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

studies will be conducted under IND 26,093. b(4)

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.

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)

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

1 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
1/31/2006 11:22:07 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

Procter & Gamble Pharmaceuticals, Inc.
Attention: Mark S. Leusch, Ph.D.
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Leusch:

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 August 16, 2005. The purpose of the meeting was to further clarify and discuss the Division's review issues for NDA 21-830 that were shared with Procter & Gamble Pharmaceuticals, Inc. in the teleconference on August 11, 2005.

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) 443-8347.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Appears This Way
On Original

Memorandum of Meeting Minutes

Meeting Date:	August 16, 2005
Meeting Time:	10:00 am – 11:00 am
Meeting Location:	Teleconference
Application Number:	NDA 21-830
Drug Name:	Asacol 800 (mesalamine) Delayed-Release tablets
Type of Meeting:	Type A
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
Dr. Mark Leusch, Associate Director, Regulatory Affairs
Dr. Steven Jungerwirth, Director, Global Clinical Development & Operations

AND

Division of Gastroenterology Products (DGP), HFD-180
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
Ronald Honchel, Ph.D., Pharmacology Reviewer
Maria Ysern, Ph.D., Chemistry Reviewer
Monika Houstoun, Pharm.D., Regulatory Project Manager
Kristen Everett, R.N., Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870
Suliman Al Fayoumi, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics II, HFD-715
Stella Grosser, Ph.D., Statistics Team Leader
Milton Fan, Ph.D., Biostatistics Reviewer

PURPOSE:

Type A meeting to clarify information discussed at August 11, 2005 Teleconference with the Procter & Gamble Pharmaceuticals, Inc. representatives not available for August 11, 2005 teleconference.

BACKGROUND:

On October 24, 2004, Procter & Gamble Pharmaceuticals, Inc. submitted NDA 21-830 for Asacol 800® (mesalamine) Delayed-Release Tablets for the indication of moderately active ulcerative colitis.

On January 7, 2005, the Agency sent a Filing Communication letter stating that potential statistical review issues were identified for studies 2000083 and 2000082.

On August 11, 2005, a teleconference occurred between Procter & Gamble Pharmaceuticals, Inc. and the Agency to discuss and clarify any outstanding statistical questions regarding their clinical studies submitted as part of their NDA 21-830.

On August 15, 2005, Procter & Gamble Pharmaceuticals, Inc. contacted the Division to request a Type A teleconference meeting to clarify issues discussed in the August 11, 2005 teleconference between Procter & Gamble Pharmaceuticals, Inc. and the Agency. The meeting request was granted via telephone on August 15, 2005.

On August 16, 2005, the Sponsor emailed the meeting background information.

DISCUSSION:

The Agency clarified the statistical issues that were discussed at the August 11, 2005 Teleconference. The Agency also stated that the reviews were being completed and that no additional information was needed at this time.

Minutes Preparer: _____
Kristen Everett, R.N.
Regulatory Project Manager

Chair Concurrence: _____
Ruyi He, M.D.
Medical Team Leader

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
9/9/2005 11:06:27 AM

Ruyi He
9/9/2005 03:55:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

Procter & Gamble Pharmaceuticals, Inc.
Attention: Mark S. Leusch, Ph.D.
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Leusch:

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 August 11, 2005. The purpose of the meeting was to discuss statistical review issues identified for studies 2000083 and 2000082 in the Division's filing communication letter.

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) 443-8347.

Sincerely,

{See appended electronic signature page}

Kristen Everett, RN
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:	August 11, 2005
Meeting Time:	3:00 pm – 4:00 pm
Meeting Location:	Teleconference
Application Number:	NDA 21-830
Drug Name:	Asacol 800® (mesalamine) Delayed-Release Tablets.
Type of Meeting:	Type C
Meeting Chair:	Ruyi He, M.D., Medical Team Leader
Meeting Recorder:	Kristen Everett, R.N., Regulatory Project Manager

BETWEEN:

Procter and Gamble Pharmaceuticals, Inc.

Dr. Linda Law, Medical Director and Project Leader, Medical and Clinical Development
Dr. Eileen King, Senior Director, Biometrics and Statistical Sciences
Dr. Chyon-Hwa Yeh, Principal Statistician, Biometrics and Statistical Sciences
Dr. Gary Thompson, Senior Director, Clinical Pharmacology and Pharmacokinetics
Dr. Gino Regalli, Senior Director, Medical and Clinical Development
Dr. Nancy Smith-Hall, Senior Pharmacovigilance Manager, Clinical Pharmacovigilance
Dr. Mike Winrow, Research Fellow, Drug Safety Assessment
Ms. Wendy Sauber, Senior Director, Regulatory Affairs
Ms. Felicia Coates, Director, Regulatory Affairs
Dr. Mark Leusch, Associate Director, Regulatory Affairs
Dr. Walter Hirth, Associate Director, Regulatory Affairs – CMC
Dr. Jane McGregor, Senior Director, Regulatory Affairs - DDMAC

AND

Division of Gastroenterology Products (DGP), HFD-180
Brian E. Harvey, M.D., Ph.D., Director
Joyce Korvick, M.D., M.P.H., Deputy Director
Ruyi He, M.D., Medical Team Leader
Ronald Honchel, Ph.D., Pharmacology Reviewer
Maria Ysern, Ph.D., Chemistry Reviewer
Monika Houstoun, Pharm.D., Regulatory Project Manager
Kristen Everett, R.N., Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870
Suliman Al Fayoumi, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics II, HFD-715
Stephen Wilson, Ph.D., Deputy Division Director
Stella Grosser, Ph.D., Statistics Team Leader
Milton Fan, Ph.D., Biostatistics Reviewer

Office of Biostatistics, HFD-700
Robert O'Neill, Ph.D., Director

PURPOSE:

To discuss statistical review issues identified for studies 2000083 and 2000082 in the Division's filing communication letter.

BACKGROUND:

On October 24, 2004, Procter & Gamble Pharmaceuticals, Inc. submitted NDA 21-830 for Asacol 800® (mesalamine) Delayed-Release Tablets for the indication of moderately active ulcerative colitis.

On January 7, 2005, the Agency sent a Filing Communication letter stating that potential statistical review issues were identified for studies 2000083 and 2000082.

On June 16, 2005, Procter and Gamble Pharmaceuticals, Inc. submitted a Type C meeting request to discuss and clarify any outstanding statistical questions regarding their clinical studies submitted as part of their NDA 21-830.

On August 9, 2005 a list of questions was received by the Agency via email.

DISCUSSION:

Responses to the questions posed by the sponsor.

P&GP Questions for the 11 August 2005 teleconference with the Division

1. The Division cited potential review issues for Studies 2000082 and 2000083 in the filing review communication letter received 13 January 2005. P&GP provided response to these potential review issues in Amendment #3 submitted on 14 January 2005 and requested Division comment to our response.

   Given the Division's recommended labeling for the Clinical Studies section of the Asacol 800 package insert, it appears these potential review issues have been resolved. P&GP has found FDA's recommended labeling acceptable apart from a few points of clarification.

P&GP wishes to confirm that the potential review issues cited in FDA's filing communication letter have been resolved.

The Agency discussed with Procter and Gamble Pharmaceuticals, Inc. that the statistical issues have not been resolved. The Agency further clarified that it was not the study design per se that was flawed, but rather the results were not robust enough to stand alone as a single study. The efficacy and statistical issues continue to be a concern. The Sponsor asked when they could expect to have input from the Agency, to which the Agency responded that they would receive an action letter on August 29, 200,5, which is the PDUFA date.

2. **P&GP would like to the Division to comment on whether there are any other deficiencies that have been identified to date as part of NDA 21-830 review.**

The Agency identified the concerns outlined in Question 1. No additional deficiencies were identified during the teleconference.

3. **Does the Division have any comments in response to P&GP's feedback on FDA's proposed label changes?**

Labeling discussion did not take place during this teleconference.

CONCLUSION:
The Agency will meet internally to formulate an official response and the Sponsor will be notified on August 29, 2005 of the action for NDA 21-830.

Minutes Preparer: _____
Kristen Everett, R.N.
Regulatory Project Manager

Appears This Way
On Original

Chair Concurrence: _____
Ruyi He, M.D.
Medical Team Leader

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
9/8/2005 01:57:25 PM

Ruyi He
9/8/2005 04:01:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830
Proctor and Gamble Pharmaceuticals, Inc.
Attention: Mark S. Leusch, Ph.D.,
U.S. Regulatory Affairs
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Leusch:

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) Tablets 800mg.

We also refer to your submissions dated February 24, 2005, containing new information to support your proposed Asacol 800 trade name and April 27, 2005, containing proposed Asacol® 800 labeling.

We have reviewed your proposed trade name, Asacol® 800, and find it acceptable.

If you have any questions, call Kristen Everett, R.N., Regulatory Project Manager, at (301) 443-8347.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation Drug 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/

Julieann DuBeau
8/1/05 12:32:30 PM

Mr. Leusch,

I have the following additional information request for NDA 21-830:

On February 18, 2003 when you requested the meeting scheduled with the Division scheduled on March 20, 2003, what was the original planned sample size and what percent of the patients were randomized into the studies 2000082 and 2000083 by that date?

If you have any questions, please feel free to call me at 301-827-9333.

Thank you,

Monika Houstoun

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

/s/

Monika Houstoun
7/11/05 05:44:22 PM

Mr. Leusch,

I have the following additional information request for NDA 21-830:

In the NDA 21-830 document you have indicated that support for the proposed human dose of 4.8 g/day of mesalamine has been previously provided in NDA 19-651. Please provide information on the adverse events of patients receiving 4.8 g/day or greater of mesalamine (Asacol).

If you have any questions, please feel free to call me at 301-827-9333.

Thank you,

Monika Houstoun

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

/s/

Monika Houstoun
7/6/05 01:40:35 PM

Mr. Leusch,

I have the following information request for NDA 21-830:

In the NDA 21-830 document you have indicated that support for the proposed human dose of 4.8 g/day of mesalamine has been previously provided in NDA 19-651. Please provide information on the mean duration of exposure and number of subjects exposed to 4.8 g/day Asacol.

If you have any questions, please feel free to call me at 301-827-9333.

Thank you,

Monika Houstoun

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

/s/

Monika Houstoun
6/28/05 07:16:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

Procter & Gamble Pharmaceuticals
Attention: Dr. Mark Leusch, U.S.Regulatory Affairs
P.O. Box 8006, SB4-2M3, Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Leusch:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Asacol® (mesalamine USP) Delayed Release Tablets, 800 mg
Review Priority Classification:	Standard
Date of Application:	October 22, 2004
Date of Receipt:	October 29, 2004
Our Reference Number:	NDA 21-830

This application was filed the application on December 28, 2004 in accordance with 21 CFR 314.101(a). The user fee goal date will be August 29, 2005.

We refer to FDA's Written Request for mesalamine issued to you on November 30, 2002 as well as your reference the Written Request in this submission and your intent to conduct pediatric studies. We have note your intent. However, in order to address the requirements set forth in the Pediatric Research Equity Act (PREA), you should expand this statement to more fully address the PREA requirements as applicable for this application.

Further explanation regarding these requirements follows:

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 note that you have not fulfilled the requirement for this application. We are deferring submission of your pediatric studies until December 31, 2005. However, in the interim, please submit your pediatric drug development plans (full protocols are not required at this time) within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Send via Courier/Overnight Mail/ or U.S. Postal Service:

Dr. Joyce Korvick, M.D., M.P.H.
Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8th Floor
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug 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/

Betsy Scroggs
1/21/05 01:07:16 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-830

Procter & Gamble Pharmaceuticals
Attention: Dr. Mark Leusch,
U.S. Regulatory Affairs
P.O. Box 8006, SB4-2M3, Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Leusch:

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) Delayed-Release Tablets, 800 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on December 28, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. For study 2000083

   The study was designed for patients who were experiencing mildly to moderately active ulcerative colitis. Patients were not stratified by severity. The primary efficacy analysis showed that the treatment difference was not statistically significant, with a p-value of 0.4411. The subgroup analysis for patients with moderate disease at baseline should be considered as an exploratory analysis.

2. For study 2000082

   The study was designed for patients who were experiencing mildly to moderately active ulcerative colitis. Patients were not stratified by severity. During the study, 100 additional patients with moderately active ulcerative colitis were added and the study objective and primary analysis was changed from studying patients with mildly to moderate active ulcerative colitis to studying only patients with moderate active ulcerative colitis. The Type I error might be inflated.

The efficacy results focusing patients with moderate disease at baseline should be considered as a subgroup analysis. The efficacy analysis including all randomized patients should be considered as a primary analysis.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you provide the primary efficacy data and the number of patients for the top five sites for all pivotal studies.

If you have any questions, call Betsy Scroggs, Regulatory Project Manager, at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R. Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation Drug 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
1/7/05 03:37:51 PM

Dr. Leusch,

This fax serves to confirm the scheduling of one Type B meeting for :

- NDA 21-830 for discussion of your proposals to support registration for the Asacol® 800 (mesalamine) delayed-release tablets at 4.8 g/day for the treatment of patients with moderately active ulcerative colitis.
- IND 26,093 for discussion of your proposal to support registration for the Asacol® 800 (mesalamine) delayed-release tablets b(4)

DATE: February 3, 2006

TIME: 1:00 pm – 2:00 pm (EST)

LOCATION: White Oak Campus
10903 New Hampshire Ave.
Silver Spring, MD 20993

TENTATIVE FDA PARTICIPANTS:
Brian E. Harvey, M.D., Ph.D., Division Director
Joyce Korvick, M.D., M.P.H., Deputy Division Director
Ruyi He, M.D., Medical Team Leader
Fathia Gibril, M.D., Medical Reviewer
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader
Suliman Al-Fayoumi, Ph.D.,Biopharmaceutics Reviewer
Jasti Choudary, B.VSc.,Ph.D., Supervisory Pharmacologist
Ronald Honchel, Ph.D., Pharmacology Reviewer
Marie Kowblansky, Ph.D., Chemistry Team Leader
Maria Ysern, M.S., Chemistry Reviewer
Stella Grosser, Ph.D., Biostatistics Team Leader
Milton Fan, Ph.D., Biostatistics Reviewer
Kristen Everett, R.N., Regulatory Project Manager

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 Everettk@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards the following number to request an escort to the conference room: Kristen Everett, 301-796-0453.

Provide the background information for this meeting (three copies to the NDA and to the IND and 15 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by January 6, 2006, we may cancel or reschedule the meeting.

It will be necessary to send either via email or via mail a diskette which will contain a Word document with (1) a list of the firm's attendees, including their titles, and (2) specific questions to be answered at the meeting. These items should be in separate files.

If you have any questions, please feel free to call me at 301-796-0453.

Thank you,

Kristen Everett

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
12/20/2005 11:31:24 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PREA PARTIAL WAIVER GRANTED

NDA 21-830

Procter and Gamble Pharmaceuticals, Inc.
Attention: Mark S. Leusch, Ph.D.
U.S. Regulatory Affairs
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Leusch:

Please refer to your submission dated May 9, 2005, requesting a partial waiver under 505B(a) of the Federal Food, Drug, and Cosmetic Act (the Act) for pediatric studies for Asacol 800® (mesalamine) Tablets.

We have reviewed your submission and agree that a waiver is justified only for pediatric studies in patients less than 5 years of age for Asacol 800® for moderately active ulcerative colitis. The reason for granting the waiver is studies are impossible or highly impractical because the number of patients is so small and geographically dispersed.

We also agree that a deferral of pediatric studies for patients between 5 to 17 years of age is justified for moderately active ulcerative colitis until December 31, 2010. The reasons for granting the deferral are studies will need to be conducted to identify appropriate doses and based on the estimated time to recruit patients. The requirements for your deferred pediatric studies will be fully addressed upon approval of this product. Deferred studies will be considered required postmarketing study commitments.

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

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastrointestinal and
Coagulation Drug 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/

Joyce Korvick
10/19/2005 03:55:23 PM
for Dr. Brian Harvey

Dr. Leusch,

This fax serves to confirm the scheduling of a Type B meeting for NDA 21-830 for discussion of your [redacted] indication for Asacol® 800 (mesalamine) delayed-release tablets and proposal of a Phase IV commitment. b(4)

DATE: November 28, 2005 **LOCATION:** White Oak Campus
Silver Spring, MD

TIME: 11:00 am – 12:00 pm (EST)

TENTATIVE FDA PARTICIPANTS:
Brian E. Harvey, M.D., Ph.D., Division Director
Joyce Korvick, M.D., M.P.H., Deputy Division Director
Ruyi He, M.D., Medical Team Leader
Fathia Gibril, M.D., Medical Reviewer
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader
Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer
Jasti Choudary, Ph.D., Supervisory Pharmacologist
Ronald Honchel, Ph.D., Pharmacology Reviewer
Marie Kowblansky, Ph.D., Chemistry Team Leader
Maria Ysern, Ph.D., Chemistry Reviewer
Stella Grosser, Ph.D., Biostatistics Team Leader
Milton Fan, Ph.D., Biostatistics Reviewer
Kristen Everett, R.N., Regulatory Project Manager

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 Everettk@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Kristen Everett, 301-796-0453; the division secretary, 301-796-2120.

Provide the background information for this meeting (three copies to the NDA and 15 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by October 31, 2005, we may cancel or reschedule the meeting.

It will be necessary to send either via email or via mail a diskette which will contain a Word document with (1) a list of the firm's attendees, including their titles, and (2) specific questions to be answered at the meeting. These items should be in separate files.

If you have any questions, please feel free to call me at 301-796-0453.

Thank you,

Kristen Everett

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
10/5/2005 11:34:33 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: 7/19/2005

TO: Betsy Scroggs, Pharm. D. Regulatory Project Manager
Eric Brodsky, M.D., Medical Officer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: Ni Khin, M.D., Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: Khairy W. Malek, M.D., Ph.D.
Medical Officer, GCP1

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-830

APPLICANT: Procter & Gamble Pharmaceuticals

DRUG: Asacol (mesalamine) Delayed-Release Tablets 800 mg

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Moderately Active Ulcerative Colitis

COSULTATION REQUEST DATE: February 9, 2005

ACTION GOAL DATE: August 29, 2005

BACKGROUND:

Asacol (Mesalamine) Delayed-Release is an approved drug in doses of 2.4 g daily for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission in a lower dose. The new study objective is to evaluate the safety and efficacy of a higher dose of

4.8 g/day in comparison with the 2.4 g/day dose. The study medication was given 3 times a day either as 400mg or 800mg tablets.

In this NDA application, the sponsor has included results from 2 protocols: protocol # 2000082 titled: "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 mildly to moderately active ulcerative colitis"; and protocol # 2000083 titled "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)." Protocol #2000083 is the same as protocol 82 except that in 82, the subjects with moderately active ulcerative colitis were enrolled. Primary efficacy parameter is the proportion of patients in each treatment group who improved from baseline at week 6 whether complete responses or partial response. A complete response is remission (complete resolution of all symptoms), a partial response is improvement. Improvement from baseline to treatment is improvement in physician's global assessment, accompanied by improvement in at least one other category (stool frequency, rectal bleeding, patient's functional assessment or sigmoidoscopy score).

Four sites were chosen for the inspection: Drs. S. Woogen, M. Lamet, B. Winston and D. Riff. Drs. Lamet and Riff's sites enrolled subjects in both protocols, while Drs. Woogen and Winston's sites conducted only protocol 2000082.

II. RESULTS:

Name (MD)	City	State	Assigned Date	EIR Received Date	Classification
Scott Woogen	Richmond	VA	March 22, 2005	May 16, 2005	NAI
Mark Lamet	Pittsburg	PA	March 22, 2005	June 20, 2005	VAI
Barry Winston	Houston	TX	March 22, 2005	June 2, 2005	VAI
Dennis Riff	Anaheim	CA	March 22, 2005	May 16, 2005	VAI

1. Scott Woogen, M.D.
   Richmond, VA

Thirty subjects were randomized to receive study drug for protocol 2000082 at this site. Three subjects were discontinued from the study, one for adverse reaction (headache), one withdrew consent, and one was discontinued by the investigator due to a change in disease status from moderate to severe. The FDA field investigator reviewed the records of 10 subjects out of 30 randomized. No regulatory violations were observed at this site. Data appear acceptable.

2. Mark Lamet, M.D.
Pittsburgh, PA.

For protocol 2000082, 9 subjects were screened with 5 screen failures and one consent withdrawal. The FDA field investigator reviewed 3 subjects' records. Inspectional findings include: there was no documentation of the identity of the individual who completed the following assessments for 3 subjects: subject ___ sigmoidoscopy assessment; subject ___ sigmoidoscopy report dated 1/30/03 and 3/25/03; and two narrative notes dated 10/23/03 and 10/23/03 for subject___ . b(6)

For protocol 2000083, 34 subjects were screened with 8 screen failures. The FDA field investigator reviewed the records of 4 subjects. Inspectional findings include: there was no documentation of the identity of the individual who completed the following assessments for 4 subjects: subject ___ patient accountability form; subject ___ sigmoidoscopy assessment score and patient's personal history form, subject ___ endoscopy report and V1 clinical assessments; and subject ___ V1 clinical assessments. Also, for subject ___ there was lack of a complete medical history at the screening visit. b(6)

These record keeping deficiencies appears not to affect the overall validity of the data. Data appear acceptable.

3. Barry Winston, M.D.
Houston, TX

Thirty two subjects were screened for protocol 2000082 at this site. Seven subjects were screen failures, one subject was discontinued from the study by the PI for non-compliance, two subjects withdrew consent before dosing, and one subject was removed from the study after he suffered a serious adverse reaction (pancreatitis). 21 subjects completed the study. The FDA field investigator reviewed the records of all 21 subjects enrolled in the study.

The inspectional observations include: two subjects #2267 and 2270 did not have stool examinations for bacterial pathogens, ova, parasites, and *C. difficile*, in the month prior to screening or at the screening visit as required by protocol. Subject # 2263 was taking ibuprofen 400 mg at screening and during the week prior to the baseline visit. The protocol prohibits concomitant use of aspirin or NSAIDS during the study. The review division should note these 2 subjects were enrolled without appropriate stool examinations. Otherwise, data from this site appear acceptable.

4. Dennis Riff, M.D.
Anaheim, CA

The FDA field investigator reviewed the records of all 14 subjects in protocol 2000082 and all 6 subjects in protocol 2000083. Inspectional observations include:

Protocol 200082

The protocol specified that patients with mild to moderate ulcerative colitis be enrolled in the study. Subjects #6007 and 6008 had severe disease activity but were enrolled in the protocol.

The following subjects' clinical assessment reports of Stool Frequency Score, Rectal Bleeding Score and Subject's Functional Assessment Score recorded by "the interactive voice system" were inadequate because of subsequent handwritten revision:

Subject	Entry Date(s)
6001	10/17-10/20/02
6002	10/17-10/20/02
6003	12/9-12/12/02
6008	4/30/03
6009	5/29/03

Physician Global Assessments for subject 6007 and 6008 at Visit 1 were not signed by the individual who performed the assessment.

Protocol 2000083

The following subjects' clinical assessment reports of Stool Frequency Score, Rectal Bleeding Score and Subject's Functional Assessment Score recorded by "the interactive voice system" were inadequate because of subsequent handwritten revision:

Subject	Entry Date(s)
5362	2/3, 2/5, 2/6, 2/9, 2/18, 2/21/02
5364	3/8, 3/9, 3/10, 3/12/02
5366	5/26, 6/1, 6/2/02

For both protocols, the number of pills returned from the site as documented in the P& G Drug Accountability Log was less than the number of pills destroyed as documented in the Destroyed/Returned Medication Inventory. The protocol required compliance checks at Visits 1 and 2, and defined non-compliance as taking less than 85% of study medication. The FDA investigator did not report any issues regarding subjects' treatment compliance. b(4)

The review division should note there were 2 subjects were enrolled with severe disease despite the protocol requirement that subjects have mild to moderate disease. There were also instances of record keeping deficiencies. Otherwise, data from this site appear acceptable.

Limitations of inspection: There were no limitations during the inspections.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, two subjects at Dr. Winston's site and two subjects at Dr. Riff's site were enrolled despite not meeting all eligibility criteria. There were record keeping deficiencies noted at Drs. Lamet and Riff's sites. These record keeping deficiencies appear not to affect the overall validity of the data. The data from these four sites appear acceptable in support of the relevant indication of the NDA.

Khairy W. Malek
Medical Officer

CONCURRENCE:

Ni Khin, M.D.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-830
HFD-45/Division File / Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/Malek
HFD-46/GCP1 Files (EIR # 11505, 3885, 9719 and 11568)

File name: O:\KM\Asacol Summary.rev.doc

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

/s/

Ni Aye Khin
7/22/05 01:48:35 PM
MEDICAL OFFICER

Mr. Leusch,

I have the following additional information request for NDA 21-830:

On February 18, 2003 when you requested the meeting scheduled with the Division scheduled on March 20, 2003, what was the original planned sample size and what percent of the patients were randomized into the studies 2000082 and 2000083 by that date?

If you have any questions, please feel free to call me at 301-827-9333.

Thank you,

Monika Houstoun

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

/s/

Monika Houstoun
7/11/05 05:44:22 PM

Mr. Leusch,

This fax serves to confirm the scheduling of a Type C, teleconference for NDA 21-830

DATE:	August 2, 2005	**LOCATION:**	Parklawn Building 5600 Fishers Lane
TIME:	11:00 am – 12:00 pm (EST)		Rockville, MD 20857

TENTATIVE FDA PARTICIPANTS:
Brian E. Harvey, M.D., Ph.D., Division Director
Joyce Korvick, M.D., M.P.H., Deputy Division Director
Ruyi He, M.D., Medical Team Leader
Stella Grosser, Ph.D., Biostatistics Team Leader
Milton Fan, Ph.D., Biostatistics Reviewer
Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader
Jasti Choudary, Ph.D., Supervisory Pharmacologist
Ronald Honchel, Ph.D., Pharmacologist
Liang Zhou, Ph.D., Chemistry Team Leader
Maria Ysern, Ph.D., Chemistry Reviewer
Monika Houstoun, Pharm.D., Regulatory Project Manager

It will be necessary to send either via email or via mail a diskette which will contain a Word document with (1) a list of the firm's attendees, including their titles, and (2) specific questions to be answered at the meeting. These items should be in separate files.

If you have any questions, please feel free to call me at 301-827-9333.

Thanks,

Monika Houstoun

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

/s/

Monika Houstoun
6/28/05 07:13:28 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

(Division/Office):	FROM:
orian Zielinski CDER/OPS/QIS	**Betsy Scroggs, Pharm.D.** **Project Managers: HFD-180** **(301) 827-1250** **scroggsb@cder.fda.gov**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1-19-2005	N/A	**21-830**	NDA submission	**October 29, 2004**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Asacol 800 mg	**Medium**	Inflammatory Bowel Disease/Ulcerative Colitis	**July 22, 2005**

NAME OF FIRM: **Procter and Gamble**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

e are requesting a consult for environmental assessment.

Background: NDA 21-830 (electronic) was received on October 29, 2004 as a 505(b)(1) application and provides to add an 800 mg strength to the approved 400 mg tablet. Under IND 26,093, Procter and Gamble (P&G) submitted general correspondence (Serial Submission # 193) dated June 14, 2002 requesting permission to modify assumptions described in the "Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications". For your reference, your consult for that submission is attached.

The User Fee Goal Date for this application is August 29, 2005.

Application: N021830 Drug Trade Name: ASACOL (MESALAMINE) 800MG
Sponsor Name: PROCTER AND GAMBLE

22-OCT-2004 N 000 Application: N021830 Document: 2602091
Location: \\CDSESUB1\N21830\N_000\2004-10-22
Goal Date: 8/29/2005

C:\Documents and Settings\SCROGGSB.FDA\Desktop\Draft Letters\Asacol EA consult request.doc

SIGNATURE OF REQUESTER Betsy Scroggs, Pharm.D., CSO HFD-180	METHOD OF DELIVERY (Check one) ☑DFS MAIL ☐ HAND
NATURE OF RECEIVER	SIGNATURE OF DELIVERER

Response to "Request for Consultation" dated Aug 29, 2002

EA for ASACOL (5-aminosalicylic acid), IND 26,093

Procter and Gamble (P&G) submitted general correspondence (Serial Submission # 193) dated June 14, 2002 requesting permission to modify assumptions described in the "Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications"

Briefly, when calculating $EIC_{(aquatic)}$, the Guidance conservatively assumes that all the active pharmaceutical ingredient (API) used in a year is introduced, first into the POTW, then into the aquatic environment. The Guidance does not distinguish between API initially introduced into the sanitary sewer system and septic systems.

One part per billion $EIC_{(aquatic)}$ corresponds to 44,300 kg API used per year because total input into the POTW is 1.214×10^{11} liters/day x 365 days/year.

Proposal

P&G wishes to calculate $EIC_{(aquatic)}$ after reducing the amount of API used by ___ because that amount is introduced into the septic systems.

b(4)

Evaluation that may be provided to Procter & Gamble

A acknowledges that a percentage of the API used will enter septic systems rather than POTWs just as we acknowledge that some of the API entering POTWs can adsorb to sludge and be applied to land. However, API introduced into a septic system still enters the environment, including potentially the aquatic environment due to hydrological transport.

For purposes of claiming a categorical exclusion under 25.31(b), the EIC is calculated by assuming that all of the API used enters the aquatic environment though POTWs. This categorical exclusion was established based on several general principles that were discussed in the proposed and final rule revising the regulations at 21 CFR Part 25.

Appropriate alternative calculations can be used but the alternative calculations should account for the entire quantity of the API used and its entry into the environment. Claiming a categorical exclusion under 25.31(b) by reducing the $EIC_{(aquatic)}$ because a portion of the API used enters another environmental compartment is not an appropriate alternative calculation.

Determining the fate and contribution of API in septic systems or sludge to overall environmental exposure is a complicated matter requiring scientific data that should be provided in an environmental assessment. When an EA is required because the $EIC_{(aquatic)}$ is 1 ppb or greater, the possible environmental entry pathways and environmental transport of the drug and spatial and temporal depletion or concentration mechanisms should be discussed and this information can lead to more refined environmental concentration estimates.

Summary that may be provided to Procter & Gamble

When calculating $EIC_{(aquatic)}$, it is unacceptable to decrease the amount of API used to account for the percentage initially introduced into septic systems in order to qualify for Categorical Exclusion from the Requirement to Prepare an EA under 25.31 (b).

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

/s/

Betsy Scroggs
1/21/05 12:34:04 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 30, 2004

To: Dr. Mark Leusch	**From:** Betsy Scroggs, Pharm.D. Consumer Safety Officer
Company P&G	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (513) 622-5363	**Fax number:** (301) – 827-1305
Phone number: (513) 622-2620	**Phone number:** 301-827-1250

Subject: NDA 21-830

Total no. of pages including cover: 1

DOCUMENT TO BE MAILED? NO

Please refer to you submission for NDA 21-830, received October 29, 2004. We have the following information request:

Provide the Drug Establishment Registration Number for:

Procter &Gamble Pharmaceuticals, Germany GmbH

Dr. Otto-Rohm Strasse 2-4

D-64331 Weiterstadt

Germany

Thank you for your attention to this.

BHS

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

/s/.

Betsy Scroggs
12/1/04 09:57:26 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 26,093

Proctor and Gamble Health Care Research Center
Attention: Mark S. Leusch, Ph.D.,
8700 Mason-Montgomery Road, P.O. Box 8006
Mason, OH 45040-9462

Dear Dr. Leusch:

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

We also refer to your amendment dated October 25, 2002 (serial # 198), containing a request for review of the proposed proprietary name, Asacol® 800 for the 800 mg mesalamine delayed-release tablet.

We have completed the review of your submission and have the following comments and advice.

We do not recommend use of the proposed proprietary name "Asacol 800" for the following reasons regarding the proposed numeric modifier:

We acknowledge the following examples you submitted as precedent for the inclusion of a numeric extension on a proprietary name:

Robaxin and Robaxin-750
Lufyllin and Lufyllin-400
Antivert, Antivert/25, and Antivert/50

In each case, the modifier differentiates the strengths of the product pairs. The use of the root name "Asacol" for the proposed product is misleading since it implies that Asacol 800 is merely a different strength of Asacol. In fact, Asacol differs from the proposed product in important ways. Asacol 800 has a recommended total daily dose that is twice that of the 400 mg tablet (2.4Gm v 4.8Gm) , and the 400 mg and 800 mg tablets are not bioequivalent. The similarities between the two products, including the same root name and dosing intervals (TID) and one shared indication of use, may give the false impression that the products can be used interchangeably. b(4)

In addition, the "800" may be left off the name, Asacol 800, when a prescription is ordered or transcribed. A prescription intended to be written for Asacol 800, appearing without the 800 might be filled with the 400 mg Asacol tablets, especially if that is all the pharmacy has in stock.

Therefore, we recommend that you choose a proprietary name different than Asacol for this different product, analogous to the use of two proprietary names, Sandimmune and Neoral, for different cyclosporine products. Since the mesalamine products are not for completely different indications, there would be little risk of a patient taking both products at the same time under different names. In order to minimize potential error, we encourage you to differentiate Asacol 800 from Asacol by use of boxing,

contrasting colors, or other means. We also suggest including a labeling statement similar to the Boxed Warning at the beginning of the package insert for Sandimmune and Neoral which clearly states these products are not to be interchanged.

If you have any questions, call Betsy Scroggs, Pharm.D., Consumer Safety Officer, at 301-827-1250.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Division of Gastrointestinal & Coagulation Drug 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/

Joyce Korvick
10/1/04 05:25:31 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-830 Supplement # N/A Efficacy Supplement Type SE-

Trade Name: Asacol
Established Name: mesalamine
Strengths: 800 mg

Applicant: Procter & Gamble
Agent for Applicant: N/A

Date of Application: October 22, 2004
Date of Receipt: October 29, 2004
Date clock started after UN: N/A
Date of Filing Meeting: December 22, 2004
Filing Date: December 28, 2004
Action Goal Date (optional): User Fee Goal Date: August 29, 2005

Indication(s) requested: Treatment of moderately active ulcerative colitis

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) No

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? The paper certifications were submitted in paper

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
  ***NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 26,093

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) May 5, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☐ NO ☒

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☒

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☒
  If no, did applicant submit a complete environmental assessment? YES ☒ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☒ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 22, 2004

BACKGROUND: Approved January 1992, Asacol (mesalamine) Delayed-Release Tablets, 400 mg is the only sulfa-free 5-ASA indicated for both mildly to moderately active UC and for the maintenance of remission. The firm compares its product to Pentasa and Dipentum in this indication category (comparative trials have not been done). For the treatment of mildly to moderately active UC the usual dosage is two 400 mg tablets t.i.d. For the maintenance of remission of UC, the recommended dosage is 1.6 g/day, in divided doses. Treatment duration in the maintenance study was six months. The drug is marketed worldwide as a 500 mg tablet as well.

"Asacol 800" the proposed proprietary name for mesalamine delayed-release 800 mg tablets submitted as a new NDA October 22, 2005 provides for a new strength and dosing regimen. "Asacol 800" is also indicated for the treatment of moderately active ulcerative colitis. However, the proposed dosing regimen for "Asacol 800" is two 800 mg tablets taken orally three times a day for a total daily dose of 4.8 grams for a duration of 6 weeks. This is twice the total daily dosage as Asacol 400mg required to treat the same indication of use. "Asacol 800" is not bioequivalent to the 400 mg tablets. b(4)

400 mg approved use mild to moderate UC for 6 weeks 1 x 400 mg po tid
maintenance of remission for UC for 6 months
800 mg proposed use: 2 x 800 mg po tid = 4.8 grams daily for 6 weeks

A DMETS review completed during the IND phase recommends not using the "800" as a modifier to the root name and in addition, not using "Asacol" as the root name. At the time of the filing meeting, the firm was considering resubmission of a new trade name at a later date, possibly February 2005.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Betsy Scroggs, Fathia Gibril, Maria Ysern, Ruyi He, Suliman Al-Fayoumi, Milton Fan, Ronald Honchel, Stella Grosser

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	Reviewer
Medical:	Fathia Gibril
Secondary Medical:	NA
Statistical:	Milton Fan
Pharmacology:	Ronald Honchel
Statistical Pharmacology:	NA
Chemistry:	Maria Ysern
Environmental Assessment (if needed):	Florian Zielinski
Biopharmaceutical:	Suliman Al-Fayoumi
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	Khairy Malik
Regulatory Project Management:	Betsy Scroggs
Other Consults:	Shannon Benedetto for DDMAC, Sammie Beam for DMET

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Betsy Scroggs, Pharm.D.
Regulatory Project Manager, HFD-180

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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

/s/

Betsy Scroggs
4/24/05 11:32:40 AM
CSO

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]			
NDA # 21-830	NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Asacol 800 (mesalamine) Delayed Release Tablets Established Name: Mesalamine Dosage Form: Tablet		Applicant: Procter & Gamble Pharmaceuticals, Inc.	
RPM: Heather Buck		Division: DGP (HFD-180)	Phone # (301) 796-1413

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☐ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

❖ User Fee Goal Date ❖ Action Goal Date (if different)	4/22/08 5/29/08
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	AE 8/29/05
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be filed in the Action Package.

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 3

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• If yes, exception for review granted *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: ☐	4/9/2008
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	☐ Yes, date
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs only: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

  (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list.	included
❖ Documentation of consent/non-consent by officers/employees	included
Decisional Memos	
Office Director Decisional Memo *(indicate date for each review)*	N/A
❖ Division Director Summary Review *(indicate date for each review)*	5/29/08
❖ Cross-Discipline Team Leader Review *(indicate date for each review)*	N/A
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	AE Letter 8/29/2005 AP Letter 5/29/08
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	5/28/08
• Original applicant-proposed labeling	10/22/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert *(write submission/communication date at upper right of first page of PPI)*	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	

• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide *(write submission/communication date at upper right of first page of MedGuide)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	4/11/08
❖ Labeling reviews and any minutes of internal labeling meetings *(indicate dates of reviews and meetings)*	☒ RPM 1/17/08 ☒ DMEDP 4/18/08, 7/20/05, 1/7/03 ☐ DRISK ☒ DDMAC 4/18/08, 8/24/05 ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	RPM Filing Review/Memo Filing Meeting: 4/24/05
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
• AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	N/A
❖ Pediatric Page *(a new Pediatric Page for each review cycle)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	See AP letter
• Incoming submissions/communications	
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	4/18/08, 4/7/08, 4/4/08, 3/21/08, 2/14/08, 1/17/08, 11/5/07, 12/4/07, 8/29/05, 8/1/05, 8/24/05, 7/11/05, 7/6/05, 6/28/05, 6/10/05, 1/21/05, 1/7/05, 11/30/04, 10/1/04
❖ Internal memoranda, telecons, etc.	5/22/08, 1/31/06, 12/20/05, 10/19/05, 11/23/05, 7/11/05, 6/28/05, 8/7/02 (2)

❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	5/5/04
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	4/22/08, 3/2/06, 12/20/05, 9/9/05, 9/8/05, 12/20/05, 9/6/04, 1/4/01
❖ Advisory Committee Meetings	☒ No AC meeting
• Date(s) of Meetings	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Quality Information	
❖ ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
❖ PAL/BUD Review(s) *(indicate date for each review)*	☒ None
❖ CMC/product quality review(s) *(indicate date for each review)*	4/17/08 8/12/05 5/18/05
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☒ Review & FONSI *(indicate date of review)*	See CMC reviews 8/12/05 & 5/18/05. FONSIs: 2/28/05 (2/25/05 & 2/10/05 reviews)
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	See CMC reviews
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 8/11/05 ☒ Acceptable ☐ Withhold recommendation
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and all supplemental applications (except CBEs)) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ ADP/T Review(s) *(indicate date for each review)*	☒ None
❖ Supervisory Review(s) *(indicate date for each review)*	☒ None
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5/23/08, 7/22/05
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None

❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	Included in P/T review, page
❖ Nonclinical inspection review summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical Team Leader Review(s) *(indicate date for each review)*	5/29/08 8/26/05 8/17/05
❖ Clinical review(s) *(indicate date for each review)*	5/29/08 8/26/05
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR ❖ If no financial disclosure information was required, review/memo explaining why not	Clinical Review 8/26/05
❖ Clinical reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Clinical microbiology reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	Clinical review 5/29/08, 8/26/05
❖ REMS review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	4/3/08, 6/6/05, 12/21/05, 9/21/05, 8/24/05, 7/22/05
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Biostatistics	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
❖ Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
❖ Statistical Review(s) *(indicate date for each review)*	5/23/08, 8/24/05, 8/5/05
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
❖ Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	5/21/08, 8/1/05

Appendix A to Action Package Checklist

NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA or the OND ADRA.

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
6/2/2008 09:28:37 AM