complete review of the data submitted and cannot be determined at this time.

b(4)

Additional Discussion:

b(4)

the final choice of study design will be determined by the sponsor. If the results of any new trial showed a treatment effect in one specific gender that was not seen in the entire population, this could lead to a public discussion of the utility of this drug and a FDA Advisory Committee. The statistical team suggests that the method published by Simon, et al, may provide the necessary statistical rigor in order to demonstrate a treatment effect. Please refer to: Freidlin B and Simon R. Adaptive signature design: An adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients. Clinical Cancer Research 11:7872-8, 2005.

4. In order to provide quality control, a central sigmoidoscopy reader will be viewing the baseline and Week 6 sigmoidoscopy tapes. P&GP is proposing that only the investigators assessment of ulcerative colitis disease activity as confirmed by the sigmoidoscopy procedures will be used for the primary and secondary analyses. The sigmoidoscopic score

evaluated by the central lab will not be used for any efficacy evaluation or analyses. Will this be acceptable to the Division?

Response:
Yes, your proposal appears to be acceptable.

5. P&GP estimates that it would require approximately 35 months to recruit the 440 patients from sites entirely located North America. Consequently, P&GP plans to expand recruitment beyond North America to include patients from Central and Eastern Europe, Russia and Ukraine. We anticipate that this will enable patients to be recruited in a more reasonable time frame (~ 8 months). We would manage recruitment to ensure that no less than 20% of the patient population would be derived from North America. Will this be acceptable to the Division?

Response:
Yes, your proposal appears acceptable at this time.

6. Does the Division have any specific feedback on the design of this study?

Response:
We are willing to offer our comments when we receive and review your full protocol. However, your proposed study may benefit from reexamining your existing data regarding a potential for weight based dosing schedule.

2 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Administrative-*_____

Success Rates in Female Patients with Moderate Disease at Baseline

Females		≤ 59 kg		>59 to ≤ 67 kg		>67 to ≤ 82 kg		> 82 kg	
		n	Rate	*n*	Rate	*n*	Rate	*n*	Rate
2000082	2.4	*13*	62%	*10*	56%	*14*	70%	*11*	61%
	4.8	*10*	59%	*13*	65%	*15*	63%	*11*	79%
2000083	2.4	*9*	64%	*6*	60%	*10*	59%	*7*	64%
	4.8	*4*	36%	*6*	55%	*6*	75%	*10*	71%
Combined	2.4	*22*	63%	*16*	57%	*24*	65%	*18*	62%
	4.8	*14*	50%	*19*	61%	*21*	66%	*21*	75%

Success Rates in Male Patients with Moderate Disease at Baseline

Males		≤ 76 kg		>76 to ≤ 84 kg		>84 to ≤ 92 kg		> 92 kg	
		n	Rate	*n*	Rate	*n*	Rate	*n*	Rate
2000082	2.4	*5*	38%	*5*	36%	*6*	43%	*13*	62%
	4.8	*13*	72%	*12*	80%	*6*	86%	*9*	64%
2000083	2.4	*5*	45%	*2*	25%	*11*	69%	*3*	33%
	4.8	*5*	63%	*9*	82%	*11*	79%	*4*	57%
Combined	2.4	*10*	42%	*7*	32%	*17*	57%	*16*	53%
	4.8	*18*	69%	*21*	81%	*17*	81%	*13*	62%

Assumptions:

True remission rate in 400 1.6 g/day group is 70%
True remission rate in 800 1.6 g/day group is 70%

Two-sided 95% confidence interval will be used for non-inferiority test

Sample size quoted is the number of subjects per group to achieve 90% power

Non-inferiority bound	Sample Size per group for 90% power	Maximum Observed Difference that will meet NI criteria
10%	442	3.9%
11%	365	4.3%
12%	307	4.7%
13%	262	5.1%
14%	226	5.5%
15%	197	5.9%

Maximum Difference that we can observe and still attain bound if we observe ~70% rate in each group

1 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Administrative-*_____

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

/s/

Kristen Everett
3/1/2006 12:16:52 PM

Ruyi He
3/2/2006 10:25:42 AM