

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-799

ENVIRONMENTAL ASSESSMENT

**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT**

FOR

**Floxin®
(Ofloxacin)
Otic Solution, 0.3%
NDA 20-799**

Daiichi Pharmaceutical Corporation

**U. S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS**

(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-799

Floxin®

(Ofloxacin)

Otic Sterile Solution, 0.3%

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 it 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 Floxin®, Daiichi Pharmaceutical Corporation has prepared an environmental assessment (attached) in accordance with 21 CFR 25.31a(b)(3) which evaluates the potential environmental impact of the manufacture, use and disposal of the product.

Ofloxacin is a chemically synthesized drug which is administered as a sterile otic (auditory canal) solution in the treatment of otitis externa and otitis media in adults and children. The drug substance will be manufactured by Daiichi Pharmaceutical Corporation in Akita City, Japan. The drug product will be manufactured by Park-Davis Sterile Products, Division of Warner-Lambert, Rochester, Michigan. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Ofloxacin may enter the environment from manufacturing sites, disposal of pharmaceutical waste, and from patient use. Due to the relatively limited projected use in this country, adverse environmental effects from distribution are not anticipated.

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. Rejected or returned drug product will be disposed of at a licensed class III landfill. 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.

ISI

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

3/25/97
Date

ISI

CONCURRED / 0
Nancy B. Sager
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Center for Drug Evaluation and Research

3/25/97
Date

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)

Copies:

HFD-520

B. V. Shetty, Ph.D., Chemist
Original to NDA 20-799, through B. V, Shetty, Ph.D.
Division File for NDA 20-799

HFD-205

FOI Copy

HFD-357

EA File
Docket File
C. Berninger

file name: c:\fonsi\20799e01.fcb

**OFLOXACIN OTIC SOLUTION
ENVIRONMENTAL IMPACT ASSESSMENT**

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* Environmental Impact Assessment Format Items 7. through 11. are not addressed in this Assessment. Because the drug product is administered topically, Regulation 21 CFR 25.31a(b)(3) applies to this submission. These format items are, therefore, not required in this assessment.

**OFLOXACIN OTIC SOLUTION
ENVIRONMENTAL IMPACT ASSESSMENT**

1. Date

October 28, 1996

2. Applicant

Daiichi Pharmaceutical Corporation

3. Address

One Parker Plaza
400 Kelby Street
Fort Lee, New Jersey 07024

4. Description of Proposed Action

a. Requested Approval

Daiichi Pharmaceutical Corporation is filing an NDA pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for FLOXIN[®] Otic (ofloxacin otic solution, 0.3%). The product is packaged in multiple-dose, low-density, polyethylene bottles, 5 mL per bottle. Each milliliter of product contains ofloxacin (0.3%) with benzalkonium chloride (0.0025%), sodium chloride, Water for Injection, hydrochloric acid, and/or sodium hydroxide to adjust pH. An abbreviated environmental impact assessment is hereby submitted pursuant to 21 CFR 25.31a(b)(3). (Please refer to Appendix 1 for certification.)

Drug Product Application Number: Pending

b. Need for Action

FLOXIN[®] Otic (ofloxacin otic solution, 0.3%) is intended for instillation into the auditory canal for the treatment of otitis externa and otitis media in adults and children, caused by gram-positive and/or gram-negative microorganisms.

c. Production Locations

(1) Drug Substance Manufacturing Facility

Daiichi Pharmaceutical Co., Ltd.

Akita Plant

1-10-1 Mukaihama Akita City

Akita 010-16, Japan

The ofloxacin drug substance is manufactured by Daiichi Pharmaceutical Co., Ltd., in Akita, Japan, in compliance with applicable environmental laws and regulations. (Appendix 2 includes a "Foreign Drug Substance Manufacturer's Statement" for Daiichi Pharmaceutical Co., Ltd.) Please refer to DMF No. _____ for ofloxacin drug substance for information regarding the chemical synthesis process.

(2) Drug Product Manufacturing Facility

Parke-Davis
Sterile Products
Division of Warner-Lambert
870 Parkdale Road
Rochester, Michigan 48307

Establishment Registration Number:	18-18977
Facility Number:	630277
EPA Identification Number:	MID 005380126
Standard Industrial Code Classification:	2830
County or Plant Location:	63
Plant UTM Coordinates:	UTM Zone 17 UTM East (KM) 434200 UTM North (KM) 2327200
TRI Facility Identification Number:	48063WRNRL870PA

Bulk solution compounding, sterile filtration, filling, and packaging and labeling operations associated with FLOXIN[®] Otic (ofloxacin otic solution, 0.3%) are performed at the Parke-Davis Sterile Products Facility in Rochester, Michigan. The Parke-Davis Rochester Facility has produced pharmaceuticals at this location since 1908.

The Parke-Davis Sterile Products Facility is located on 82 acres of land in Oakland County on the east side of the city of Rochester, which is approximately 30 miles north of Detroit, in the state of Michigan. The property consists of mainly grass and buildings and lies adjacent to the Clinton River, approximately 35 miles upstream from Lake St. Clair. The manufacturing facility campus consists of 33 buildings and employs an average of 570 individuals. The closest structure to any Parke-Davis Rochester Facility building is approximately 50 feet away. The facility campus is completely enclosed by a chain-link fence.

- Access is maintained and monitored by a full-time security force. Surroundings consist of a city park to the south, residential homes to the north, light manufacturing to the east, and vacant land to the west. More than 60% of the surrounding property is undeveloped and used by natural wildlife. Approximately 40% of the surrounding land is forested and is part of the Clinton River Flood Basin. Approximately 20% of the total land is abandoned farmland that consists of field grass and young trees.

d. Locations of Use

(1) The End-User of the Drug Product

The end-users of the drug product will be hospitals, clinics, and patients in their homes.

(2) Specific Geographic Locations

There is no particular geographic area in which use of the subject drug would be concentrated.

e. Disposal Sites

(1) Drug Substance Manufacturer

Waste drug substance is disposed of by the manufacturer in accordance with applicable Japanese environmental laws. (Please refer to Appendix 2 for signed statement from the manufacturer.)

(2) Drug Product Manufacturer

Rejected drug product is sorted according to its hazard classification. The product waste is then either crushed to reduce volume or transported intact to an off-site incinerator. The crushed solid particles of glass and plastic are triple-rinsed and combined with incinerator ash and disposed of as a special waste in a Class III landfill. Nonhazardous liquids are combined with plant cleaning and cooling water at the municipal waste treatment plant, where it is treated by an activated sludge process. All hazardous waste liquids and solid materials (except those excluded materials such as asbestos) are manifested, transported off-site by a licensed waste hauler, and destroyed by incineration or treatment in accordance with local, state, and federal environmental regulations. (Please refer to Appendix 3 for a signed statement of compliance for the drug product manufacturer.)

(3) End-Users

Empty or partially-empty packages will be disposed of according to hospital, pharmacy, or clinic procedures. Those empty or partially-empty packages used in residences will be disposed of by the community's solid waste management system, which may include landfills and incineration. Minimal quantities of unused drug may be disposed of in the sewer system.

5. Identification of Chemical Substances That Are the Subject of the Proposed Action

a. Drug Substance Nomenclature

(1) Established Name

Ofloxacin

(2) Brand/Proprietary Name

FLOXIN®

(3) Chemical Names

(a) (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

(b) 7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (±)-

b. Drug Substance Characteristics

(1) Chemical Abstracts Registration Number

82419-36-1

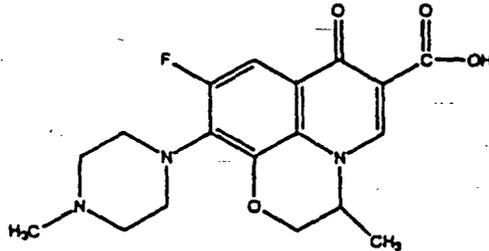
(2) Molecular Formula

$C_{18}H_{20}FN_3O_4$

(3) Molecular Weight

361.38

(4) Structural Formula



(5) Physical Description

Odorless, slightly yellowish white crystalline powder. (Please refer to Appendix 4 for the Material Safety Data Sheet for Ofloxacin.)

c. Formulation Excipients

Please refer to the following table.

Table I
 Formulation Excipients

CAS No.	Components	Concentration (mg/mL)	Quantity (g) per Batch (150 kg)
7647-14-5	Sodium Chloride, USP	9.0	
N/A	Benzalkonium Chloride, NF	0.025	
7647-01-0	Hydrochloric Acid, NF	As required [ⓐ]	As required [ⓐ]
1310-73-2	Sodium Hydroxide, NF	As required [ⓐ]	As required [ⓐ]
N/A	Water for Injection, USP	q.s.	kg + q.s. to final weight

N/A = Not available.

ⓐ = Hydrochloric acid (%) and sodium hydroxide solutions are used for pH adjustments during preparation of the ofloxacin otic bulk solution.

d. Impurities

There are no known impurities likely to be found at levels %.

6. Introduction of Substances Into the Environment

a. Substances Expected to be Emitted

CAS No.	Name	Emission Form
N/A	Benzalkonium Chloride, NF	Air, liquid-waste stream, solid waste
7647-14-5	Sodium Chloride, USP	Liquid-waste stream, solid waste
7647-01-0	Hydrochloric Acid, NF	Negligible amount in liquid-waste stream
1310-73-2	Sodium Hydroxide, NF	Negligible amount in liquid-waste stream
82419-36-1	Ofloxacin	Air, liquid-waste stream, solid waste

N/A = Not available.

b. Controls Exercised

Please refer to c.(1) and c.(2), below.

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

(1) Drug Substance Manufacturer

The ofloxacin drug substance is manufactured by Daiichi Pharmaceutical Co., Ltd., in Akita, Japan, in compliance with applicable environmental laws and regulations. Please refer to Appendix 2 for a signed statement from the manufacturer.

(2): Drug Product Manufacturer

(a) Waste Disposal and Minimization

It is anticipated that minimal quantities of drug product will be introduced into the immediate environment during the compounding, filling, and packaging processes performed at the Parke-Davis Rochester Facility. Wash and rinse water from equipment cleaning will contain residual drug product and excipients. Airborne particles of drug substance may be generated during the compounding process; however, dust collection systems in the facility will route the dust into an air-handling system designed to filter out the solid particles prior to discharge to the atmosphere outside the building.

The Parke-Davis facility utilizes established procedures to minimize solid and liquid-waste production. Solid waste is removed by established housecleaning procedures, recycling and incineration. Chemical shipping containers, pallets, and overwrapping materials are recycled, and protective clothing is washed and sterilized off-site then returned for re-use. All product waste from the manufacturing lines is sorted according to its hazard classification. The product is then either crushed to reduce volume or transported intact to an off-site incinerator. The crushed solid particles of glass and plastic are triple-rinsed, then combined with incinerator ash, and disposed of as a special waste in a Class III landfill. The liquid or rinse material, if nonhazardous, is combined with plant cleaning and cooling water at the municipal waste treatment plant where it is treated by an activated sludge process. All hazardous waste liquids and solid

: materials (except those excluded materials such as asbestos) are manifested, transported off-site by a licensed waste-hauler, and destroyed by incineration or treatment in accordance with local, state, and federal environmental regulations.

(b) Air Resources

Air emissions are regulated by the Michigan Air Pollution Act and the Federal Clean Air Act. Compliance with these acts is controlled by the Michigan Department of Environmental Quality (DEQ). Indoor air quality is monitored by Parke-Davis and ambient air quality is tested on an as-needed basis. A list of air permits is included in Appendix 5.

(c) Water Resources

Aqueous resources are regulated by a number of governing laws and regulations. Compliance with these programs is administered by the Michigan Department of Environmental Quality and the Detroit Water and Sewerage Department, city of Detroit. The Parke-Davis Rochester Facility receives its water from underground wells owned by the city of Rochester. The immediate surrounding community is either served by Rochester city water or water from the city of Detroit. All of Rochester's waste water, except storm water, is discharged to the city of Detroit waste water treatment plant where it is treated by an activated sludge process. The storm water is discharged through the storm water discharge system into the Clinton River. Information pertaining to water permits is included in Appendix 5.

d. Discussion of the Effect of Approval on Compliance With Current Emission

Increase in production of the subject drug product is not expected to have any bearing on the firm's ability to continue to comply with state, federal, and local laws pertaining to emissions. (Please refer to Appendix 6 for calculations.)

e. Expected Introduction Concentrations

(1) Expected Introduction Concentration From Use

The following equation was used to calculate the quantity of drug available for consumption by the end-user:

$$A = b \times c \times d$$

where:

A = kg/year produced

b = Number of batches to be made

c = Amount of drug substance in one batch

d = Expected yield

- The expected introduction concentration (EIC) entering into the aquatic environment from patient use, assuming all available product estimated for the fifth year is consumed, with even distribution throughout the U.S. per day, is calculated as follows:

$$\text{EIC-Aquatic (ppm)} = A \times B \times C \times D$$

where:

- A = kg/year produced
B = $1/1.115 \times 10^{11}$ (liters per day entering POTW's)¹
C = 1/365 (number of days in year)
D = 10^6 mg/kg (conversion factor)

$$\text{EIC-Aquatic} = <1 \text{ ppb}$$

Please refer to Appendix 6 for calculations.

(2) Expected Introduction Concentration From Disposal

As stated previously in this environmental impact assessment, disposal methods utilized by the drug product manufacturer are in compliance with EPA and state agencies. It is not anticipated that large quantities of the drug product will be disposed of at the manufacturing site through the sewer system.

7. - 11. Format Items 7. through 11. are not addressed in this Assessment.

¹ 1.115×10^{11} liters per day entering publicly owned treatment works ("POTW's"), Source: *Guidance for Industry: For the Submission of an Environmental Assessment in Human Drug Applications and Supplements*; Center for Drug Evaluation and Research: November 1995.

12. List of Preparers

Amy Domanowski, Ph.D.
Director, Regulatory Affairs
Daiichi Pharmaceutical Corporation

Michael C. Beckloff
Chief Executive Officer
Beckloff Associates, Inc.

13. Certification

Please refer to Appendix 1.

14. References

Drug Master File No

15. Appendices

Nonconfidential

1. Sponsor Certification
2. Foreign Drug Substance Manufacturer's Statement [in compliance with Format Item (6)(b) and (6)(c)].
3. Drug Product Manufacturer's Statement
4. Ofloxacin Material Safety Data Sheet

Confidential

5. Parke-Davis, Rochester Facility, Environmental Permits (B-100 Manufacturing)
6. Expected Introduction Concentrations

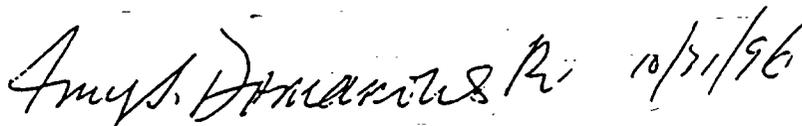
Appendix 1

Nonconfidential

Sponsor Certification

The undersigned official certifies that the information presented in the Environmental Impact Assessment for FLOXIN[®] Otic (ofloxacin otic solution, 0.3%) is accurate and complete to the best of the knowledge of the firm or agency responsible for preparation of the EA.

The undersigned official certifies that the Environmental Impact Assessment summary document (pages 1 - 14) and Appendices 1, 2, 3, and 4 (pages 15 - 21) contain nonconfidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR Section 1506.6.



Amy Domankowski, Ph.D.

Director, Regulatory Affairs

Daiichi Pharmaceutical Corporation

Appendix 2

Nonconfidential

Foreign Drug Substance Manufacturer's Statement

The Daiichi Pharmaceutical Co., Ltd., facility where ofloxacin drug substance is manufactured is maintained in accordance with all applicable Japanese environmental laws pertaining to control of emissions and disposal of waste products associated with drug synthesis.



Masaaki Kobayashi

General Manager of Quality Assurance Department

Daiichi Pharmaceutical Co., Ltd.

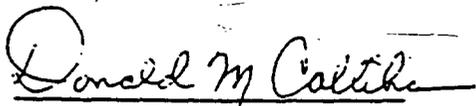
Appendix 3

Nonconfidential

Drug Product Manufacturer's Statement of Compliance

The undersigned official certifies that the information presented in the Environmental Impact Assessment for FLOXIN® Otic (ofloxacin otic solution, 0.3%) as applicable to the Drug Product Manufacturing facility is accurate and complete to the best of the knowledge of the firm or agency responsible for preparation of the EA.

The undersigned official certifies that the Environmental Impact Assessment summary document (pages 1 - 14) and Appendices 1, 2, 3, and 4 (pages 15 - 21) contain nonconfidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR Section 1506.6.

 10/27/96

Donald M. Callihan
Director of Engineering
Parke-Davis Sterile Products
Division of Warner-Lambert

Appendix 4

Nonconfidential

Ofloxacin Material Safety Data Sheet

REF. NO. _____

Material Safety Data Sheet

DATE PREPARED : June 1994

SECTION I - IDENTITY

CAS NO. : 83380-47-6
COMMON NAME : Ofloxacin
(As Used on Label and List)
CHEMICAL NAME : (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid
FORMULA : $C_{18}H_{20}FN_3O_4$ m.w. 361.37
MANUFACTURER'S NAME : DAIICHI PHARMACEUTICAL CO., LTD.
EMERGENCY TELEPHONE NO. : 03-272-0611
ADDRESS (Number, Street, City, State, and ZIP Code) : 14-10, Nihonbashi 3-Chome, Chuo-ku, Tokyo 103 Japan
TELEPHONE NUMBER FOR INFORMATION : 03-3272-0611

SECTION II - HAZARDOUS INGREDIENTS/IDENTITY INFORMATION

HAZARDOUS COMPONENTS : Non-hazardous according to the criteria of OSHA hazard-communication standard.

SECTION III - PHYSICAL/CHEMICAL CHARACTERISTICS

BOILING POINT : n.a.
SPECIFIC GRAVITY ($H_2O = 1$) : n.a.
VAPOR PRESSURE (mm Hg.) : n.a.
MELTING POINT : 260 - 270°C (dec.)
VAPOR DENSITY (AIR = 1) : n.a.
EVAPORATION RATE : n.a.
(Butyl Acetate = 1)
SOLUBILITY IN WATER : 1g/500ml
APPEARANCE AND ODOR : Slightly yellowish white crystalline powder and odorless

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (Method used) : n.a.
FLAMMABLE LIMITS : n.a.

DAIICHI PHARMACEUTICAL CO.LTD

14-10, NHOHNBASHI 3-CHOME,
CHUO-KU, TOKYO 103 JAPAN

EXTINGUISHING MEDIA : Water spray, dry chemical, carbondioxide or foam as appropriate for surrounding fire and materials.

SPECIAL FIRE FIGHTING PROCEDURES : As with all fires, evacuate personnel to safe area, firefighters should use selfcontained breathing equipment and protective clothing.

UNUSUAL FIRE AND EXPLOSION HAZARDS : When heated to decomposition material emits toxic fumes of NOx. This material is assumed to be combustible.

SECTION V - REACTIVITY DATA

STABILITY UNSTABLE :
STABLE : x
CONDITION TO AVOID : Light and ultraviolet rays
INCOMPATIBILITY (Materials to avoid): n.a.
HAZARDOUS DECOMPOSTION BYPRODUCTS : When heated to decomposition material emits toxic fumes of NOx.

HAZARDOUS POLYMERIZATION
MAY OCCUR :
WILL NOT OCCUR : x
CONDITIONS TO AVOID :

SECTION VI - HEALTH HAZARD DATA

ROUTE(S) OF ENTRY INHALATION ? : x
SKIN :
INGESTION ? : x

HEALTH HAZARDS (Acute and Chronic)
Acute : Eye, skin, and/or respiratory tract irritation
Chronic : n.a.

CARCINOGENICITY NTP : none
LARC MONOGRAPHS ? : none
OSHA REGULATED ? : none

SIGNS AND SYMPTOMS OF EXPOSURE : n.a.
MEDICAL CONDITIONS GENERALLY : n.a.
AGGRAVATED BY EXPOSURE

EMERGENCY AND FIRST AID PROCEDURE :

Remove from exposure. Remove contaminated clothing. Persons developing serious hypersensitivity reactions must receive immediate medical attention. Upon eye or skin contact, flush affected area with copious quantities of water. Obtain medical attention. If not breathing give artificial respiration. If breathing is difficult give oxygen.

DAIICHI PHARMACEUTICAL CO.LTD

14-10, NIHONBASHI 3-CHOME,
CHUO-KU, TOKYO 103 JAPAN

SECTION VII - PRECAUTIONS FOR SAFE HANDLING AND USE

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED : Wear NIOSH approved dust mask and rubber gloves. Sweep up spillage.
WASTE DISPOSAL METHOD : Dispose of waste in accordance with all applicable Federal, State and local laws.
PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE : Store in tight container as defined in the United States Pharmacopoeia.
OTHER PRECAUTIONS : none

SECTION VIII - CONTROL MEASURES

RESPIRATORY PROTECTION (Specify type): Dust mask required
VENTILATION LOCAL EXHAUST : Recommended
MECHANICAL (General) : Recommended
SPECIAL : n.a.
OTHER : n.a.
PROTECTIVE GLOVES : Latex or rubber
EYE PROTECTION : Glasses or goggles
OTHER PROTECTIVE CLOTHING OR EQUIPMENT : Cover skin and eyes

DAIICHI PHARMACEUTICAL CO., LTD.

Yuji Matsuda

Y. Matsuda, Manager
Production Planning & Administration
Department
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