CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-998

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-998

Celecoxib 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 Celecoxib Capsules, G.D. Searle & Co. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product. Celecoxib is a chemically synthesized drug which is intended for the management of pain and for the acute and long-term treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

Celecoxib may enter both the aquatic and terrestrial environment from patient use and disposal. Although degradation mechanisms have been demonstrated for the aquatic and terrestrial environment, they are slow. As the drug is expected to persist in the environment for some time, the toxicity of celecoxib to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. 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 used and disposed of 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.

11/18/98
DATE

PREPARED BY
Nancy B. Sager
Environmental Officer
Center for Drug Evaluation and Research

11-23-98
DATE

CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

APPENDICES

Appendix 1. **NON-CONFIDENTIAL APPENDICES**

Appendix 1.1 Citation of and Statement of Compliance with Applicable Emission Requirements

Searle
P.O. Box 363826
San Juan, Puerto Rico 00936-3826
Telephone 609 746 6201

April 15, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
(HFD-357)
5600 Fishers Lane
Rockville, Maryland 20857

Re: COMPLIANCE WITH ENVIRONMENTAL AND OCCUPATIONAL REGULATIONS

SEARLE

Dear Sirs:

This letter certifies that Searle, located at:

99 Jardines Street
Caguas, Puerto Rico 00725

is in full compliance with all air, solid waste, hazardous waste and waste water permits. This letter also certifies that Searle is in complete compliance with all required occupational regulations governing the safety of its workforce.

The proposed manufacture of the SC-58635 drug product is not expected to cause environmental permits to be violated nor cause plant safety to be compromised. The current programs implementing good environmental management practices, policies and procedures will remain in effect.

Sincerely,

Daniel Lebrón
President & General Manager

Searle
P. O. Box 2347
Augusta, Georgia 30903
Telephone (706) 823-6000

April 16, 1998

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-357)
5600 Fishers Lane
Rockville, Maryland 20857

Re: Compliance Certification for Manufacture of Drug Substance

SEARLE

Dear Sirs:

This letter certifies that Searle, located at 1750 Lovers Lane in Augusta, Georgia, is in full compliance with federal, state, and local air, wastewater, solid and hazardous waste environmental regulations and permit conditions.

I also certify that Searle is in complete compliance with all occupational regulations governing the safety of the workforce responsible for the manufacturing, handling, and packaging of the drug substance.

Approval for the manufacture of the celecoxib drug substance will not cause an environmental permit violation to occur at the facility, nor will plant safety be compromised. The environmental management practices, policies, and procedures currently in place at the Searle manufacturing site will remain in effect.

Sincerely,

William DeFer
Site Manager

Appendix 1.2 **MSDS for SC-58635**

MATERIAL SAFETY DATA SHEET

ECTION 1 CHEMICAL PRODUCTS & COMPANY IDENTIFICATION

. SEARLE
). BOX 5110
:CAGO, IL 60680

FOR EMERGENCY SOURCE INFORMATION
CONTACT: ENV. HEALTH & SAFETY
(847) 982-7000

-58635

CAS Number: 169590-42-5
RTECS: Not Assigned

3STANCE: Celecoxib

ADE NAMES/SYNONYMS: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-
:azol-1-yl]benzenesulfonamide; SC58635

CREATION DATE: 5/17/94 REVISION DATE: 11/3/97

ECTION 2 COMPOSITION/INFORMATION ON INGREDIENTS

MPONENT	CAS NUMBER	PERCENTAGE	EXPOSURE GUIDELINES (8-hr. TWA)
-58635	169590-42-5	100	Not established

ECTION 3 HAZARDS IDENTIFICATION

RATINGS (Scale 0-4): Health=2 Fire=1 Reactivity=1
(U=Unknown)

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EMERGENCY OVERVIEW:
Celecoxib is a white solid material developed as an anti-inflammatory drug. The toxicological, physical and other potential hazards associated with this chemical have not been fully characterized. Care should be exercised in handling.
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ENTIAL HEALTH EFFECTS:

ALATION:
SHORT TERM EXPOSURE: No information regarding inhalation hazards
LONG TERM EFFECTS: No information regarding inhalation hazards

N CONTACT:
SHORT TERM EXPOSURE: No information regarding skin irritation
LONG TERM EFFECTS: No information regarding skin contact

CONTACT:
SHORT TERM EXPOSURE: May cause irritation
LONG TERM EFFECTS: See Short Term Exposure

ION:

SHORT TERM EXPOSURE:
Based on early studies, it appears that the predominant adverse effects of clinical use of this drug are: Flu-like symptoms, headache, fever, chills, fatigue, joint and muscle aches, flushing, cardiac arrhythmias, superventricular tachycardia, congestive heart failure and platelet count decreases.
LONG TERM EFFECTS: No information regarding ingestion hazards

CINOGEN STATUS: No information available

ECTION 4 FIRST AID MEASURES

ALATION:
Remove to fresh air, monitor blood pressure, respiration, temperature and general condition. Get medical attention promptly.

N CONTACT:
Remove contaminated clothing. Wash skin with soap and water. Get medical attention if irritation develops.

CONTACT:
Immediately flush eyes with large amounts of water for 15 minutes. Get medical attention promptly.

ESTION:
Provide general support and monitor blood pressure, respiration, emperature and general condition. Get medical attention promptly.

E TO PHYSICIAN: See Section 11
IDOTE: No antidote appropriate. Supportive care as indicated.

ECTION 5 FIRE FIGHTING MEASURES

E AND EXPLOSION HAZARD: Will burn if involved in a fire

SH POINT: Not applicable

ER FLAMMABLE LIMIT: Not applicable

ER FLAMMABLE LIMIT: Not applicable

OIGNITION: Not applicable

MMABILITY CLASS (OSHA): Not known

ARDOUS COMBUSTION PRODUCTS:
Hydrogen fluoride, oxides of nitrogen and sulfur

INGUISHING MEDIA:
Use dry chemical, carbon dioxide, water spray, regular foam or xtinguishing agent suitable for surrounding fire.

EFIGHTING:
Evacuate area and fight fire from a safe distance. As in any fire, ear pressure demand self-contained breathing apparatus, and full protective gear.

ECTION 6 ACCIDENTAL RELEASE MEASURES

UPATIONAL SPILL:
Vacuum material with HEPA filtered vacuum cleaner or wet sweep. Collect waste for proper disposal. Keep unnecessary people away. Do not flush spilled material into sewer.

ECTION 7 HANDLING AND STORAGE

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with adequate ventilation. Avoid breathing dust. Avoid contact with s, skin or clothing. No special storage provisions necessary.

ECTION 8 EXPOSURE CONTROLS/PERSONAL PROTECTION

SUREMENT METHOD: Not established

ATION: Local exhaust ventilation

PROTECTION: Safety glasses

THING: Long sleeves (if potential for skin contact) and disposable coveralls.

VES:
Chemically resistent gloves should be used. This compound has not been specifically evaluated for glove suitability.

PIRATORY PROTECTION:
Choice of respirators can vary depending on individual circumstances. The specific application should be evaluated to determine if the following recommendations are appropriate.

HEPA air-purifying respirator for operations with adequate ventilation but with some potential for exposure (such as manual transfer operations).

Supplied-air respirator for operations without adequate ventilation.

FIREFIGHTING AND OTHER IMMEDIATELY DANGEROUS TO LIFE OR HEALTH DITIONS WEAR: Self-contained breathing apparatus

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ION 9 PHYSICAL AND CHEMICAL PROPERTIES

SCRIPTION: White solid
LAR WEIGHT: 381.38
JLAR FORMULA: C17H14F3N3O2S
ILING POINT: Not applicable
EZING/MELTING POINT: 156-157 C
POR PRESSURE: Not applicable
POR DENSITY: Not applicable
ECIFIC GRAVITY: Not known
TER SOLUBILITY: Not soluble in water
LATILITY: Not applicable
OR THRESHOLD: Not known
APORATION RATE: Not applicable
SCOSITY: Not applicable
LVENT SOLUBILITY:
Acetone, ethanol, DMSO, ethyl acetate and methylene chloride
: Not applicable

SECTION 10 STABILITY AND REACTIVITY

ACTIVITY: Stable under normal conditions of temperature and pressure.

NDITIONS TO AVOID: Not known

COMPATIBILITIES: Not known

OUS DECOMPOSITION:
Hydrogen fluoride, oxides of nitrogen and sulfur

LYMERIZATION: Not known

SECTION 11 TOXICOLOGY INFORMATION

E EFFECTS: Minimal irritant in rabbits

N EFFECTS: Non-irritating in rabbits

TE TOXICITY DATA:
Rat--Oral LD50: > 2000 mg/kg
Dog--Oral LD50: > 2000 mg/kg

AGENICITY:
Negative in the Ames Assay. Negative in mammalian assays for mutagenicity. Negative for direct DNA damage in vitro.

CINOGENICITY: Not known

ONIC EFFECTS:
A NOEL of 20 mg/kg/day was reported in a six (6) month study in rats.

CHRONIC EFFECTS:
Gastrointestinal injury (300 mg/kg/day and higher) and renal effects (1000 mg/kg/day) have been observed in mice in a 2 week dietary study. The no-observed-effect-level (NOEL) was 100 mg/kg/day in males and 300 mg/kg/day in females.

A NOEL of 20 mg/kg/day was reported in a 13 week oral dose study in rats.

In a 4 week oral dog study, mortality/moribundity was seen at doses of 100 mg/kg/day and higher. A NOEL of 35 mg/kg/day was reported in a 13 week oral dose study in dogs. Gastrointestinal injury and renal effects were noted at doses of 50 mg/kg/day and higher. The NOEL dose was 25 mg/kg/day. These target organ effects are consistent with those reported for NSAIDS.

RODUCTIVE:
Evidence of embryotoxicity was observed at exposures greater than ten times the projected efficacious exposure. This effect is consistent with effects reported for non-steroidal anti-inflammatory drugs (NSAIDS).

ATOGENICITY:
No evidence of malformations produced by SC-58635 was observed in studies in rats and rabbits.

AL EFFECTS:
Negative for antigenicity in studies with mice and guinea pigs. Negative in a guinea pig maximization study for dermal sensitization.

GET EFFECTS:
Gastrointestinal tract and kidney.

INCREASED RISK FROM EXPOSURE: Not known

ITIONAL DATA: None

ECTION 12 ECOLOGICAL INFORMATION

IRONMENTAL OVERVIEW:
The environmental and ecological aspects of this chemical have not been fully characterized. Care should be used in handling.

TE AQUATIC TOXICITY: Not known

RADABILITY: Not known

BIOCONCENTRATION FACTOR (BCF): Not known

OCTANOL/WATER PARTITION COEFFICIENT: Not known

ION 13 DISPOSAL INFORMATION

:inerate in approved facility. Observe all federal, state and local
:tions when disposing of this substance.

SECTION 14 TRANSPORTATION INFORMATION

ZARDOUS MATERIALS DESCRIPTION/PROPER SHIPPING NAME: IATA (air): Other
gulated substance, 9, ID 8027; DOT (ground): Not regulated

ZARD CLASS: 9

ENTIFICATION NUMBER: ID 8027

SECTION 15 REGULATORY INFORMATION

NECS NUMBER: Not assigned
ZA STATUS: Not applicable
RCLA SECTION 103 (40CFR302.4): Not applicable
RA SECTION 302 (40CFR355.30): Not applicable
RA SECTION 304 (40CGR355.40): Not applicable
RA SECTION 313 (40CFR372.65): Not applicable
HA PROCESS SAFETY (29CFR1910.119): Not applicable
LIFORNIA PROPOSITION 65: Not applicable
RA: Not applicable

RA HAZARD CATEGORIES, SARA SECTIONS 311/312 (40 CFR 370.21)
JTE HAZARD: Not applicable
RONIC HAZARD: Not applicable
RE HAZARD: Not applicable
ACTIVITY HAZARD: Not applicable
DDEN RELEASE HAZARD: Not applicable

e information here provided is believed to be accurate and represents
e best information currently available to Searle, and Searle assumes no
ability resulting from its use. Users should make their own
vestigations to determine the suitability of the information for their
rticular purposes.