

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 019651/S005**

**ENVIRONMENTAL ASSESSMENT AND/OR FONSI**

**ENVIRONMENTAL ASSESSMENT**  
**AND**  
**FINDING OF NO SIGNIFICANT IMPACT**  
**FOR**  
**ASACOL® Delayed Release Tablets**  
**(400 mg)**  
**(mesalamine)**

**NDA 19-651/S-005**

**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF GASTROINTESTINAL AND**  
**COAGULATION DRUG PRODUCTS (HFD-180)**

FINDING OF NO SIGNIFICANT IMPACT  
NDA 19-651/S-005  
Asacol® (mesalamine) Delayed Release Tablets, 400 mg

Indicated for maintenance of remission of ulcerative colitis

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center of Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Asacol® (mesalamine) Delayed Release Tablets, 400 mg Procter & Gamble Pharmaceuticals, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product.

In support of their supplemental new drug application (S-005), Procter & Gamble Pharmaceuticals, Inc. has submitted an environmental assessment (EA). The new EA information does not present new information on the manufacture of mesalamine and Asacol® (mesalamine) Delayed Release Tablets, 400 mg. The manufacturing aspect of the EA remains the same with respect to manufacturing at the approved facilities, and the drug product formulation remains the same.

Approval of the supplemental application will make Asacol® (mesalamine) Delayed Release Tablets, 400 mg available to a larger group of patients as reflected in the additional indication. The drug product will be used for maintenance of remission of ulcerative colitis. The fate and effects of mesalamine remain unchanged from the original EA.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

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*Melwil*



4/30/97  
DATE

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PREPARED BY:  
Arthur B. Shaw, Ph.D.  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Office of New Drug Chemistry

MAY - 5 1997

5/1/97  
DATE

*/S/*

DIVISION CONCURRENCE:  
ERIC P. DUFFY, PH.D.  
Chemistry Team Leader  
Office of New Drug Chemistry, HFD-820

5/5/97  
DATE

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APPROVED: 010  
NANCY B. SAGER  
Environmental Scientist, HFD-353  
Center for Drug Evaluation and Research

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Attachment I: EA Review

CC: Original NDA 19-651/S-005  
357 HFD-004/FONSI File 19-651/S-005  
357 HFD-004/Docket File  
205 HFD-019/FOI Copy  
HFD-180/AShaw  
R/D init.: EDuffy/4-29-97  
ABS/dob F/T 4-30-97/WP: c:\wpfiles\chem\S\19651005.2AS

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NDA 19-651  
ENVIRONMENTAL ASSESSMENT

## ENVIRONMENTAL SUMMARY

Procter & Gamble Pharmaceuticals, Inc. has filed a supplemental NDA for Asacol (Mesalamine) Delayed-Release Tablets, for the maintenance of remission of ulcerative colitis. This is a new indication for Asacol Tablets, with a different dosing regimen and longer duration as well. As with the original NDA, both drug substance and drug product will be manufactured outside the US, with only printing and packaging operations in Norwich, New York. Production estimates and environmental exposure calculations may be found in Confidential Appendix D. Consideration of metabolism decreases the expected environmental concentration significantly the qualifying concentration of No environmental impact is expected from approval of this action, as the increase in manufacturing volume of mesalamine is of the previously approved Asacol indication, and , of total industry volume.

APPENDIX 4. Study 87086

List of Adverse Events.

Table 28  
Adverse Events - All Patients

COSTART	Placebo N = 87 n (%)	Asacol 0.8 g/day N = 90 n (%)	Asacol 1.6 g/day N = 87 n (%)
Headache	43 (49.4%)	47 (52.2%)	41 (47.1%)
Rhinitis	31 (35.6%)	39 (43.3%)	35 (40.2%)
Diarrhea	43 (49.4%)	27 (30.0%)	35 (40.2%)
Pain Abdo	38 (43.7%)	27 (30.0%)	29 (33.3%)
Flatul	26 (29.9%)	19 (21.1%)	24 (27.6%)
Pain	10 (11.5%)	17 (18.9%)	20 (23.0%)
Pharyngitis	13 (14.9%)	20 (22.2%)	18 (20.7%)
Asthenia	14 (16.1%)	9 (10.0%)	17 (19.5%)
Nausea	13 (14.9%)	17 (18.9%)	15 (17.2%)
Fever	11 (12.6%)	11 (12.2%)	12 (13.8%)
Constip	11 (12.6%)	4 (4.4%)	11 (12.6%)
Pain Back	10 (11.5%)	19 (21.1%)	9 (10.3%)
Flu Synd	17 (19.5%)	13 (14.4%)	9 (10.3%)
Colitis Ulcer	7 (8.0%)	7 (7.8%)	9 (10.3%)
Hem GI	7 (8.0%)	7 (7.8%)	9 (10.3%)
Stool Abnorm	7 (8.0%)	7 (7.8%)	9 (10.3%)
Infect	3 (3.4%)	6 (6.7%)	9 (10.3%)
Dizziness	6 (6.9%)	6 (6.7%)	8 (9.2%)
Pain Chest	5 (5.7%)	7 (7.8%)	7 (8.0%)
Arthralgia	8 (9.2%)	7 (7.8%)	7 (8.0%)
Myalgia	4 (4.6%)	6 (6.7%)	7 (8.0%)
Cough Inc	14 (16.1%)	6 (6.7%)	7 (8.0%)
Sinusitis	5 (5.7%)	11 (12.2%)	6 (6.9%)
Tenesmus	4 (4.6%)	6 (6.7%)	6 (6.9%)
Rectal Dis	2 (2.3%)	5 (5.6%)	6 (6.9%)
Vomit	6 (6.9%)	1 (1.1%)	6 (6.9%)
Nervousness	2 (2.3%)	5 (5.6%)	5 (5.7%)
Dyspepsia	8 (9.2%)	5 (5.6%)	5 (5.7%)
Insomnia	4 (4.6%)	8 (8.9%)	4 (4.6%)
Hypertonia	3 (3.4%)	4 (4.4%)	4 (4.6%)
Gastroenteritis	1 (1.1%)	4 (4.4%)	4 (4.6%)
Malaise	3 (3.4%)	2 (2.2%)	4 (4.6%)
Dysmenorrhea	2 (2.3%)	1 (1.1%)	4 (4.6%)
Paresthesia	4 (4.6%)	1 (1.1%)	4 (4.6%)
Pruritus	6 (6.9%)	0 (0%)	4 (4.6%)
Joint Dis	0 (0%)	2 (2.2%)	3 (3.4%)
Urin Frequency	0 (0%)	2 (2.2%)	3 (3.4%)
Vision Abnorm	0 (0%)	2 (2.2%)	3 (3.4%)
Hematuria	1 (1.1%)	1 (1.1%)	3 (3.4%)
Lung Dis	0 (0%)	0 (0%)	3 (3.4%)
Hem Rectal	4 (4.6%)	0 (0%)	3 (3.4%)
Anxiety	2 (2.3%)	4 (4.4%)	2 (2.3%)
Bronchitis	2 (2.3%)	3 (3.3%)	2 (2.3%)
Abdo Enlarge	0 (0%)	3 (3.3%)	2 (2.3%)
Arthritis	2 (2.3%)	3 (3.3%)	2 (2.3%)
Dysuria	1 (1.1%)	1 (1.1%)	2 (2.3%)
Monilia Vagina	1 (1.1%)	1 (1.1%)	2 (2.3%)
Amblyopia	0 (0%)	1 (1.1%)	2 (2.3%)

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Table 28 - Continued  
Adverse Events - All Patients

COSTART	Placebo N = 87 n (%)	Asacol 0.8 g/day N = 90 n (%)	Asacol 1.6 g/day N = 87 n (%)
Dry Mouth	0 (0%)	1 (1.1%)	2 (2.3%)
Epistaxis	0 (0%)	1 (1.1%)	2 (2.3%)
Lacrimation Dis	0 (0%)	1 (1.1%)	2 (2.3%)
Prostat Dis	0 (0%)	1 (1.1%)	2 (2.3%)
Somnolence	3 (3.4%)	0 (0%)	2 (2.3%)
Urticaria	1 (1.1%)	0 (0%)	2 (2.3%)
Asthma	0 (0%)	0 (0%)	2 (2.3%)
Cystitis	0 (0%)	0 (0%)	2 (2.3%)
Deaf	0 (0%)	0 (0%)	2 (2.3%)
Vaginitis	0 (0%)	0 (0%)	2 (2.3%)
Migraine	4 (4.6%)	7 (7.8%)	2 (2.3%)
Ear Dis	0 (0%)	5 (5.6%)	1 (1.1%)
Rash	8 (9.2%)	3 (3.3%)	1 (1.1%)
Vasodilat	0 (0%)	3 (3.3%)	1 (1.1%)
Allerg React	3 (3.4%)	2 (2.2%)	1 (1.1%)
Dyspnea	3 (3.4%)	2 (2.2%)	1 (1.1%)
Chills	1 (1.1%)	2 (2.2%)	1 (1.1%)
Pneumonia	1 (1.1%)	2 (2.2%)	1 (1.1%)
Urin Abnorm	1 (1.1%)	2 (2.2%)	1 (1.1%)
Edema Periph	0 (0%)	2 (2.2%)	1 (1.1%)
Palpitat	0 (0%)	2 (2.2%)	1 (1.1%)
Anorexia	2 (2.3%)	1 (1.1%)	1 (1.1%)
Depression	2 (2.3%)	1 (1.1%)	1 (1.1%)
Infect Urin Tract	2 (2.3%)	1 (1.1%)	1 (1.1%)
Cramps Leg	3 (3.4%)	0 (0%)	1 (1.1%)
Alopecia	2 (2.3%)	0 (0%)	1 (1.1%)
Sweat	2 (2.3%)	0 (0%)	1 (1.1%)
Pain Ear	2 (2.3%)	5 (5.6%)	0 (0%)
Hangover	2 (2.3%)	2 (2.2%)	0 (0%)
Impotence	1 (1.1%)	2 (2.2%)	0 (0%)
Pain Pelvic	1 (1.1%)	2 (2.2%)	0 (0%)
Lymphadeno	0 (0%)	2 (2.2%)	0 (0%)
Pain Kidney	0 (0%)	2 (2.2%)	0 (0%)
Rash Mac Pap	0 (0%)	2 (2.2%)	0 (0%)
Skin Dis	2 (2.3%)	0 (0%)	0 (0%)
Taste Pervers	2 (2.3%)	0 (0%)	0 (0%)

Patients could report more than one COSTART.

N = total number of patients exposed to treatment. n = number of patients experiencing the event. (%) = n/N.  
Supporting data can be found in Appendix 5, Table 28.8.

Table 29 presents the investigator-noted adverse events by COSTART in decreasing order of occurrence as determined by the Asacol 1.6 g/day group. Only those incidents of 2% or greater occurrence are listed. As described in Section 3.12.1, any symptoms or intercurrent illnesses reported by the patient were evaluated by the investigator as to the likelihood that they were adverse reactions to study treatment. If the investigator thought that the incidents were adverse events, they were recorded as such on the case report form. This table presents only those incidents that were specifically noted as adverse events by the investigator. Both the number of events and the number of patients reporting an event are far less when only investigator-noted adverse events are tabulated than when both investigator-noted and sponsor-noted events are tabulated. As in the tabulation of both investigator-noted and sponsor-reported events, the percentage of patients reporting various events appears to differ only slightly among the treatment groups. The complete results are presented in Table 28.9, Appendix 5.

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APPENDIX 5

Narratives of Patients; Pages 83-87, Vol. 43.

NDA 19-651  
Environmental Assessment

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**ENVIRONMENTAL ASSESSMENT**  
**(Mesalamine)**  
**ASACOL DELAYED-RELEASE TABLETS**

**NDA #19-651**

1. **Date:** Original 7/29/96, amended 1/24/97, 3/10/97, and 4/10/97
2. **Sponsor:** Procter & Gamble Pharmaceuticals, Inc.
3. **Address:** 11450 Grooms Rd.  
Cincinnati, Ohio 45242
4. **Description of Proposed Action:**
  - a. Requested Approval

Procter & Gamble Pharmaceuticals, Inc. has filed a supplement, #S-005, to NDA #19-651 for distribution of Asacol, 400 mg tablets, packaged in for the maintenance of remission of ulcerative colitis. This EA has been submitted pursuant to 21 CFR § 25.31a(a).

b. Need for Action

Ulcerative colitis (UC) is an inflammatory disease of the colonic and rectal mucosa affecting about 500,000 patients in the US, characterized by alternating periods of exacerbation and remission. Acute UC symptoms include diarrhea, abdominal pain, rectal bleeding and mucosal and submucosal inflammation and ulceration. The underlying cause of UC is unknown, although several therapies which use mesalamine (5-aminosalicylic acid, or 5-ASA) as the active ingredient are used to treat symptoms of mildly to moderately active disease and maintain remission (1).

mild to moderately active ulcerative colitis. The usual dosage in adults is two 400 mg tablets taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks. Asacol Tablets contain a

aminosalicylic acid (mesalamine), hereafter referred to as 5-ASA

which delays release of 5-ASA until the tablet reaches an environment

to deliver effective concentrations of mesalamine to the colon

This delivery system is superior to those of other therapies by eliminating the side-effects caused by sulfa based carriers (Sulfasalazine) and non-targeted release throughout the GI tract (Pentasa).

Recent clinical data (3) has demonstrated the safety and efficacy of Asacol Tablets in the maintenance of UC remission at doses of 0.8 and 1.6 g/d for up to 6 months. The proposed dosing for this maintenance of remission indication for ulcerative colitis supplement is for one 400 mg tablet to be taken twice a day for a total daily dose of 0.8 grams for an undetermined duration. Some patients may require a higher daily dose of 1.6 g, or four 400 mg tablets per day.

#### c. Production Locations

The drug substance, 5-aminosalicylic acid (5-ASA) will be produced at

The community is situated in the eastern part of the county of

The community is surrounded by farmland, lakes, and thick stands of forest. is located in the district on a 3 km x 1.5 km guarded plat situated 1.5 km from the center of the community. The industrial district is located between two lakes and the which forms the western boundary of the district. is

the receiver of the industrial district treated effluents. The lake has two feeder streams in addition to the

The 5-ASA drug substance manufacturing operation is done in full accordance with GMP's, and is maintained through the use of appropriate Standard operating procedures (SOP's). These SOP's also maintain the condition of the physical facilities, the training and procedures used by operation personnel, and the general control procedures used in the manufacturing operation. Details of the manufacturing

process may be found in . An authorization letter for FDA review of this file is found in Appendix A.

Bulk drug substance will be shipped to Procter & Gamble Pharmaceuticals-Germany GmbH, Dr.-Otto-Rohm Strasse 2-4, 64331 Weiterstadt, Germany. The plant is located in the industrial estate of Weiterstadt approximately 1 km from the boundary of the city of Darmstadt, 4 km from the town center of Weiterstadt, and 25 km south of Frankfurt. The manufacturing plant is surrounded by other heavy industry. Drug substance is shipped in head drums with

The 5-ASA is then manufactured into Asacol tablets in combination with the following excipients:

<b>MATERIAL</b>	<b>CAS #</b>
Lactose	64044-51-5
Sodium Starch Glycolate	9063-38-1
Povidone	9003-39-8
Talc	14807-96-6
Magnesium Stearate	557-04-0
Colloidal Silicon Dioxide	7631-86-9
Copolymer	25086-15-1
Dibutylphthalate	84-74-2
Iron Oxide (red)	1309-37-1
Iron Oxide (yellow)	51274-00-1
Polyethylene Glycol	25322-68-3

The Asacol drug tablet manufacturing operation is done in full accordance with GMP's, and is maintained through the use of appropriate Standard operating procedures (SOP's). These SOP's also maintain the condition of the physical facilities, the training and procedures used by operation personnel, and the general control procedures used in the manufacturing operation. Details of the manufacturing process as well as a description of the manufacturing site may be found in Procter & Gamble Pharmaceuticals, Inc. authorizes FDA to review this file in support of this submission.

will be accomplished at the North Norwich plant of Procter & Gamble Pharmaceuticals, Inc., Route 12, Norwich, NY, 13814.

east and State Rt. 12 on the west. The property is the southern limit of an economic development zone to the north, and is bordered by the Chenango County Recycling Center to the west and agricultural and grazing acreage to the south. The surrounding countryside is designated as the Chenango Valley, situated in north central New York State, in the foothills of the Appalachian Mountains.

d. Locations of Use

Asacol tablets will be distributed throughout the US and are intended to be dispensed through hospitals, medical clinics and by prescription via professional medical personnel for home use.

e. Disposal Sites

All returned, rejected or out of specification raw materials and products as well as solid waste containing drug product will be returned to the Procter & Gamble Pharmaceuticals North Norwich Plant, New York Plant for disposal in accordance with all federal, state and local regulatory requirements at an off-site, New York State DEC approved pharmaceutical waste incineration facility or landfill.

At U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures. In the home, empty or partially empty containers will be typically disposed of by a community solid waste management system which may include landfill, incineration and recycling, although minimal quantities of unused drug may be disposed to the sewer system.

5. **Identification of Chemical Substances:**

a. Nomenclature:

- i. USAN - Mesalamine
- ii. Brand/Proprietary Name - Asacol tablets
- iii. Chemical Names

(1) Chemical Abstracts Name: 5-Amino-2-hydroxybenzoic acid

(2) Common names: 5-ASA

## 5-Aminosalicylic acid

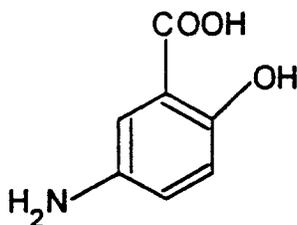
b. CAS #: 89-57-6

c. Molecular Formula:  $C_7H_7NO_3$

d. Molecular Weight: 153.1

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e. Structural Formula:



f. Physical Description: Off white to light brown powder; decomposes at approximately 280°C; solubility in water is 0.9 mg/ml at 25°C; volatility of substance is negligible; pH of saturated solution of 5-aminosalicylic acid in sterile water at 21°C is 4.19. DSC tests conducted in vented and sealed pans under nitrogen, at a heating rate of 20°C/minute showed no thermal activity occurred prior to main degradation endotherm which peaks at about 295-298°C. The 5-aminosalicylic acid does not degrade at temperatures below 240°C under the above conditions. The 5-aminosalicylic acid is considered not to be hygroscopic since it remains anhydrous based on studies conducted with sample lots under conditions of 72% RH for 17 days and 100% RH for 3 days (moisture content determined by thermogravimetry).

h. Impurities: N/A

**6. Introduction of Substances into the Environment:**

a. Substances Expected to be Emitted

Procter & Gamble Pharmaceuticals-Germany GmbH - A description of the manufacturing process for the drug product may be found in \_\_\_\_\_, listed under the product name

A process summary with detailed flow charts may be found in Confidential Appendix F. The list of substances emitted during the manufacturing process (with CAS #) is identical to those listed under Procter & Gamble Pharmaceuticals (North Norwich) below.

Procter & Gamble Pharmaceuticals (North Norwich) - Approval of the proposed action may result in a small amount of waste product from printing and packaging operations, as well as packaging material waste. Drug product waste will consist primarily of dust from broken tablets. Tablets are composed of the following materials:

MATERIAL	CAS #
Lactose	64044-51-5
Sodium Starch Glycolate	9063-38-1
Povidone	9003-39-8
Talc	14807-96-6
Magnesium Stearate	557-04-0
Colloidal Silicon Dioxide	7631-86-9
Copolymer	25086-15-1
Dibutylphthalate	84-74-2
Iron Oxide (red)	1309-37-1
Iron Oxide (yellow)	51274-00-1
Polyethylene Glycol	25322-68-3

Printing operations utilize

materials consist of

Waste packaging  
bottles, cotton, printed labels and cartons.

These are the only contributions to the solid waste stream expected from the printing and packaging of Asacol tablets.

b. Controls Exercised

All manufacturing, packaging, and labeling operations will be done in full accordance with GMP's and are maintained through the use of appropriate Standard Operating Procedures (SOP's). These SOP's also maintain the condition of the physical facilities, the training and procedures used by operation personnel, and the general control procedures used in the manufacturing, packaging and labeling operations.

Wastewater - Drug substance may enter the aquatic environment as a component of effluent from the plant's on-site wastewater treatment plant. The source of the product and raw material will primarily be from equipment and process area washdown and cleaning procedures. Floor drains will carry the wash water to a central discharge pipe from the building, and from there, directly to an on-site treatment system consisting of 1 settling and two aeration lagoons. Each aeration lagoon has a capacity of 1,250,000 gallons, the settling lagoon has a 385,000 gallon capacity and the entire process has a 35 day retention time. The system is designed for 150,000 gal/day discharge, permitted for 72,500 gal/day and actually discharges approximately 45,000 gal/day. The effluent is monitored on a weekly basis for compliance with a wide variety of discharge parameters, including flow, pH, temperature, BOD, COD etc. The system is well under the discharge limitations for all listed parameters.

Atmospheric - The North Norwich Plant is located in an attainment area for all 6 criteria air pollutants. Air emissions are typically several orders of magnitude below permitted levels. Two separate

are employed to reduce the process air emissions. Up to 80% of the air is recycled back into the plant after a

Solid waste - All labeled product, raw materials and any product-containing manufacturing aids (e.g., filters) are picked up by \_\_\_\_\_ and transported to \_\_\_\_\_ for incineration by \_\_\_\_\_ Actual incineration is done under NYSDEC permit # 10-86-0345. Non-product containing solid waste such as packaging components will be recycled or disposed to the \_\_\_\_\_. The Procter & Gamble Co. has mandated a corporate-wide waste minimization plan for all manufacturing facilities with a goal of reducing non-hazardous waste by 10% annually.

Hazardous waste - No hazardous wastes are generated during the drug printing and packaging operations, however a small amount may be utilized in the QA laboratory. These wastes are segregated and picked up by Rollins Environmental Services and disposed of properly according to EPA permit listed in Appendix B.

Manufacturing - Material Safety Data Sheets (MSDS) for all raw materials are available to personnel in the appropriate areas.

Safety equipment: Personnel in the chemical processing areas are provided with appropriate protective equipment including protective gloves, clothing, respirators, safety shoes, and eye and hearing protection. Further, personnel receive training and instruction in their proper use and disposal.

Air handling equipment: The manufacturing process areas are designed to minimize risk and exposure of the employees to airborne particulates and fumes. Process area air is vented through two separate dust collector systems, the air being forced through a prefilter, filter and a final HEPA filter before being returned to the production facility. The dust collector systems undergo routine cleaning, maintenance, and filter changes to insure efficiency.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

forth in permits, consent decrees and administrative orders applicable to the manufacturing operations as listed in Appendix B.

Material Safety Data Sheets (MSDS) for the drug substance are provided in the original environmental assessment, NDA 19-651 found in Appendix E.

Environmental compliance

Environmental compliance statement for Procter & Gamble Pharmaceuticals, Inc., Germany, the manufacturer of the drug product, is found in Appendix B.

d. Effect of Approval on Compliance with Current Emission Requirements

Manufacturing volume will increase less than 10% as a result of approval of this application and thus, will have no effect on the compliance of the any of the three manufacturing facilities listed in this document. All three facilities are well within allowable limits with regard to any environmental permits as stated in Appendix B.

e. Expected Introduction Concentrations

- i. Expected Introduction Concentration from Use - Please refer to Confidential Appendix D
- ii. Expected Introduction Concentration from Disposal - Solid waste generated from the packaging operations will be disposed to the Chenango County Refuse Disposal Facility in North Norwich, New York. Disposal to this sanitary landfill is permitted by the New York Dept. of Environmental Conservation (DEC), permit # 7A-018, with an expiration date of April, 1997.

**7. Fate of Emitted Substances in the Environment:**

TIER 0: CDER has performed a retrospective review of toxicity information available in EA's previously submitted in support of NDA's and NDA supplements. The data have routinely shown no observed effects on relevant standard environmental test organisms at drug concentrations and therefore are unlikely to have a significant effect on the environment (4). Since the maximum expected environmental concentration (EEC) of 5-ASA from approval of this application has been calculated significantly (see Confidential Appendix D), format items 7, 8, 9, 10 and 11 have been omitted.

**12. List of Preparers:**

Burney S. Schwab  
Environmental Affairs Manager  
Procter & Gamble Co.  
Health Care Research Center  
Mason, Ohio 45040

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**Qualifications:**

- B.S. in Biological Science, M.S. level Microbiology
- 19 years in environmental research
- Author of 12 environmental publications

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13. Certification:

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of Procter & Gamble Pharmaceuticals, Inc.

Date: 4/11/97

Signature: Salvatore L. Mercurio  
Salvatore L. Mercurio

Title: Ass't Secretary, Procter & Gamble Pharmaceuticals, Inc.

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#### 14. References:

1. Asacol (mesalamine) Delayed-Release Tablets, Product Monograph.. Procter & Gamble Pharmaceuticals. March 1995 (Appendix C)
2. Asacol package insert. In Physicians Desk Reference, Medical Economics Data Production Company, Montvale, NJ. 1994.
3. Study # 87086, Vol. 43, page 6, this submission, #S-005.
4. Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation and Research (CDER), November, 1995.
5. A. E. Corey et al. Bioavailability of Single and Multiple Doses of Enteric-coated Mesalamine and Sulphasalazine. J. Inter. Med. Res. 1990. 18: 441-453.
6. M. C. M. Rijk et al. Disposition of 5-Aminosalicylic Acid from 5-Aminosalicylic Acid-Delivering Drugs during Accelerated Intestinal Transit in Healthy Volunteers. Scand. J. Gastroenterol. 1989. 24(10): 1179-1185.

**15. Appendices:**

**B. North Norwich Plant emission permit table; Statements of Compliance for manufacturing facilities in Sweden, and Germany.**

**C. Asacol (mesalamine) Delayed-Release Tablets, Product Monograph. Procter & Gamble Pharmaceuticals.**

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## **APPENDIX B**

**NORTH NORWICH PLANT EMISSION PERMIT TABLE**

**COMPLIANCE STATEMENTS FOR MANUFACTURING  
FACILITIES IN SWEDEN AND GERMANY**

**NORTH NORWICH PLANT**  
**EMISSION PERMIT TABLE**

<b>EMISSION</b>	<b>AGENCY</b>	<b>PERMIT #</b>	<b>EXP. DATE</b>
Wastewater	DEC*	NY0004138	2/1/98
Air (2)	DEC	84000	5/15/01
	DEC	132	5/15/01
Hazardous Waste	EPA	NYD99130458 5	N/A
Petroleum BST**	DEC	7-004820	5/23/01
Waste Transport	DEC	7A-018	4/97

\* Department of Environmental Conservation

\*\* Bulk Storage Tanks

**Procter & Gamble**  
PHARMACEUTICALS

*Procter & Gamble Pharmaceuticals - Germany GmbH*  
*Dr.-Otto-Röhm-Straße 2-4, 64331 Weiterstadt · Postfach 1001 61, 64201 Darmstadt*  
*Telefon 061 511877-0, Telefax 061 511895594*

**STATEMENT OF COMPLIANCE**

The undersigned certify on behalf of Procter & Gamble Pharmaceuticals - Germany GmbH, that the company complies with the German, Hessen and local environmental laws, in particular emissions requirements, in its manufacturing operations.

**Procter & Gamble Pharmaceuticals - Germany GmbH**



**Peter H. Rother**  
**Plant Manager, Weiterstadt**

APPEARS THIS WAY  
ON ORIGINAL



**Thomas M. Finn**  
**General Manager**

APPEARS THIS WAY  
ON ORIGINAL

# **APPENDIX C**

**ASACOL (MESALAMINE) DELAYED-RELEASE**

**TABLETS, PRODUCT MONOGRAPH**

13 Page(s) Redacted

See original

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