CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-799

CHEMISTRY REVIEW(S)

Duvall-Miller 520

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-799 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 1/15/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/18/96	12/20/96	12/30/96

NAME & ADDRESS OF APPLICANT: Daiichi Pharmaceutical Corporation
One Parker Plaza
Fort Lee, New Jersey 07024

APR 7 1997

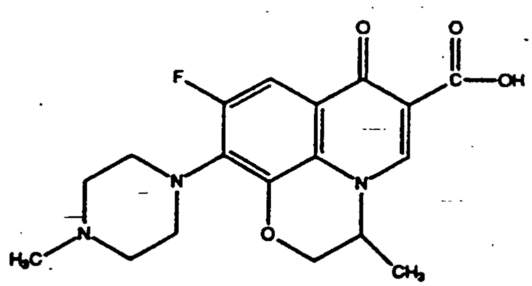
DRUG PRODUCT NAME
Proprietary: Floxin Otic
Nonproprietary/USAN: Ofloxacin Otic Solution 0.3%
Code Names/#'s:
Chemical Type:
Therapeutic Class: 3S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Otitis externa in adults and children.

DOSAGE FORM: Solution
STRENGTHS: 0.3%
ROUTE OF ADMINISTRATION: Otic
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



Molecular Formula: $C_{18}H_{20}FN_3O_4$

Molecular Weight: 361.38

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

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-, (±)-

SUPPORTING DOCUMENTS:

DMF
NDA 19-735 - Floxin (ofloxacin tablets)
NDA 20-087 - Floxin (ofloxacin injection) I.V.

The firm has submitted a letter of authorization dated June 28, 1996 from R. W. Johnson to refer to these two NDA's. Also, NDA 19-921 - Ofloxacin Ophthalmic Solution (Allergan Inc.).

APPEARS THIS WAY
ON ORIGINAL

RELATED DOCUMENTS (if applicable):

NDA 19-735
NDA 20-087
NDA 19-921

CONSULTS:

EA - consulted on 1/29/97
Trade Name - consulted on 2/19/97
Inspections - requested on 1/27/97
Sterile Manufacturing Procedure - consulted on 1/29/97

REMARKS/COMMENTS:

The firm plans to use Floxin Otic (ofloxacin otic solution) 0.3% for the treatment of otitis externa in adults and children, chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane, and acute otitis media in children with tympanostomy tubes. Floxin is a fluoroquinolone class of antibacterial drugs.

The DMF meets all the requirements for the drug substance.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505 of the Act. Specific items which are not approvable are identified under the following headings: Container/Closure, and Stability.

/S/ 4/7/97

B. Vithal Shetty, Ph.D.
Review Chemist

cc: Orig. NDA 20-799
HFD-520/Division File
HFD-520/BVShetty
HFD-520/MO/McDonald
HFD-520/Pharm/Ellis
HFD-520/Micro/King
HFD-520/CSO/Duvall-Miller
HFD-520/DKatague
R/D Init by: DKatague DBK 4/7/97

Darrell Miller

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-799 **CHEM. REVIEW #:** 2 **REVIEW DATE:** 6/4/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	5/30/97	6/2/97	6/3/97

NAME & ADDRESS OF APPLICANT: Daiichi Pharmaceutical Corporation
One Parker Plaza
Fort Lee, New Jersey 07024

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Nonproprietary/USAN: Ofloxacin Otic Solution 0.3%
Code Names/#'s:
Chemical Type:
Therapeutic Class: 3S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Otitis externa in adults and children.

DOSAGE FORM: Solution
STRENGTHS: 0.3%
ROUTE OF ADMINISTRATION: Otic
DISPENSED: __X__Rx _____OTC

COMMENTS

The firm, in a letter dated May 30, 1997, has responded to the CMC deficiencies stated in Chemist's review #1 dated 1/15/97.

1. With regard to the expiration date, the firm proposes 24 months expiry date for Floxin Otic 0.3%. The firm has submitted stability data for three registration batches and three experimental batches for the duration of 12 months at 25°C/60%RH, 30°C/40%RH and 40°C/20%RH. At 25°C/60%RH, the produet is within specification, but at higher temperature, the concentration of the drug substance is increased due to the loss of water. The firm would like to extend the expiration date to 36 months.

   On the basis of the stability data at 25°C/60%RH, the expiration date of 24 months may be approved at present.

   ACCEPTABLE

2. In response to the extractable materials from container/closure system, the firm has used the USP 23 physicochemical conditions and the product formulation as the extracting medium. The firm states that there were no detectable extractables with UV absorption ranging from nm in ofloxacin otic solution after 24 hours at 70°C. The pH remained at and appearance of the solution did not change.

ACCEPTABLE

APPEARS THIS WAY
ON ORIGINAL

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

4. With regard to the final printed label, the firm has submitted draft copies of the labels and package insert. Approval is subject to final review.

CONCLUSION:

The NDA may not be approved for lack of 1) methods validation; 2) [redacted]R, and 3) sterilization evaluation data.

/S/ 8/18/97

B. Vithal Shetty, Ph.D.
Review Chemist

cc: Orig. NDA 20-799
HFD-520/Division File
HFD-520/BVShetty
HFD-520/MO/McDonald
HFD-520/Pharm/Ellis
HFD-520/Micro/King
HFD-520/CSO/Duvall-Miller
HFD-520/DKatague
R/D Init by: DKatague DK 8/18/97

520 DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls NOV 26 1997

NDA #: 20-799 **CHEM. REVIEW #:** 3 **REVIEW DATE:** 10/8/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	8/14/97		

NAME & ADDRESS OF APPLICANT: Daiichi Pharmaceutical Corporation
One Parker Plaza
Fort Lee, New Jersey 07024

DRUG PRODUCT NAME

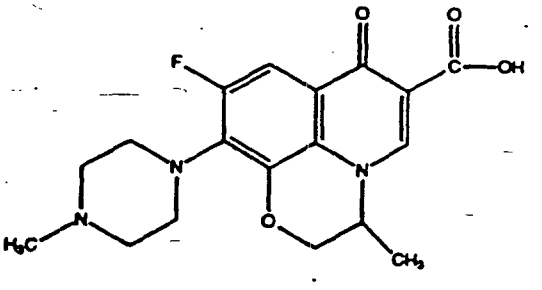
Proprietary:	Floxin Otic
Nonproprietary/USAN:	Ofloxacin Otic Solution 0.3%
Code Names/#'s:	
Chemical Type:	
Therapeutic Class:	3S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Otitis externa in adults and children.

DOSAGE FORM: Solution
STRENGTHS: 0.3%
ROUTE OF ADMINISTRATION: Otic
DISPENSED: X Rx _____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



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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-,(±)-

COMMENTS:

Method Validation had been carried out by the Philadelphia District, HFR-MA160. The report dated August 14, 1997 states that the method appears to be suitable but the firm should clarify the following points:

CONCLUSION:

The NDA is approvable from the chemistry, manufacturing and control standpoint. The only pending item is the sterilization review from Microbiology. The following items are found acceptable.

NOTE:

1. EER dated 8/18/97- attached

2. EA: FONSI has been issued
   ACCEPTABLE

3. Trade Name:
   ACCEPTABLE

4. Chemistry Review: It has been completed. All deficiencies have been answered.

5. Labeling: Final printed label with respect to Description and How Supplied is acceptable.

6. Methods Validation has been completed with minor modification.

/S/ 11/26/97

B. Vithal Shetty, Ph.D.
Review Chemist

cc: Orig. NDA 20-799
HFD-520/Division File
HFD-520/BVShetty
HFD-520/MO/ Mc Donald
HFD-520/Pharm/Ellis
HFD-520/Micro/King
HFD-520/CSO/ Durall-Miller
HFD-520/DKatague
R/D Init by: DKatague DBK 11/26/97

DAVALL MILLER
520

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

DEC 1 1997

NDA #: 20-799 CHEM. REVIEW #: 4 REVIEW DATE: 12/1/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	8/14/97		

NAME & ADDRESS OF APPLICANT: Daiichi Pharmaceutical Corporation
One Parker Plaza
Fort Lee, New Jersey 07024

DRUG PRODUCT NAME
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ANDA Suitability Petition/DESI/Patent Status:
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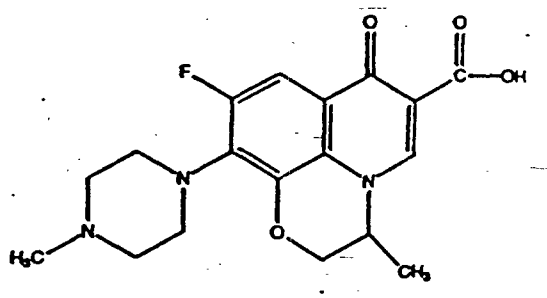

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7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (±)-

COMMENTS:

Sterilization method was evaluated by Dr. Paul Stinavage of HFD-805. Attached is his review dated November 26, 1997 recommending approval.

CONCLUSION:

This NDA may be approved from the chemistry, manufacturing and control standpoint. Method validation report was completed on 8/14/97 with some points needed for clarification. The points needed to be clarified (see Chemist Review #3 dated 11/26/97) should be communicated to the firm with the approval letter.

/S/ 12/1/97

B. Vithal Shetty, Ph.D.
Review Chemist

CC: Orig. NDA 20-799
HFD-520/Division File
HFD-520/Shetty
HFD-520/MO/McDonald
HFD-520/Pharm/Ellis
HFD-520/CSO/Duvall-Miller
HFD-502/CHEM/TL/Katague
R/D Init by: DKatague DBK 12-1-97
DBK/12-1-97