CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20535

CHEMISTRY REVIEW(S)

Division of Anti-inflammatory, Analgesic and Dental Drugs
HFD-550
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-535

REVIEW #1 **DATE REVIEWED:** December 18, 1995

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	12-29-94	12-30-94	1-09-95
AMENDMENT	- -	- -	- -

NAME & ADDRESS OF APPLICANT:

Wyeth-Ayerst Laboratories
P. O. Box 8299
Philadelphia, PA 19101-8299

DRUG PRODUCT NAME

Proprietary: NA
Established: Bromfenac Sodium
Code Name/#: AHR-10282B, WAX-121165A
Chem.Type/Ther.Class:

PHARMACOL. CATEGORY: Management of acute and chronic pain, including pain of osteoarthritis and primary dysmenorrhea

DOSAGE FORM: Capsules
STRENGTHS: 25 mg and 50 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

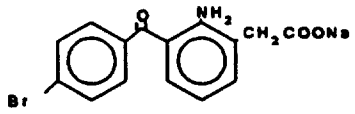
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-amino-3-(4-bromobenzoyl) benzeneacetic acid sodium salt sesquihydrate

For molecular structure, see next page.

REMARKS:

CONCLUSIONS & RECOMMENDATIONS: Not approve.



Bromfenac sodium

$C_{15}H_{11}NO_3BrNa.1.5H_2O$

Molecular Weight: 383.18

1. DMF status:

   DMF #

2. Consultation review status:

   A copy of EA submission has been sent to HFD-004 by CSO Hal Blatt for a consultation review.

3. EER status: A copy of EER requesting inspection of the manufacturing facilities has been forwarded to the Compliance. A copy of the EER is attached to this review.

4. Method validation:

   Copies of method validation packages have been forwarded to the Philadelphia District and St. Louis Lab.

5. Container /closure systems:

Packaged in HDPE bottles, sizes from 30 mL to 1500 mL depending on the market and peel seal blisters and push through blisters. All HDPE bottles and blisters will be packaged in chipboard cartons.

6. Expiration dating period: Request 36 months initially. Firm has revised the expiration date to 24 months.

CONCLUSIONS & RECOMMENDATIONS:

Recommend not approve. Additional information is requested.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-535
HFD-550/Division File
HFD-550/BHo
HFD-550/CKoerner

Bart Ho, Review Chemist

12/18/95

Charlotte A. Yaciw
Acting Chemistry Team Leader

Division of Anti-inflammatory, Analgesic and Dental Drugs HFD-550
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-535

REVIEW #2 **DATE REVIEWED:** December 18, 1995

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	12-29-94	12-30-94	1-09-95
AMENDMENT 1	8-14-95	9-05-95	9-07-95
AMENDMENT 2	9-13-95	9-21-95	9-21-95
AMENDMENT 2	11-22-95	11-24-95	12-06-95

NAME & ADDRESS OF APPLICANT:

Wyeth-Ayerst Laboratories
P. O. Box 8299
Philadelphia, PA 19101-8299

DRUG PRODUCT NAME

Proprietary: NA
Established: Bromfenac Sodium
Code Name/#: AHR-10282B, WAX-121165A
Chem.Type/Ther.Class:

PHARMACOL. CATEGORY: Management of acute and chronic pain, including pain of osteoarthritis and primary dysmenorrhea

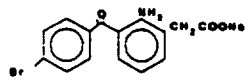
DOSAGE FORM: Capsules
STRENGTHS: 25 mg and 50 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-amino-3-(4-bromobenzoyl) benzeneacetic acid sodium salt sesquihydrate

For molecular structure, see next page.

CONCLUSIONS & RECOMMENDATIONS: Recommend approve with comment.



Bromfenac sodium
$C_{15}H_{11}NO_3BrNa \cdot 1.5H_2O$
Molecular Weight: 383.16

1. DMF status:

   DMF ‡

2. Consultation review status:

   Environmental assessment report was sent to HFD-004 by CSO Hal Blatt for a consultation review and has not yet been returned.

3. EER status:

   a. Inspection of the manufacturing facility at Guayama, Puerto Rico was conducted by the review chemist and inspector Jose Alicea of Puerto Rico District in the week of September 11, 1995. The facility at Guayama, Puerto Rico was found acceptable.

   b. Inspections of the facility at Rouses Point and the facility of the drug substance manufacturer, were also found acceptable.

Note: Wyeth-Ayerst has, on September 13, 1995, withdrawn Rouses Point facility as an alternate site for the packaging of bromfenac drug product.

4.Method validation:

Method validation conducted by the Philadelphia District lab has been completed. The method was found satisfactory. The validation package is attached to this review. The St. Louis Lab has not yet submitted its report.

5. Container /closure systems:

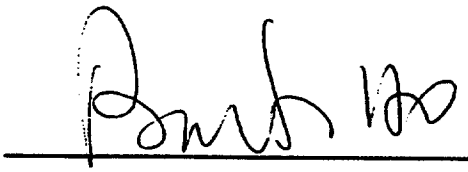
Packaged in HDPE bottles with sizes from 30 mL to 1500 mL depending on the market and peel seal blisters and push through blisters. Twenty four months room temperature stability data has been generated with drug product stored in HDPE bottles of 4's, 100's, and 1000's and with drug product stored in four different combinations of blister packaging materials. Results are all satisfactory and that qualifies the product be stored in these types container/closure systems. All HDPE bottles and blisters packs will be packaged in chipboard cartons.

6. Expiration dating period:

Requested 36 months initially. Firm has revised the expiration date to 24 months.

CONCLUSIONS & RECOMMENDATIONS: Approve with comment:

We recommend that a limit for total quantities of degradation products present in the drug product be established.



Bart Ho, Review Chemist

cc:
Orig. NDA 20-535
HFD-550/Division File
HFD-550/BHo
HFD-550/CSO

HFD-550, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
Review of chemistry, manufacturing, and controls

NDA #: 20-535

REVIEW #3 **DATE REVIEWED:** July 15, 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	12-29-94	12-30-94	1-09-95
AMENDMENT 1	8-14-95	9-05-95	9-07-95
AMENDMENT 2	9-13-95	9-21-95	9-21-95
AMENDMENT 3	11-22-95	11-24-95	12-06-95

NAME & ADDRESS OF APPLICANT:

Wyeth-Ayerst Laboratories
P. O. Box 8299
Philadelphia, PA 19101-8299

DRUG PRODUCT NAME
Proprietary: NA
Established: Bromfenac Sodium
Code Name/#: AHR-10282B, WAX-121165A
Chem.Type/Ther.Class:

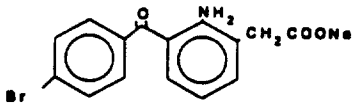
PHARMACOL. CATEGORY: Management of acute and chronic pain, including pain of osteoarthritis and primary dysmenorrhea

DOSAGE FORM: Capsules
STRENGTHS: 25 mg and 50 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
2-amino-3-(4-bromobenzoyl) benzeneacetic acid sodium salt sesquihydrate

For molecular structure, see next page.

CONCLUSIONS & RECOMMENDATIONS: Recommend to approve.



Bromfenac sodium

$C_{15}H_{11}NO_3BrNa \cdot 1.5H_2O$

Molecular Weight: 383.18

1. DMF status:

   DMF #

2. EER status:

   a. Inspection of the manufacturing facility at Guayama, Puerto Rico was conducted by the review chemist and inspector Jose Alicea of Puerto Rico District in the week of September 11, 1995. The facility at Guayama, Puerto Rico was found acceptable.

   b. Inspections of the facility at Rouses Point and the facility of the drug substance manufacturer, were also found acceptable.

      Note: Wyeth-Ayerst has, on September 13, 1995, withdrawn Rouses Point facility as an alternate site for the packaging of bromfenac drug product.

      On a routine Philadelphia District's cGMP inspection of . , the manufacturing site for the bromfenac sodium drug substance, the inspector found numerous cGMP violation: was in the middle of manufacturing bromfenac at the time the investigation was conducted. Many violations were therefore related to this NDA. A 483 was issued to the firm and approval of the NDA was put on hold. Firm has been inspected again and was found acceptable.

4.Method validation:

Method validation conducted by the Philadelphia District lab has been completed. The method was found satisfactory.

5. Container /closure systems:

Packaged in HDPE bottles with sizes from 30 mL to 1500 mL depending on the market and peel seal blisters and push through blisters. Twenty four months room temperature stability data has been generated with drug product stored in HDPE bottles of 4's, 100's, and 1000's and with drug product stored in four different combinations of blister packaging materials. Results are all satisfactory that qualifies the product be stored in these types container/closure systems. All HDPE bottles and blisters packs will be packaged in chipboard cartons.

6. Expiration dating period: Requested 36 months initially. Firm has revised the expiration date to 24 months.

CONCLUSIONS & RECOMMENDATIONS: Recommended for approval in the previous reviews.

Bart Ho, Review Chemist

cc:
Orig. NDA 20-535
HFD-550/Division File
HFD-550/BHo
HFD-550/CSO
HFD-830/Chen
HFD-324/MLynch
DISTRICT OFFICE

Hasmukh B. Patel 7-15-97
Team Leader, Husmukh Patel

Filename: N20535RV3.ABH

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20535

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

BROMFENAC CAPSULES

(BROMFENAC SODIUM)

NDA 20-535

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC,
AND OPHTHALMOLOGIC DRUG PRODUCTS
(HFD-550)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-535

BROMFENAC

(BROMFENAC SODIUM)

Capsules

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 for 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 Bromfenac Capsules, Wyeth-Ayerst Laboratories has prepared an environmental assessment in accordance with *21 CFR 25.31a(a)*, (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. The maximum expected environmental concentration is at a level that normally relieves the applicant from completing format items 7, 8, 9, 10, 11, and 15 in accordance with the tier 0 approach specified in the "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements".

Bromfenac Sodium is a chemically synthesized non-steroidal anti-inflammatory drug indicated for the short-term and long-term

management of pain, including pain of osteoarthritis and primary dysmenorrhea. The drug substance will be manufactured by The drug product will be manufactured by Ayerst-Wyeth Pharmaceuticals, Inc., State Road No. 3, Km 142.1, Guayama, Puerto Rico. The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

Bromfenac Sodium may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. 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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APPEARS THIS WAY
ON ORIGINAL

8/16/96
DATE

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

8/16/96
DATE

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment - FOI copy
Material Safety Data Sheets

APPEARS THIS WAY
ON ORIGINAL

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ENVIRONMENTAL ASSESSMENT INFORMATION

Bromfenac Sodium (25 and 50 mg) Capsules

March 19, 1996

TABLE OF CONTENTS

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1. DATE

March 19, 1996

2. NAME OF APPLICANT

Wyeth-Ayerst Laboratories

3. ADDRESS

P.O. Box 8299
Philadelphia, PA 19101-1245

4. DESCRIPTION OF PROPOSED ACTION

4.1 Requested Approval

Wyeth-Ayerst Laboratories is requesting approval for the production and marketing of 25 mg and 50 mg strengths of bromfenac sodium capsules. This document is arranged as specified in the Center for Drug Evaluation and Research's (CDER) *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (Nov. 1995).

4.2 Need For Action

Bromfenac sodium is a non-steroidal anti-inflammatory drug indicated for the short-term and long-term management of pain, including pain of osteoarthritis and primary dysmenorrhea.

4.3 Location of Production

Manufacturer of the Drug Substance

Bromfenac sodium is synthesized by:

None of the input material used to manufacture the drug substance are proprietary and there is no production conducted at other locations. is an approved supplier of bromfenac sodium and its production takes place at the facility.

An Environmental Compliance Statement from the Environmental Assessment section of _ is located in Appendix C. It certifies that bromfenac sodium is manufactured according to all applicable environmental requirements.

Manufacturer of the Drug Product

The production of bromfenac sodium capsules may take place entirely at:

Ayerst-Wyeth Pharmaceuticals, Inc. (AWPI)
State Road No. 3, Km 142.1
Guayama, Puerto Rico 00784

The Ayerst-Wyeth (AWPI) plant is located in the southern region of the island of Puerto Rico, approximately 3 kilometers north of the Caribbean Sea and 2 kilometers southwest of Guayama along the north side of State Road No. 3. This region is characteristically warmer and drier than other parts of the island due to the influence of the easterly tradewinds and the proximity of the Cordillera Central to the north. According to the USDA (1977), there is no dry or wet season; however, the period between December through April is drier than the remainder of the year. Heavier rains often occur in May and October.

The area surrounding the plant is typical of a rural industrial setting consisting of lands occupied by sugar cane fields and other manufacturing operations. The plant is bordered on the south by sugar cane fields, on the west by another pharmaceutical facility and a parking lot, on the east by an electrical substation, and on the north by Whitehall Laboratories, another pharmaceutical company owned by American Home Products. There are no private residences located near the facility. The facility is located on a 90 acre site, with one main manufacturing building occupying 700,000 square feet.

Packaging of the final drug product may also take place at:

Wyeth-Ayerst Laboratories
64 Maple Street
Rouses Point, NY 12979

The drug product is packaged in high-density polyethylene bottles (HDPE), peel seal blisters and push through blisters. All HDPE bottles and blisters will be packaged in chipboard cartons. Non-contaminated and damaged packing componants will be disposed of as solid waste at the Schuyler Falls, NY landfill.

The Wyeth-Ayerst facility is located in the northeast corner of New York State near the US-Canadian border. The plant is located on an 82 acre site, with two main facilities that consist of 28 buildings occupying 617,000 square feet.

The facility is located in the Village of Rouses Point, NY. The land surrounding the facility is of a flat topography. The facility is bordered by Lake Champlain on the east, by a school on the southeast and by a trailer park on the northwest. The area surrounding the Village of Rouses Point can be described as farmland.

Since minimal emissions occur during packaging, statements in this report regarding environmental controls, waste management, worker protection, manufacturing processes, use of resources and energy, and training and emergency procedures mainly refer to the drug product manufacturing at the Ayerst-Wyeth facility in Guayama, Puerto Rico.

4.4 Locations of Drug Product Use and Disposal

As a prescription drug indicated for the management of short-term and long-term pain, including pain of osteoarthritis and primary dysmenorrhea, this drug will be distributed to locations throughout the United States for oral administration. The amount that is eliminated or excreted will enter the wastewater stream.

Rejected raw material will be shipped back to the supllier.

Returned, recalled, or expired goods will be disposed of in an appropriate manner according to established procedures by Wyeth-Ayerst. The goods may be collected, processed and incinerated at the following location.

Wyeth-Ayerst Laboratories
31 Morehall Road
Frazer, PA 19355

This WAL facility is located in a hilly, light industrial/commercial, suburban area with a temperate climate. The Wyeth-Ayerst facility operates under the following permits:

Permit Name	Permit Number	Issue Date	Expiration Date
Solid Waste Incinerator Permit	400516	12/12/1984	7/4/1997
Municipal Waste Incinerator Permit	15-301-071	7/10/1991	7/30/1998

Incineration may also take place at the following location:

Permit Name	Permit Number	Issue Date	Expiration Date
RCRA Part B Permit: . Department of Pollution Control and Ecology Hazardous Waste Management Permit.		5/26/1988	7/2/1998
Permit Modification Approval Letter		2/19/1992	7/2/1998
USEPA HSWA Hazardous Waste Permit		7/10/1988	7/2/1998
Department of Pollution Control and Ecology -- Air Permit		8/15/1990	none
Department of Pollution Control and Ecology -- Water Permit Renewal submitted 5/2/95		10/28/1990	10/31/1995

Incineration may also take place at the following location.

Permit Name	Permit Number	Issue Date	Expiration Date
RCRA Part B NJDEP Hazardous Waste Facility Permit Renewal application submitted 3/1993		3/31/1989	3/31/1994
US EPA HSWA Permit Renewal application submitted 3/1993		3/31/1989	3/31/1994

Nonhazardous waste may be incinerated at the following location.

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a
u.

Permit Name	Permit Number	Issue Date	Expiration Date
NYSDEC Solid Waste Permit Renewal application submitted 12/1994		5/15/90	5/14/95
NYSDEC Air Permit Renewal application submitted 12/1994		5/11/94	5/14/95

The goods may be sent to the following address for grinding:

Wyeth-Ayerst Laboratories
611 E. Nield Street
West Chester, PA 19382

This WAL facility is located on a 30 acre site in a flat, urban area with a temperate climate.

for subsequent landfill at:

Permit Name	Permit Number	Issue Date	Expiration Date
Solid Waste Disposal Permit		6/24/92	6/24/2002
Form R Special Waste Permit		3/1994	none

Rejected, outdated or returned goods may also be collected and processed at:

for subsequent incineration at:

Permit Name	Permit Number	Issue Date	Expiration Date
Solid Waste Permit		12/31/91	Review 12/1996
Landfill Permit		8/25/1995	8/25/1996
Air Quality Permit		7/12/91	7/1/1996
Water Authority Waste Water Permit		12/20/91	6/30/1996

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THE PROPOSED ACTION

5.1 Nomenclature

5.1.1 Chemical Name

2-amino-3-(4-bromobenzoyl)benzeneacetic acid sodium salt sesquihydrate

5.1.2 United States Adopted Name (USAN)

Bromfenac sodium

5.1.3 Laboratory Codes

AHR-10282-B
WAX-121165A

5.2 CAS Registry Number

120638-55-3

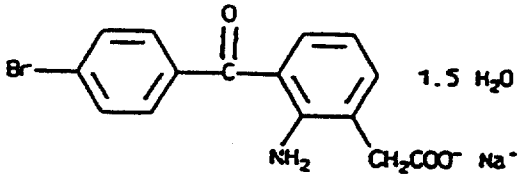
5.3 Molecular Weight

383.17 g/mol

5.4 Molecular Formula

$C_{15}H_{11}BrNO_3Na \cdot 1.5\ H_2O$

5.5 Structural Formula



5.6 Physical Description

5.6.1 Appearance

Bromfenac sodium is a yellow to orange, non-hygroscopic, crystalline powder.

5.6.2 Solubility

Solvent	Solubility (mg/mL)
0.1 N HCl (pH 1.16)	0.05
0.1 M phosphate buffer (pH 7.41)	95.0
0.1 M carbonate buffer (pH 9.12)	225.0
glycerin	260
ethanol	8
PEG-400	313
propylene glycol	150

5.6.3 Melting Point

138-140°C

5.6.4 Acid Dissociation Constant

$pK_a = 4.29$

5.6.5 n-Octanol/Aqueous Buffer Partition Coefficient

Medium	pH	P_{app}*
0.1 M acetate buffer	4.95	39
0.1 M phosphate buffer	7.41	3.22
0.1 M carbonate buffer	9.83	1.31
0.001 N NaOH	12.6	1.64

* P_{app} is the overall apparent partition coefficient and is equal to the sum of the partition coefficients for the undissociated and dissociated species.

5.7 Material Safety Data Sheet (MSDS)

The Material Safety Data Sheet for bromfenac sodium is included in Appendix A.

5.8 Drug Product Composition

Drug product composition information is found in Appendix E.

5.9 Degradation Products

Degradation product information is found in Appendix E.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Substances Expected To Be Emitted During Drug Substance Production and Controls Exercised

The synthesis of bromfenac sodium will take place at the facility identified in paragraph 4.3. Whenever possible, the material, byproducts, and/or emissions from manufacturing are reused/regenerated/recycled back into the process. Where reuse/recycling is not feasible, the materials in question are disposed of or emitted in accordance with appropriate laws and regulations. An Environmental Compliance Statement from the Environmental Assessment section of the Drug Master File (DMF) is located in Appendix C and certifies that bromfenac sodium is maufactured according to all federal, stae and local environmental rules and regulations.

There are no proprietary intermediates used in the manufacture of the drug substance which are produced at other facilities. The drug product is exclusivly manufactured at

6.2 Substances Expected To Be Emitted During Drug Product Production and Controls Exercised

Blending, encapsulation and packaging of the drug product identified in paragraph 5 may take place at the AWPI facility identified in paragraph 4.3. Packaging may also take place at the Wyeth-Ayerst facility also identified in paragraph 4.3. Manufacturing control and permit information for the AWPI facility are described below.

Aqueous Waste

All process related aqueous wastes pass through an on-site complete activated sludge treatment plant with ozonation, treating an average daily flow of 100,000 gpd. The Waste Water Treatment Plant (WWTP) consistently achieves 98% and greater Biochemical Oxygen Demand (BOD) and Chemical Oxygen Demand (COD) removal. Addition of this process is not expected to cause an exceedance of the permitted average daily flow of 236,000 gpd for this discharge point.

The AWPI facility discharges treated waste to Las Mareas Bay under NPDES Permit No. PR0024724. The EPA inspects the AWPI wastewater treatment plant annually (at a minimum). This facility is in compliance with its permit which incorporates the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439).

Solvent Waste

No solvents are used during the production and packaging of bromfenac sodium capsules.

Air Emission

During all manufacturing at this plant, particulates are removed from the work environment via local HEPA filters and dust collection systems. Particulate emissions would not be expected to pose an environmental hazard. Personal safety equipment is worn by operators when handling the drug substance. A 99.99% removal of particulate matter is achieved prior to discharge to the atmosphere. A permit to operate this emission source is granted by the Environmental Quality Board in Guayama, PR. Periodic inspections are conducted by the local authority to ensure all control devices are operated in accordance with the permit parameters.

Solid Wastes

Solid wastes generated during the manufacture and packaging of this product consist of the following:

capsule rejects and damaged product
QA/QC samples and related wastes
exhausted HEPA filters used to purify room air and exhaust

These wastes will be collected and incinerated at one of the following locations:

following permits:

Permit Name	Permit Number	Issue Date	Expiration Date
Environmental Quality Board			
Nonhazardous Facility Operating License			
a. Incineration Operating License		1/18/1993	1/19/1997
b. Recollection Operating License		1/25/1995	1/19/1998
Air Emission Permit		6/25/1993	6/25/1995
(New Title V Operating Permit pending)			
'Jse Permit		6/1/1987	none

Permit Name	Permit Number	Issue Date	Expiration Date
Environmental Quality Board			
Nonhazardous Facility Operating License			

a. Incineration Operating License	9/9/1993	9/9/1996
b. Transportation Operating License	7/22/1994	7/22/1997
Permit	6/30/1995	Pending
Air Emission Permit	7/18/1994	3/31/1996
Use Permit	4/29/1994	none

Non-contaminated, damaged, empty bottles and packaging components will be disposed of as solid wastes at the Guayama, Puerto Rico landfill.

Pollution Prevention

The facility has in place a pollution prevention program. The participants are actively involved in designing the processes for products such as bromfenac sodium capsules.

Addition of this process is not reasonably expected to adversely impact the environment.

6.3 Citation of and Statement of Compliance with Applicable Requirements

6.3.1 Drug Substance Manufacturer

facility identified in paragraph 4.3 is in compliance with all applicable environmental programs. Please refer to Appendix C for a copy of the Environmental Assessment section of the Drug Master File for this facility certifiying that the manufacture of this drug product is in compliance with all applicable environmetal rules and regulations.

6.3.2 Drug Product Manufacturer

The pollution control devices and waste disposal methods described in paragraph 6.2 serve to minimize environmental emissions from the production of bromfenac sodium capsules.

The AWPI facility located in Guayama, Puerto Rico complies with the following federal and state regulations:

Clean Air Act, as Amended

The AWPI facility in Guayama, PR operates under air Permit #PFE-LC-30-0593-0626-I-II-0 (expiration 2/27/2000). Addition of this process is not reasonably expected to affect the compliance status of this facility.

Federal Water Pollution Control Act of 1972, the Clean Water Act, and the Water Quality Act of 1987, as amended

The AWPI facility is in compliance with the state-issued sewage discharge permit No. PR0024724 (expiration 11/30/95, renewal submitted 5/27/95) and with the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439), as described in paragraph 6.2. Addition of this process is not reasonably expected to affect the compliance status of this facility.

The AWPI facility also holds a permit for irrigating the grounds with waters generated from cooling tower blowdown and boiler blowdown. The permit limit is 47,100 gallons per day with a condition of nonirrigation, when precipitation has saturated the ground, making irrigation ineffective.

Resource Conservation and Recovery Act (RCRA) of 1976 and Amendments of 1984

This facility is in compliance with all federal and state regulations governing hazardous waste generators.

Nonhazardous solid waste generated from manufacturing and packaging this product will be disposed of at fully permitted landfills. Any hazardous waste generated from this process will be destroyed at RCRA-permitted disposal facilities in accordance with all applicable regulations.

Wastewater treatment sludge from this facility is subjected to aerobic digestion and dewatering (via sludge drying beds) prior to landfill disposal. Although the EPA's "Standards for the Disposal of Sewage Sludge" (40 CFR 503) do not apply to Industrial Sludges, the AWPI facility sludge has been examined and determined to be in compliance with the "Ceiling limits" for the constituents addressed by this recently promulgated regulation.

Workplace

Chemicals in the workplace are stored, handled, and managed in accordance with Good Manufacturing Practice (GMP) and OSHA standards. Ventilation, air filtration, personal protection equipment, and industrial hygiene monitoring are employed to ensure containment of chemicals and minimal exposure of workers and the workplace to chemicals. GMP regulations are followed for all equipment and operating procedures.

6.4 Effect of Approval on Compliance with Current Emission Requirements

The manufacture of bromfenac sodium capsules will not create any adverse environmental effects. The addition of this process the the AWPI facility will not cause the facility to exceed permit limits for solid waste, wastewater or air. No

endangered or threatened species will be affected and natural resources in critically shore supply will not be depleted.

6.5 Concentration of Bromfenac Sodium in the Environment From From Product Use and Disposal

Bromfenac sodium capsules will be distributed to locations throughout the United States for oral administration. The amount that is eliminated or excreted will enter the wastewater stream. For purposes of this Environmental Assessment, the parent molecule is used to estimate environmental concentrations.

6.5.1 Expected Introduction Concentration (EIC) From Use

The EIC for the aquatic compartment, assuming all bromfenac sodium is used, is evenly distributed throughout the United States per day and without metabolism or depletion mechanisms taken into account is listed below. See Appendix F for EIC calculation.

$$\mathbf{EIC = 1.04 \times 10^{-4}\ ppm}$$

The EIC for the terrestrial compartment is estimated to be zero because any small fraction of bromfenac sodium that might be adsorbed onto the sludge of the wastewater treatment plant will be disposed of in a landfill.

The EIC for the atmospheric compartment is estimated to be zero since bromfenac sodium is a crystalline solid at room temperature and is expected to have a negligible vapor pressure.

6.5.2 Expected Introduction Concentration (EIC) From Disposal

The EIC from disposal is zero since all rejected product and pharmaceutical waste containing bromfenac sodium is disposed of via incineration.

6.6 Expected Environmental Concentration (EEC)

The expected environmental concentration (EEC) of bromfenac sodium has been calculated to be 1.04×10^{-5} mg/l. This concentration was calculated by taking the EIC (1.04×10^{-4} mg/l), a worst case discharge scenario, and assuming a conservative dilution factor of one order of magnitude. The result, 1.04×10^{-5} mg/l, is a conservative estimate of the concentration of bromfenac sodium in the surface waters of the United States. No further depletion mechanisms have been taken into account in this calculation.

6.7 Maximum Expected Emitted Concnetration

The maximum expected emitted concentration (MEEC) is equal to the expected environmental concentration (EEC) or the expected introduction concentration (EIC), whichever is greater. In the case of bromfenac sodium, the MEEC is 1.04×10^{-4} mg/l.

6.8 Tier 0 Requirements

According to the CDER's *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, a drug product will qualify for a Tier 0 classification if its maximum expected environmental concentration (MEEC) is less than 1 part per billion. A Tier 0 classification normally relieves the applicant from completing Environmental Assessment format items 7,8,9,10,11, and 15.

The MEEC of bromfenac sodium, as discussed in paragraph 6.7, is 1.04×10^{-4} mg/l (0.000104 ppm) or 0.104 parts per billion (ppb). Thus, bromfenac sodium qualifies as a Tier 0 drug substance.

12. LIST OF PREPARERS

Diane L. Smith, Ph.D.
Wyeth-Ayerst Laboratories

Craig Seyfried
Wyeth-Ayerst Laboratories

Eunice G. Kulesza
Wyeth-Ayerst Laboratories

The preparers' resumes are provided in Appendix B.

13. CERTIFICATION

The undersigned certifies that the information presented is true, accurate, and complete to the best of the knowledge of Wyeth-Ayerst Laboratories.

Date March 19, 1996

Signature Craig F. Seyfried

Craig Seyfried
Director-Environmental Control
Wyeth-Ayerst Laboratories

14. REFERENCES

1. Pharmaceutical Manufacturers Association, 1991, *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA*. July 1991.

2. U.S. Food and Drug Administration, *Environmental Technical Assistance Handbook*. PB87-175345. U.S. Department of Commerce National Technical Information Service. Springfield, VA, 1987.

3. Center for Drug Evaluation and Research, *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, Nov. 1995.

15. APPENDICES

NON-CONFIDENTIAL

Appendix A	Material Safety Data Sheet
Appendix B	Preparers' Resumes

CONFIDENTIAL

Appendix C	Environmental Assessment From
Appendix D	Five Year Market Estimates
Appendix E	Drug Product Information
Appendix F	Expected Introduction Concentration

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Appendix A

Material Safety Data Sheet

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A.H. ROBINS COMPANY
1211 Sherwood Avenue
Richmond, Virginia 23220

MATERIAL SAFETY DATA SHEET

IDENTIFICATION

NAME: *2-Amino-3-(4-bromobenzoyl)benzeneacetic acid, sodium salt, sesquihydrate*
TRADE NAME AND SYNONYMS: Bromfenac Sodium, AHR-102828
CHEMICAL FAMILY: Arylacetic Acid Salt
PHARMACEUTICAL CLASSIFICATION: Anti-inflammatory/Analgesic
FORMULA: $C_{15}H_{11}BrNNaO_3 \cdot 1.5\ H_2O$
CAS REGISTRY NUMBER: [120638-55-3]

HEALTH HAZARD DATA

THRESHOLD LIMIT VALUE: None established

TOXICITY:

- Oral LD_{50} (mg/kg): Rat (female) 39.6; Rabbit >100 <316; Dog >215. Intravenous LD_{50} (mg/kg): Rat (male) 46.0; Rat (female) 15.0.
  Lifetime studies in rats and mice and one-year administration to monkeys revealed no evidence of carcinogenicity. Ames test for mutagenicity was negative.

EMERGENCY PROCEDURES:

- In case of contact, immediately flush eyes with copious amounts of water, wash skin with soap and water
- If inhaled, remove to fresh air
- Call a physician

PHYSICAL DATA

SOLID: MELTING RANGE: 270-280°C
FORMULA WEIGHT: 383.18
SOLUBILITY IN WATER: >10%
APPEARANCE AND ODOR: Yellow powder, odorless

FIRE AND EXPLOSION HAZARD DATA

EXTINGUISHING MEDIA:

- Carbon dioxide, dry chemical powder or polymer foam
- Water spray

SPECIFIC FIRE FIGHTING PROCEDURES:

- Use self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes

UNUSUAL FIRE AND EXPLOSION HAZARDS:

- Emits toxic fumes under fire conditions

REACTIVITY DATA

STABILITY:
- Stable

INCOMPATIBILITIES:
- NA

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS:
- Carbon monoxide, carbon dioxide, nitrogen oxides

HAZARDOUS POLYMERIZATION:
- Will not occur

SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED:
- Wear self-contained breathing apparatus, rubber boots, and heavy rubber gloves
- Sweep up, place in a bag for waste disposal
- Avoid raising dust
- Ventilate area and wash spill site after material pickup is complete

WASTE DISPOSAL METHOD:
- Material may be burned in an incinerator meeting federal, state, and local regulations
- Observe all federal, state, and local disposal laws

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE

USE CHEMICAL SAFETY GOGGLES
USE COMPATIBLE CHEMICAL-RESISTANT GLOVES
USE OSHA/MSHA-APPROVED RESPIRATOR, IF REQUIRED
USE IN A WELL-VENTILATED FUME HOOD
AVOID CONTACT AND INHALATION
KEEP CONTAINER CLOSED
STORE IN A COOL DRY PLACE

Appendix B

Preparers' Resumes

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DIANE L. SMITH

Wyeth-Ayerst Laboratories
150 Radnor-Chester Rd. Bldg D-3
Saint Davids, PA 19087
(610) 902-3542

EDUCATION

Oregon State University, Corvallis, OR
Doctor of Philosophy, June 1994
Major: Analytical Chemistry — GPA: 3.9/4.0

Iowa State University, Ames, Iowa
Master of Science, August, 1987
Major: Analytical Chemistry — GPA: 3.5/4.0

Stockton State College, Pomona, New Jersey
Bachelor of Science, May 1983
Majors (2): Chemistry — Major GPA: 3.8/4.0
Environmental Studies

CAREER RELATED EXPERIENCE

Wyeth-Ayerst Laboratories Inc., Saint Davids, Pennsylvania
Environmental Scientist, Environmental Control Group 3/1994-present
- Coordinate and Oversee all Environmental Fate and Effects Testing.
- Prepare Environmental Assessments for FDA New Drug Applications.

Oregon State University, Corvallis, Oregon
Research and Teaching Assistant, Chemistry Department 1991-1994
- Developed glow discharge/plasma gas chromatography detectors
- Studied relationships between instrument response and analyte structure
- Conducted multivariate statistical data analysis-Chemometrics

Mobil Oil Corporation, Princeton, New Jersey
Senior Environmental Chemist, Toxicology Division, 1988-1990
- Methods development using HPLC, GC, AA and FTIR
- Environmental/Chemical fate testing: EPA and EINECS methods
- Managed Chemical Repository Unit

Ames Laboratory/Iowa State University, Ames, Iowa
Research and Teaching Assistant, Chemistry Department, 1984-1987
- Developed new applications for ion chromatography
- Supervised undergraduate chemistry laboratories
- Instructed classroom recitations and help sessions

Los Alamos National Laboratory, Los Alamos, New Mexico
Graduate Research Assistant, Summers of 1984 and 1985
- Installed and operated air monitoring instrumentation
- Prepared standard operating procedures and maintenance schedules
- Surveyed general soil characteristics
- Analyzed effects of chemical stabilizers on local soils and vegetation

Cape May County Health Department, Cape May Court House, NJ
Consultant and Analyst for Water Quality Survey, 1982-1983
- Conducted pesticide analysis using gas chromatography with ECD/FPD
- Performed heavy metal analysis using atomic absorption techniques

Stockton Environmental Laboratory, Pomona, New Jersey
Water And Refuse Analyst, 1981-1983

DIANE L. SMITH

SPECIAL SKILLS

HPLC with UV-VIS and RI detection
Gas Chromatography with ECD, FPD, FID, PID
Ion Chromatography with post column detection
Chemometrics HCA and PCA Exploratory Techniques
Electronics and Computer Interfacing
Atomic Absorption Spectroscopy (Flame and Graphite Furnace)
Fourier Transform Infrared Spectroscopy
Air Monitoring Instrumentation: O_3, SO_2, CO, NO_x
Bomb Calorimetry & Wet Chemistry Techniques

PUBLICATIONS

D.L. Smith and E.H. Piepmeier, A Multivariate Approach to Fingerprint Identification of Organic Compounds Using an Oscillating Glow Discharge Detector for Gas Chromatography, *Analytical Chemistry*, accepted November 1994.

D.L. Smith and E.H. Piepmeier, Fingerprint Identification of Organic Compounds Using an Oscillating-Plasma Glow Discharge Detector for Gas Chromatography, *Analytical Chemistry*, 1994, 66, 1323-1329.

D.L. Smith and J.S. Fritz, Rapid Separation of Calcium and Magnesium by Ion Chromatography With Post Column Detection, *Analytica Chimica Acta*, 1988, 201, 87-93.

PRESENTATIONS

Oregon State University Graduate Congress 93, April 25, 1993
A Multivariate Approach to Using Electrical Plasma Oscillations in a Low Pressure GC Detector For Quantifying and Identifying Organic Compounds

ISU Analytical Chemistry Division - Formal Presentation of Literature
Topic: Displacement Chromatography, November 1985
Counter Current Chromatography, April 1986

SHORT COURSES

Executive Enterprises, Inc. October, 1994
Title: Environmental Regulation Course

National Water Well Association, November, 1989
Title: Risk Assessment for the Ground Water Scientist
Title: Environmental Site Assessments

SCHOLARSHIPS AND AWARDS

N.L. Tartar Research Fellowship, Summers 1992 and 1993
Oregon State University Chemistry Department Fellowship
Iowa State University Industrial Scholarship
ISU Chemistry Department Outstanding Graduate Teaching Assistant
National Dean's List
American Institute of Chemists Senior Undergraduate Award

PROFESSIONAL MEMBERSHIPS

American Chemical Society, 1983-present

ACTIVITIES

OSU Graduate Student Recruitment Team
Mobil Oil Corporation
Supervisors Committee Member, Safety Committee
Chromatography Task Force
Stockton Chemistry Society: Secretary
Residence Assistants Selection Committee Member

Craig F. Seyfried
(215) 948-6906

104 Buckwalter Rd.
Royersford, PA 19468

Personal | Married | 5'9" | 39 yrs. old

Education

Completed 3 additional graduate courses in Microeconomic Theory and Application (1988-89)

MBA from Rensselaer Polytechnic Institute, 1982

M.S. in Environmental Health from Temple University, 1978

B.S. in Environmental Science and Resource Management from Lehigh University, 1976

Experience

Wyeth-Ayerst Laboratories Inc., Radnor PA

Associate Director, Environmental Control - July 1992 to present

Manager, Environmental Control - October 1987 - July 1992

Transferred to Central Engineering as the result of the merger of two divisions of American Home Products. Reports to the Vice President - Central Engineering and is responsible for administering environmental policy for all companies under division direction. Implements corporate environmental policies, auditing programs, conducts pre-acquisition assessments, provides guidance and ensures corporate compliance with SARA III and other recently enacted legislation. Provides technical guidance on Central Engineering projects and to facility operations. Edits and publishes intercompany Environmental News Bulletin. Manages and maintains division environmental database. Deals with state and federal agencies on matters of enforcement.

Ayerst Laboratories Inc., Rouses Point, NY

Assistant Director of Engineering Services - December 1986 to October 1987

Responsible for environmental, safety and industrial hygiene engineering as well as security functions at the Ayerst Laboratories Manufacturing and Animal Health Research facilities. Directly supervised the Project Engineer Environmental and Safety, and the Manager of Security. Reported directly to the Vice President of Engineering.

Manager Environmental and Safety - September 1983 to December 1986

Planned and implemented all projects related to pollution control, employee health, safety and fire protection. Prepared necessary permits and negotiated with federal, state and local agencies for approval. Supervised Project Engineer Environmental and Safety.

Project Engineer Environmental and Safety - December 1979 to September 1983

Performed duties related to industrial hygiene, safety and pollution control. Installed various pieces of pollution control equipment including vacuum pumps, packed tower scrubbers, bulk storage tanks and continuous monitoring euqipment. Conducted safety meetings and supervised technicians in the performance of personal monitoring of employee exposures.

Leeds & Northrup Co., North Wales, PA - January 1978 to December 1979

Corporate Environmental and Safety Specialist

Ensured continued compliance with OSHA, EPA and other regulatory agencies. Provided professional consultation on problems relating to employee and product safety, performed industrial hygiene surveys and environmental audits.

Bethlehem Steel Corporation, Bethlehem, PA - September 1976 to August 1977

Coordinated and maintained an air quality monitoring network surrounding ten plants and mines in Eastern U.S. and Canada.

Air Products and Chemicals, Trexlertown, PA - Summer 1976

Wastewater Research and Development Technician

Performed studies to determine optimum backmixing configurations in activated sludge systems.

Miscellaneous

Adjunct Professor for Southern Illinois University 1983 - 1987.
Instructor for the State University of New York at Plattsburgh, 1986-87.

I enjoy running, golf, hockey and most other sports.

Professional Memberships

American Industrial Hygiene Association; Water Pollution Control Association; National Fire Protection Association; Registered Environmental Assessor-State of California.

EUNICE G. KULESZA

Wyeth-Ayerst Laboratories
150 Radnor-Chester Rd. Bldg. C-3
St. Davids, PA 19087
(610) 902-3524

EDUCATION

Drexel University, Philadelphia, PA
Masters of Science, 1986
Major: Environmental Science

Lehigh University, Bethlehem, PA
Bachelor of Arts, 1985
Major: Biology

EMPLOYMENT EXPERIENCE

Wyeth-Ayerst Laboratories, American Home Product, Corp.
Radnor, PA: 4/95 - present
Transferred to Wyeth-Ayerst Laboratories division headquarters as a result of American Cyanamid Company's take over by American Home Product, Corp.

Environmental Specialist: 4/95 - present
Provide technical and regulatory expertise in all aspects of environmental compliance to upper management, seventeen manufacturing and five R & D facilities in American Home pharmaceutical division. Conduct environmental audits and assessments of company manufacturing and laboratory sites. Track and summarize current federal and state regulations for facilities in seven states. Act as liaison between facility personnel, upper management and regulatory agencies. Work closely with the legal department relative to fines, appeals and administrative consent orders. Coordinate and oversee all environmental fate and effects testing. Prepare environmental assessment documents for FDA.

Lederle Laboratories, American Cyanamid Co.
Bound Brook, NJ: 1987-1995

Manager, Environmental & Safety Department: 8/93 - 4/95
Supervised a technical staff of eight in all aspects of environmental, safety and health compliance. This included adherence to federal, state, local and company regulations regarding air, water, solid waste, pollution prevention, TCPA, OSHA, SARA 312 & 313 and Workers' Compensation. Reported to Plant Manager and Divisional Environmental Coordinator. Was responsible for a budget of $1.3 million. Lectured frequently at company environmental programs. Served as a member of the management team responsible for successfully downsizing and reorganizing the Bound Brook facility.

Environmental Manager: 9/92 - 8/93
Coordinated the efforts of a technical staff of three to fulfill all the requirements of federal, state, local and company environmental regulations. Interfaced with company remediation staff relative to ongoing Superfund activities at the facility. Acted as company liaison to The Chemical Industry Council in Trenton. Member of NJDEP subcommittee writing air regulations for industry. Active member of an industry/ government consortium at NJ Institute of Technology in which the applicability and sensibility of NJ environmental regulation was investigated.

Environmental & Industrial Hygiene Specialist: 3/90 - 9/92
Developed and implemented a plant program to comply with the Clean Air Act of 1990. Supervised consultant for this $230,000 project with excellent results. Maintained NPDES water compliance program. Developed air and water data for SARA 313 report as well as other environmental requirements such as air permit applications, emission and effluent reports. Lectured at plant and divisional meetings, developed and conducted training programs for plant personnel. Conducted plant inspections and tours for regulatory inspectors.

Webcraft Technologies, Inc.
North Brunswick, NJ: 2/87 - 10/87

Safety/Environmental Engineer
Developed a plant hazardous waste removal program and coordinated with outside consultants on various projects for a large offset web printing company. Conducted all industrial hygiene sampling, safety meetings, training session and plant tours for company and government personnel.

Clayton Environmental Consultants, Inc.
Edison, NJ: 6/86 - 2/87

Industrial Hygienist
Conducted industrial hygiene assessments in industrial and non-industrial environments, identifying exposures, recommending corrective measures and communicating this information to client and management in written and oral presentation. Expertise in the field of asbestos assessment and abatement, including on-site sample analysis.

ACCOMPLISHMENTS/PROFESSIONAL DEVELOPMENT

Audited divisional environmental program, coordinated necessary improvements, 1995.
Developed plant-wide implementation plan for new effluent regulations, 1995.
Coordinated week long EPA Region II Multi-Media plant inspection, 1993.
Presented Clean Air Act implications program to CEO of company, 1992.
Member of corporate research team investigation health effects of isocyanates, 1989.
EPA accredited AHERA inspector, 1988.
Proficiency Analytical Testing (PAT) Certification for Asbestos. 1986.