CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-799

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

FLOXIN® Otic (ofloxacin solution) 0.3% NDA

Request For Waiver Of In Vivo Bioequivalence Requirements

Pursuant to 21 CFR 320.22, Daiichi Pharmaceutical Corporation requests a waiver of in vivo bioequivalence requirements. The inclusion of this request was discussed and agreed upon at the Meeting for this product, which was held with representatives of the Anti-Infective Division of FDA

As described in the Developmental Pharmaceutics Section (Item 3B (2), Volume 1.2, p. 022-031) and in the Comparison of the Manufacturing Process and the Analytical Profile of the Phase III Clinical Batch to the United States Registration Batches (Item 3B(2) Attachment 5, Volume 1.4, p. 002-014 and Item 6 Attachment C, Drug Formulation Development Summary, Volume 1.23, p. 045-055), the clinical supplies of ofloxacin otic used in the clinical trials conducted under US IND were manufactured in The commercial drug product is manufactured by Contract Manufacturer Parke-Davis, Rochester, MI (Division of Warner Lambert, Morris Plains, NJ). The referenced documents provide evidence that the identity, strength, quality, or purity of the final drug product have not been affected by the change in manufacturing site. The ofloxacin otic solution manufactured by Parke-Davis is equivalent to the ofloxacin otic solution manufactured by

Floxin® Otic (Ofloxacin Otic Solution), 0.3%
Daiichi Pharmaceutical Corporation

Item 13 and 14 Patent Information and Certification:

(a) Patent Number and Date of Expiration:
Patent # 5,401,741
Expiry Date: March 27, 2012

(b) Type of patent (drug, drug product, or method of use):
Method of Use Patent

(c) Name of Patent Holder:
Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan

(d) Name of U.S. Agent (representative) authorized to receive notice of patent certification:

Jennifer Benenson, Esq.
General Counsel
Daiichi Pharmaceutical Corporation

Declaration:

The undersigned declares that Patent No. 5,401,741 covers the formulation, composition, and/or method of use of Floxin® Otic (Ofloxacin Otic Solution). This product is the subject of this application for which approval is being sought.

Takeshi Shigihara
Director
Corporate Planning and Administration

Date: October 25, 1996

S:\RA\PATENT.DOC

Floxin® Otic (Ofloxacin Otic Solution), 0.3%
Daiichi Pharmaceutical Corporation

Item 13 and 14 Patent Information and Certification (Continued):

EXCLUSIVITY STATEMENT

Exclusivity: Three (3) years of exclusivity is claimed under 314.108(b)(4)

Pursuant to 21 CFR 314.50(j) and 314.108, Daiichi Pharmaceutical Corporation certifies that the clinical investigations in the application meet FDA's definition of "new clinical investigations," that they are "essential to approval" and that they were sponsored by the applicant.

Amy S. Domanowski, Ph.D.
Director
Regulatory Affairs

Date: October 25, 1996

S:\RA\PATENT.DOC

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-799 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: FLOXIN (ofloxacin otic soln) Action: AP AE NA

Applicant Daiichi Pharmaceutical Therapeutic Class quinolones, 3S

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate X inadequate ___

Indication in this application Otitis Externa, Acute Otitis Media in peds w/ tympanostomy tubes, Chronic Suppurative Otitis Media w/ perforate tympanic membranes (For supplemen answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

X
___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Project Manager 12/8/97
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-799
HFD-520 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

DAIICHI PHARMACEUTICAL CORPORATION

One Parker Plaza
Fort Lee N.J. 07024
Tel: (201) 944-4333
Corporate Office Fax: (201) 944-4364
Medical R&D Fax: (201) 944-8526

FLOXIN® Otic NDA

Debarment Certification

Daiichi Pharmaceutical Corporation certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetic Act, as amended, 21 U.S.C. §§ 335a (a) and (b), in connection with this application.

Amy S. Domanowski, Ph.D.
Director, Regulatory Affairs

S:\RA\DEBAR.1

764

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, (HFD-540)

From: Division of New Drug Chemistry III HFD-830/520
Attention: Dr. Vithal Shetty Phone: 827-2187

Date: 2/19/97

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Floxin Otic NDA/~~ANDA~~# 20-699

Company Name: Daiichi Pharmaceutical, Corp

Established name, including dosage form: Ofloxacin Otic Solution 0.3%

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthly): For the treatment of otitis externa in adult and children, chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane and acute otitis media in children with tympanostomy tubes.

Initial comments from the submitter (concerns, observations, etc.):

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev May.94

Consult #764 (HFD-540)

FLOXIN OTIC ofloxacin otic solution

FLOXIN is a trademark for a currently approved product line containing ofloxacin.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 3/27/97, Chair
CDER Labeling and Nomenclature Committee

MEMORANDUM OF TELECON

DATE: Thursday, December 4, 1997

APPLICATION NUMBER: NDA 20-799; FLOXIN® Otic (ofloxacin otic solution) 0.3%

BETWEEN:

Name: Dr. Amy Domanowski, Senior Director, Regulatory Affairs
Dr. Lois Hinman, Associate Director, Regulatory Affairs
Dr. Elyane Lombardy, Executive Director, Research & Development
Dr. Mindell Seidlin, Senior Director, Anti-Infectives, Clinical Research
Dr. Marvin Wetter, Director Drug Safety
Phone: (201) 944-5608
Representing: Daiichi Pharmaceutical Corporation

AND

Name: Ms. Beth Duvall-Miller, Project Manager
Dr. Cheryl McDonald, Medical Officer
Dr. Janice Soreth, Medical Team Leader
Dr. Gary Chikami, Acting Division Director
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: FLOXIN® labeling; CSOM indication and *Staphylococcus aureus* in OE indication

FLOXIN® Otic (ofloxacin otic solution) 0.3%, NDA 20-799, was submitted on December 18, 1996. Labeling negotiations were initiated on December 1, 1997, with a facsimile of labeling recommendations from the Agency based on its internal meeting on December 1, 1997. A face to face labeling meeting was held on December 3, 1997, with the above named Daiichi and FDA personnel as well as additional FDA reviewers.

In this meeting, in addition to general labeling issues, Daiichi presented their arguments for inclusion of the chronic suppurative otitis media indication and *Staphylococcus aureus* as a causative pathogen for the Otitis Externa indication in the package insert. The Division agreed to follow up this meeting with a response to these issues within 1 to 2 days. This telecon was scheduled for that purpose.

Dr. Chikami confirmed the following:

- Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membrane will be granted as an indication in the **INDICATIONS AND USAGE** section. Subsequently, *Proteus mirabilis* will be added to the list of Gram-negative aerobes in the **Microbiology** subsection of the labeling.
- *Staphylococcus aureus* will be added as a causative pathogen for Otitis Externa.
- The Division will propose wording for lines 123-124 of the **PRECAUTIONS** section.

- The Division will provide feedback on the Medication Guide the week of December 8, 1997.
- Other outstanding labeling revisions will be negotiated via telephone and facsimile as needed.

Daiichi agreed to submit revised draft labeling, both hard copy and diskette, with the changes agreed to in this telecon and in the face to face meeting held on December 3, 1997.

/S/

Beth Duvall-Miller
Project Manager

cc:
Original NDA 20-799
HFD-520/Div. File
HFD-520/CSO/B. Duvall-Miller
HFD-520/MO/C. McDonald

Concurrence only:
HFD-520/SCSO/J. Bona 12/8/97
HFD-520/ActDivDir/G. Chikami 12/8/97

Drafted: bdm/December 8, 1997/M:\TELECON\N20799.2
r/d initials: BDM 12/8/97
final:

TELECON

Duvall-Miller
520

MAY 30 1997

NDA 20-799

Daiichi Pharmaceutical Corporation
Attention: Amy Domanowski, Ph.D.
Senior Director, Regulatory Affairs
One Parker Plaza
Fort Lee, NJ 07024

Dear Dr. Domanowski:

Please refer to your pending December 18, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Floxin® Otic (Ofloxacin Otic Solution) 0.3%.

We have completed our review of the chemistry section of your submission regarding sterility and have identified the following deficiencies:

1. Regarding the sterilization of the container/closure components for product packaging:

   a. The composition of sterilizer loads used for production should be described. Each load configuration should be validated or a rationale for not including the load in validation should be provided. This should include descriptions (diagrams) of the placement of biological indicators within the load. If the components used for validation are not the same as those used for product packaging, a rationale for their use should be included. The source of the biological indicators should be specified. Incubation conditions and growth media used for growth of the biological indicators should be described.

2. Regarding the sterilization of process equipment:

   a. Locations of thermocouples and biological indicators within validation loads should be specified. Load configurations should also be specified for each autoclave. Each load configuration should be validated or a rationale for not completing the validations provided.

   b. Validation data generated during validation of the tank sterilization station should be submitted. Validation cycle parameters for the tank sterilizing station should be specified. Tanks, including tank volumes sterilized using this equipment, should be specified. Validation data for each different tank configuration sterilized using this equipment should be provided. These should include identification of the biological

indicators used (manufacturer, D-values, spore populations, lot numbers, etc.), the number of biological indicators and their placement within the tank should also be included.

3. Regarding the media fill data presented:

   a. The gross failure of Lot #TC0379 is troubling. The descriptions provided indicate that the receiving tank is within the sterile area during filling. Environmental monitoring data indicate that there were no out-of-specification results obtained during this fill. Yet, a vent filter failure resulted in contamination of the entire units filled during this simulation. An explanation for this observation should be provided.

4. Regarding the environmental monitoring program:

   a. Settling plates, viable particle sampling, and plates are used to monitor critical areas during filling. It is not clear where, within the critical area, these samples are obtained. The specific monitored locations within the filling areas should be provided, keeping in mind that monitoring at or near the filling heads is imperative.

5. Regarding antimicrobial effectiveness testing of the product:

   a. Data generated during antimicrobial effectiveness testing of the product at the low specification for benzalkonium chloride should be provided.

   It is not necessary to perform antimicrobial effectiveness testing at all of the time points listed in the stability protocol. Antimicrobial effectiveness testing should be performed on product at the end of the shelf life specification for the first three production lots.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-799
HFD-520/Div. Files
HFD-520/CSO/B. Duvall-Miller
HFD-520/SCSO/J. Bona
HFD-520/ActTLChem/D. Katague
HFD-805/Consult/P. Stinavage
HFD-520/SMO/J. Soreth 5/29/97
HFD-830/ONDC Division Director (only for CMC related issues)

Concurrence:
HFD-520/SCSO/J. Bona 5/23/97
HFD-520/ActTLChem/D. Katague
HFD-520/SMO/J. Soreth 5/29/97
HFD-520/ActDivDir/G. Chikami
5/29/97

Drafted by: bdm/May 12, 1997/M:\NDADEF\20799.1
Initialed by:
final: BDM 5/23/97

INFORMATION REQUEST (IR)

APR 24 19

NDA 20-799

Daiichi Pharmaceutical Corporation
Attention: Amy Domanowski, Ph.D.
Director, Regulatory Affairs
One Parker Plaza
Fort Lee, NJ 07024

Dear Dr. Domanowski:

Please refer to your pending December 18, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FLOXIN® Otic (ofloxacin otic solution) 0.3%.

To complete our review of the chemistry section of your submission, we request the following:

1. Samples stored at 40°C/<20%RH under both the inverted and upright positions showed a slow eluting, unidentified component in the drug product by Please identify and quantify the component.

2. Please submit data to show that no extractables leach into the product with molecular weights greater than 600 Daltons since molecular weights of 600 Daltons or less were not detected by

3. Please state proposed expiry date for the drug product.

4. Please send final copies of the printed label.

5. Please submit additional stability data as it becomes available in support of the proposed expiration date.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/ 4-22-97

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-799
HFD-520/Div. Files
HFD-520/CSO/B. Duvall-Miller
HFD-520/Chem/V. Shetty
HFD-520/TLChem/D. Katague
HFD-520/SMO/J. Soreth
HFD-520/MO/McDonald
HFD-520/SCSO/J. Bona
HFD-830/ONDC Division Director (only for CMC related issues)

Concurrence:
HFD-520/SCSO/J. Bona 4/9/97
HFD-520/Chem/V. Shetty 4/9/97
HFD-520/TLChem/D. Katague 4/9/97
HFD-520/ActDivDir/D. Feigal 4/14/97
4-22-97

Drafted by: bdm/April 8, 1997/M:\CMCCOM\N20799.1
Initialed by:
final: 4/9/97

INFORMATION REQUEST (IR)

HFD-520/ DUVALL-MILLER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-799

Daiichi Pharmaceutical Corporation
Attention: Dr. Amy Domanowski
Director, Regulatory Affairs
One Parker Plaza
Fort Lee, NJ 07024

FEB 7 1997

Dear Dr. Domanowski:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Floxin® Otic (ofloxacin otic solution) 0.3% sterile solution

Therapeutic Classification: Standard

Date of Application: December 18, 1996

Date of Receipt: December 18, 1996

Our Reference Number: 20-799

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 14, 1996 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact Ms. Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-799
HFD-520/Div. Files
HFD-520/CSO/B. Duvall-Miller
HFD-520/SMO/J. Soreth
HFD-520/MO/C. McDonald
HFD-520/ActTLChem/D. Katague
HFD-520/Chem/B.V. Shetty
HFD-520/TLPharm/R. Osterberg
HFD-520/Pharm/A. Ellis
HFD-520/TLMicro/A. Sheldon
HFD-520/Micro/D. King
HFD-520/TLBioPharm/F. Pelsor
HFD-520/TLStats/D. Lin
HFD-520/Stats/J. Jiang
DISTRICT OFFICE

drafted: bdm/December 31, 1996/M:\A&R\N20799.WPD
Final: BDM 2/7/97

ACKNOWLEDGEMENT (AC)

HFD-520
Duvall-Miller

MEMORANDUM OF TELECON

DATE: April 9, 1997

APPLICATION NUMBER: NDA 20-799; FLOXIN® Otic (ofloxacin otic solution) 0.3%

BETWEEN:

Name: Dr. Amy Domanowski
Mr. Robert Edwards
Phone: (201) 944-5608
Representing: Daiichi Pharmaceutical Corporation

AND

Name: Ms. Beth Duvall-Miller, Project Manager
Dr. Joel Jiang, Statistician
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Statistical information pertaining to historical and current practice comparator groups

In previous telephone conversations with Daiichi (3/27/97 and 4/3/97), the issues of missing demographic information for Protocols 006 and 007 (current and historical practice groups respectively) and listing 3, Protocol 008, were addressed. This telecon was a follow-up to these concerns as well as other statistical concerns as they appear in the CANDA, CANDA volumes, and Hard Copy NDA submission.

Demographic information, Protocols 006 and 007:

Dr. Jiang had indicated that the demographic information for these comparator groups was not fully available. Daiichi confirmed that the available information for these comparator groups was limited. This information was not submitted in the listing worksheets.

Listing 3, Protocol 008 (previous medications):

This listing on the CANDA was not loaded properly and subsequently did not contain the information that was intended for it. Dr. Jiang responded that this information is not important in the statistical analysis, however, Daiichi will submit the information on diskette with instructions on how to load it on the CANDA.

CANDA patient information:

Dr. Jiang pointed out discrepancies between the number of observations and the number of patients in the Intent to Treat (ITT) groups for both the historical and current practice comparator arms, when referencing the CANDA (queries) and the CANDA volume listings.

Dr. Domanowski and Mr. Edwards were unable to account for these discrepancies. They will follow-up with a fax to account for and/or correct these discrepancies.

In the current practice data set, Dr. Jiang noted that patient numbers are replicated. Mr. Edwards explained that the patient numbers are not unique across centers, but the information sorted by patient and center is unique.

Miscellaneous:

Dr. Domanowski noted the following final items: 1) she will follow-up with Dr. King's (microbiology reviewer) voice mail; 2) confirmed that she had spoken with Dr. Shetty about the re-submitted Methods Validation information and that there were deficiencies noted in his Chemistry review that will be conveyed to Daiichi by letter; and 3) has the draft label available in Macintosh formatting. Ms. Duvall-Miller responded that she would fax the list of deficiencies once they are finalized and that the preferred labeling format is IBM.

/S/

Beth Duvall-Miller
Project Manager

cc: Original NDA 20-799
HFD-520/Div. File
HFD-520/CSO/B. Duvall-Miller 4/14/97
HFD-520/BioStat/J. Jiang (J)

drafted: bdm/April 14, 1997/M:\TELECON\N20799.1

TELECON

Daiichi Pharmaceutical Corporation
One Parker Plaza, Fort Lee, NJ 07024
Tel: 201-944-4333
Corporate Fax: 201-944-4364
Medical R&D Fax: 201-944-8526

December 15, 1997

Gary K. Chikami, M.D., Acting Director
Attention: Document Control Room
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA 20-799
FLOXIN® Otic
(Ofloxacin Otic Solution) 0.3%
Labeling

Dear Dr. Chikami:

We are in receipt of the FDA labeling on FLOXIN® Otic, package insert text received December 12, 1997 and comments on the Medication Guide received December 11, 1997. This letter formally acknowledges our agreement with these communications. The completed text of both documents dated December 15, 1997, with FDA suggestions included, are attached.

If there are any questions or concerns on the content of this submission, please call me immediately at 201-944-5608.

This submission contains trade secret and commercial or financial information which is privileged or confidential and entitled to protection from disclosure and handling by the Food and Drug Administration under the agency's regulations in 21 CFR Part 20.

Sincerely,

Amy S. Domanowski

Amy S. Domanowski, Ph.D.
Senior Director, Regulatory Affairs

Attachments
cc: Ms. Beth Duvall-Miller, CSO (Full Copy)

S:\RA\BETH\FLOXNDA\1997\SUBMISS\LETTERS\DECEM15.DOC

DAIICHI PHARMACEUTICAL CORPORATION

One Parker Plaza
Fort Lee, NJ 07024
Tel: (201) 944-4333
Corporate Fax: (201) 944-4364
Medical R&D Fax: (201) 944-8526

February 28, 1997

Dr. Matthew T. Thomas
FDA Clinical Investigations Branch
HFD 344 Room 125
Metro Park North 1
7520 Standish Place
Rockville, MD 20855

NDA 20-799
FLOXIN® Otic
(Ofloxacin Otic Solution) 0.3%

Dear Dr. Thomas:

In response to your request of February 18, 1997, we are providing the following information:

1. List of titles of studies with indications and list of principal investigators with address by site for all five Phase III registration protocols.

2. By investigator site for each study, the number of subjects enrolled, the number of clinically evaluable subjects, and the number of microbiologically evaluable subjects (as assessed by sponsor).

3. Also by investigator site for each study, presentation of the number of subjects per site, the total number of adverse events (AEs) per site, and the number of subjects with AEs per site.

4. List of all foreign studies supporting claims submitted in NDA 20-799.

Note that the responses to items 1-2 and 4 above are taken directly from the NDA with volume and page numbers indicated. Please refer to the attached Table of Contents.

The response to Item #3 above, concerning AEs by site, both total AEs and number of subjects with AE's, has been generated as a table from the STAT CANDA. Of course, this is from the data in the hard copy NDA and can easily be generated by the reviewing statistician as well.

Please let me know if you have any questions concerning this submission.

Sincerely,

Amy S. Domanowski

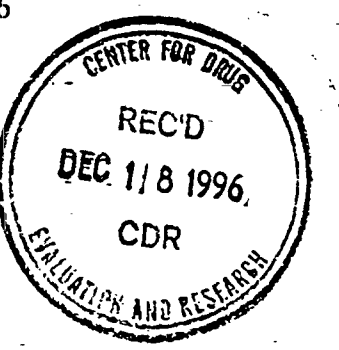
Amy S. Domanowski, Ph.D.
Director, Regulatory Affairs

ASD/ban
Attachments
cc: Ms. Beth Duvall Miller, CSO, Project Management (Full copy)
Document Control Room (2 copies)

DAIICHI PHARMACEUTICAL CORPORATION

One Parker Plaza
Fort Lee, NJ 07024
Tel: (201) 944-4333
Corporate Fax: (201) 944-4364
Medical R&D Fax: (201) 944-8526

December 18, 1996



David Feigal, MD
Anti-Infective Division
Center for Drug Evaluation and Review
Food and Drug Administration
Central Document Control Room
12229 Wilkins Avenue
Rockville, MD 20855

NDA # 20-799
FLOXIN ® Otic
(Ofloxacin Otic Solution) 0.3%

Dear Dr. Feigal:

Pursuant to 505(b)(1) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.50, Daiichi Pharmaceutical Corporation hereby submits a New Drug Application (NDA) for 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.

The completed Form FDA 356H, which immediately follows this cover letter, indicates that Daiichi Pharmaceutical Corporation, Fort Lee, NJ, is the US Agent and US representative for the NDA holder, Daiichi Pharmaceutical Company, Ltd., Tokyo, Japan.

The complete Archival Copy of the submitted application contains a total of 385 volumes. Details of the content of the NDA are described in the Item 1 Index. Case report forms, totaling 193 Volumes, are submitted in NDA Item 12 for all subjects enrolled in phase I clinical pharmacology and phase III registration studies conducted under US IND for Ofloxacin Otic Solution, along with selected CRFs from non-IND studies conducted overseas.

In addition to the Archival Copy, the Technical Section Review Copies, each with the required copy of the first NDA volume containing the NDA Index and Summary (Items 1 and 2, respectively) are also submitted. An extra copy each of the Methods Validation Section (Item 3 C) for the Chemistry Reviewer, Dr. James Timpe, and the Environmental

Assessment Section (Item 3 E) for Dr. Nancy Sager, HFD-357, are also provided. The Sterility Process Validation Section (Item 3 D), along with a copy of Volume 1.1 containing the NDA Index and Summary is included for the Microbiology Reviewer. Field copies of NDA Item 3 Chemistry and Manufacturing Controls Section, including the NDA Index and Summary (11 volumes) are being sent concurrently to the Parsippany, NJ and Detroit, MI district offices, as previously arranged. We certify that the field copies are identical to the Archival Copy.

Please be advised that the Clinical Data Section (Item 8) is identical in content to the Statistical Section (Item 10). Also, the summary and reports presented in Item 6, the Human Pharmacokinetics and Bioavailability Section, are the same as those presented in Item 8C, Clinical Pharmacology Section.

Pursuant to 21 CFR 320.22, we request a waiver of *in vivo* bioequivalence requirements. The inclusion of this request was agreed upon at the Meeting for this product, which was held Please refer to the attached waiver request for further information.

A Computer Assisted NDA (CANDA) has been developed for both the Medical Reviewer and the Statistical Reviewer to ease the review of the NDA. The CANDA contains all documentation that is included in NDA Item 8, Clinical Data Section and in Item 12, Case Report Forms, the draft of the Package Insert has also been included in the CANDA. Daiichi representatives met with FDA representatives concerning various aspects of the medical and statistical CANDA(s) on April 17-18, 1996 and August 21-22, 1996. Arrangements for delivery of the CANDA equipment is planned for December 23, 1996.

Reference is made to the User Fee Cover Sheet, Form FDA 3397, identifying the User Fee number for this application as 3127. This form may be found following the NDA 356H Form and the Bioequivalence Waiver Request.

A debarment certification, located just after the User Fee Cover Sheet, is also included.

If there are any questions concerning this submission, please contact me at (201)-944-5608.

Sincerely,

Amy S. Domanowski

Amy S. Domanowski, Ph.D.
Director, Regulatory Affairs

cc: Ms. Beth Duvall-Miller, Anti-Infective Division (Cover Letter Only) Office, HFD-520

Ms. Regina T. Brown, Parsippany FDA District Office, Waterview Corporate Center, 10 Waterview Boulevard, Third Floor, Parsippany, NJ 07054; NDA Items 1, 2, 3 (CMC)

Mr. Melvin O. Robinson, Detroit FDA District Office, 1560 E. Jefferson Avenue, Detroit, MI 48207; NDA Items 1, 2, 3 (CMC)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
18 Dec 96	
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**
520	20-799

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314).*

NAME OF APPLICANT Daiichi Pharmaceutical Co., LTD	DATE OF SUBMISSION 12/18/96
ADDRESS *(Number, Street, City, State and Zip Code)* 14-10 Nihonbashi 3-Chome Chuo-ku, Tokyo 103 Japan	TELEPHONE NO. *(Include Area Code)* 03-3272-0611
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA 20-799

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
ofloxacin otic solution	Floxin® Otic

CODE NAME *(If any)*	CHEMICAL NAME
	(±)-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

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
otic solution	otic	0.3%

PROPOSED INDICATIONS FOR USE

- otitis externa in adults and children
- chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane
- acute otitis media in children with tympanostomy tubes

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

CENTER FOR DRUG REC'D DEC 20 1996 MEGA DOC RM EVALUATION AND RESEARCH

CENTER FOR DRUG REC'D DEC 18 1996 CDR EVALUATION AND RESEARCH

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

DAIICHI PHARMACEUTICAL CORPORATION

One Parker Plaza
Fort Lee, NJ 07024
Tel: (201) 944-4333
Corporate Fax: (201) 944-4364
Medical R&D Fax: (201) 944-8526

March 4, 1997

B.V. Shetty, Ph.D., Chemistry Reviewer
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA 20-799
FLOXIN® Otic
(Ofloxacin Otic Solution) 0.3%

Dear Dr. Shetty:

This correspondence responds to your recent requests concerning ofloxacin drug substance information, including methods validation. We are now able to provide you with two desk copies of the one volume DMF Amendment, just submitted to the FDA yesterday, March 3, 1997. One copy is for yourself and one for the District Office.

Please refer to the Table of Contents for the location of the specifications, test methods and method validation reports.

Do not hesitate to call me at (201) 944-5608, if I can be of further assistance.

Sincerely,

Amy S. Domanowski

Amy S. Domanowski, Ph.D.
Director, Regulatory Affairs

ASD/ban
Attachment
cc: Ms. Beth Duvall Miller, CSO, Project Management (Letter only)

DAIICHI PHARMACEUTICAL CORPORATION

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April 24, 1997

David Feigal, M.D., Acting Director
Attention: Document Control Room
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA 20-799
FLOXIN® Otic
(Ofloxacin Otic Solution) 0.3%
Four Month Safety Update

Dear Dr. Feigal:

We hereby submit the Four Month Safety Update to the Ofloxacin Otic NDA 20-799 submitted on December 18, 1996. Please see the attached Table of Contents.

The Four Month Safety Update includes data on an additional 170 subjects (ofloxacin treated and non-treated) from the ongoing and still blinded Phase IIIB protocol 013. The total number of subjects reported in this update is n=1132. A cut off date of February 7, 1997 was used for IND studies and February 1, 1997 for foreign data.

If you have any questions concerning this Safety Update, please contact me at (201) 944-5608.

This submission contains trade secret and commercial or financial information which is privileged or confidential and entitled to protection from disclosure and handling by the Food and Drug Administration under the agency's regulations in 21 CFR Part 20.

Sincerely,

Amy S. Domanowski, Ph.D.
Senior Director, Regulatory Affairs

ASD/bar
Attachments
cc: Ms. Beth Duvall Miller, CSO, Project Management (Cover Letter)
Dr. Cheryl McDonald (Full Copy)

DAIICHI PHARMACEUTICAL CORPORATION

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May 12, 1997

Dick King, Ph.D.
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
FDA Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA 20-799
Floxin® Otic
(Ofloxacin Otic Solution) 0.3%
Response to FDA Request for Information
Microbiology

Dear Dr. King:

As requested in the teleconference held on April 10, 1997, we are providing you the Access Tables containing the demography and microbiology data from the Floxin® Otic registration trials on otitis externa (Protocols 002 and 003) and otitis media (006, 007 and 008).

The diskette also contains the data dictionaries in Excel for the demography and microbiology tables with definitions of the fields presented in the Access Tables. Hard copy of the dictionaries are also attached with samples of the tables for your review. Note that the MIC and Zone (KB) data are given only for ofloxacin.

We recommend that you copy the files on the diskette onto your hard drive.

Do not hesitate to call (201) 944-4333 if there are any questions and ask for me or Robert Edwards. We trust you will find these helpful.

S:\RA\BETH\FLOXNDA\1997\SUBMISSI\LETTERS\MAY12.DOC

This submission contains trade secret and commercial or financial information which is privileged or confidential and entitled to protection from disclosure and handling by the Food and Drug Administration under the agency's regulations in 21 CFR Part 20.

Sincerely,

Amy S. Domanowski, Ph.D.
Senior Director
Regulatory Affairs

Enclosure
cc: Ms. Beth Duvall-Miller (Cover letter only)

DAIICHI

Daiichi Pharmaceutical Corporation
One Parker Plaza, Fort Lee, NJ 07024
Tel: 201-944-4333
Corporate Fax: 201-944-4364
Medical R&D Fax: 201-944-8526

October 8, 1997

Cheryl L. McDonald
MEDICAL OFFICER (IN
HFD-520
Room S341
Corporate 2
9201 Corporate Blvd.
Rockville, MD 20850

NDA 20-799
FLOXIN® Otic
(Ofloxacin Otic Solution) 0.3%
Response to FDA Request for Information

Dear Ms. McDonald:

This correspondence responds to a recent request posed by Dr. Cheryl McDonald to Dr. Amy S. Domanowski, Ph.D. on September 22, 1997, concerning the justification for a single study (Protocol 006) to support the indication for chronic suppurative otitis media in adolescents and adults with perforated tympanic membranes.

This submission contains trade secret and commercial or financial information which is privileged or confidential and entitled to protection from disclosure and handling by the Food and Drug Administration under the agency's regulations in 21 CFR Part 20.

Sincerely,

Amy S. Domanowski

Amy S. Domanowski, Ph.D.
Senior Director, Regulatory Affairs

ASD/ban
Attachments
cc: Ms. Beth Duvall Miller, CSO, Project Management
Janice M. Soreth, Medical Officer

DAIICHI

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MEMORANDUM

TO: A. Domanowski PhD

FROM: Mindell Seidlin MD

DATE: October 8, 1997

SUBJECT: Response to FDA query regarding single study in CSOM

CC: E. Lombardy MD
J. Milazzo

Query: Review the justification for a single study to support the indication for chronic suppurative otitis media in adolescents and adults with perforated tympanic membranes.

Response:

The reasons that a single study was planned and performed in this indication are:

- this indication is closely related clinically and microbiologically to the other otitis media indication which was studied, acute otitis media in children with tympanostomy tubes
- the relative dearth of subjects eligible for participation in the trial

The design of the clinical program to support the otitis media indications for ofloxacin otic solution was reviewed with the agency during a meeting held on 8/24/94.

The trials in CSOM and acute otitis media in children with tympanostomy tubes were viewed as supportive of each other because of similarities in the signs and symptoms, pathophysiology and microbiology of infection. Both groups of patients have infections in the middle ear with non-intact tympanic membranes. For both groups of patients the key symptom is otorrhea. Pain and fever are unusual in subjects with otitis media with non-intact membranes regardless of age or the presence or absence of a tympanostomy tube. The infections in both cases can occur as a result of infection with pathogens which gain access to the

middle ear either from the pharynx via the eustachian tube or pathogens which enter the middle ear from the external auditory canal through the perforation or tympanostomy tube. Thus *P. aeruginosa*, *S. aureus* and *P. mirabilis* are common pathogens in both patient populations. The youngest children are more apt to become infected with the respiratory (pharyngeal) pathogens (regardless of the presence of a tube or perforation) because the eustachian tube in young children is virtually horizontal which favors reflux of secretions from the pharynx. With growth and development, the eustachian tube becomes more vertical and reflux is considerably less common. The pathogens in children with tubes over the age of 6 years closely resemble those found in adolescents and adults with perforated tympanic membranes. Several references have been previously provided which document the pathogens usually isolated in children with CSOM and children with tympanostomy tubes. One additional recent reference is appended.

Our otitis media studies in children with tympanostomy tubes (Protocols 007 and 008) confirm this pattern of pathogens. (See table below) There were only two "respiratory pathogens", (*S. pneumoniae*) among the 60 pathogens isolated from baseline otorrhea cultures in the 37 microbiologically evaluable children over the age of 6 years in both treatment arms of both protocols. In Protocol 006, (which included subjects ≥12 years old) there were two isolates each of *S. pneumoniae* and *H. influenzae* among the 145 pathogens isolated from baseline otorrhea cultures in 99 microbiologically evaluable subjects.

Distribution of Baseline Target Ear Pathogens by Age of Subject (007 & 008): Ofloxacin Group

Pathogen	0	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	>8 yr	Total
H. influenzae	2	29	14	9	1	2	1	0	0	0	58
M. catarrhalis	0	14	7	6	1	1	0	0	0	0	29
S. pneumoniae	0	25	20	9	1	6	3	1	0	0	65
S. aureus	0	9	6	7	6	5	5	4	3	9	54
P. aeruginosa	0	5	8	5	5	6	2	5	4	3	43
All Other	0	7	7	4	5	5	9	5	2	9	53
Total pathogens	2	89	62	40	19	25	20	15	9	21	302
Total subjects	2	59	36	26	13	17	11	8	6	12	190

Distribution of Baseline Target Ear Pathogen by Age of Subject
Augmentin® Group

Pathogen	0	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	>8 yr	Total
H. influenzae	0	23	7	3	3	1	2	0	0	0	39
M. catarrhalis	0	8	1	1	0	0	0	0	0	0	10
S. pneumoniae	0	26	7	2	0	2	0	0	0	1	38
S. aureus	0	7	1	1	2	3	2	3	4	2	25
P. aeruginosa	0	25	2	1	0	1	0	0	1	0	7
All Other	0	4	5	3	1	3	1	3	1	0	21
Total pathogens	0	70	23	11	6	10	5	6	6	3	140
Total subjects	0	45	14	8	6	6	3	4	5	2	93

There are few reports in the literature specifically about pathogens found and treatment responses in children with acute otitis media and tympanostomy tubes. There are several reports, primarily from third world countries on the microbiology of CSOM in children. The pattern of isolates reported in these studies appears quite similar to what has been found in our studies, further supporting the use of trials in these two indications to support each other.

Protocol 006 (CSOM in adolescents and adults with perforated tympanic membranes) was designed in parallel with the other otitis media indication (AOM in children with tympanostomy tubes). It was clear that there are currently relatively few US patients with chronically perforated tympanic membranes. The usual practice of aggressive treatment of acute otitis media in children with intact tympanic membranes results in fewer children experiencing spontaneous perforations than was the case in earlier years. In addition, otolaryngologists in this country have developed new techniques for tympanoplasty which have further reduced the prevalence of this condition. Indeed, because of the dearth of eligible subjects in the US, we found it necessary to turn to sites in a lesser developed country, Guatemala, in order to complete enrollment in this study.

Attached reference: Ibekwe AO, Shareef ZA, Benayam A. Anaerobes and Fungi in Chronic Suppurative Otitis Media. Ann Otol Rhinol Laryngol 1997; 106: 649

ANAEROBES AND FUNGI IN CHRONIC SUPPURATIVE OTITIS MEDIA

A. OLU IBEKWE, FRCS
ZAIN AL SHAREEF, MD, FACH ARZT
ASHRAF BENAYAM, MBBS
TABUK, SAUDI ARABIA

Microbiology of 102 ears with chronic suppurative otitis media was studied for aerobes, anaerobes, and fungi. Forty-four percent were pure cultures, 33.3% were mixed, and 18.6% had no growth. Seventy-four percent were aerobes, 25% fungi, and only 0.9% anaerobes. *Pseudomonas aeruginosa* (22.5%) was the most common isolate, followed by *Staphylococcus aureus* and the *Aspergillus* species. The possible reasons for low yield of anaerobes and the pathogenic roles of anaerobes and fungi in chronic suppurative otitis media are discussed. It is advocated that in investigating pathogenic organisms in chronic suppurative otitis media, requests should include anaerobes and fungi.

KEY WORDS — anaerobes, chronic suppurative otitis media, fungi, microbiology.

INTRODUCTION

Chronic suppurative otitis media (CSOM), whether atticoantral or tubotympanic disease, is associated with mixed bacterial flora. In the past, cultures from CSOM grew only aerobic organisms.[1-3] The isolation of anaerobic organisms from otogenic brain abscess[4] and the fact that anaerobic organisms outnumber aerobic organisms in oral flora suggested that anaerobes are involved in middle ear infections.[5] This idea led to the use of improved anaerobic bacteriologic techniques in the investigation of bacterial flora of CSOM. With these improved techniques, 20% to 50% of isolates in CSOM[6-10] are likely to be anaerobic. In all these studies, no mention was made of fungi.[1-10] It has always been assumed that fungi do not play any significant role in CSOM. However, fungi have been isolated in CSOM, especially from hot, humid regions of the world.[11-13] We therefore decided to study the microbiology of CSOM with the aim of determining the various pathogens, especially anaerobes and fungi, and their role in CSOM.

MATERIALS AND METHODS

This prospective study was carried out between November 1992 and June 1995. Patients with active CSOM attending the outpatient clinic of the Otolaryngology Department of North West Armed Forces Hospital, Tabuk, Saudi Arabia, and seen by the first author (A.O.I.) were involved in the study. The samples were collected from the middle ear via an aural speculum with use of a Mini-Tip Culturette (collection and transport system) containing 0.5 mL of modified Stuart's medium prepared by Becton Dickinson and Company, Cockeysville, Md.

The contents of the transport medium are sodium glycerophosphate, sodium thioglycolate, calcium chloride dihydrate, and water. The medium is capable of sustaining growth of aerobes, anaerobes, and fungi. The samples were inoculated into blood agar with 5% sheep's blood, chocolate agar, and MacConkey's agar plates within 1 hour of collection. The plates were incubated under carbon dioxide and examined at 24 hours and 48 hours for aerobes. For anaerobes, the material was plated on trypticase soy agar with 5% defibrinated sheep's blood, prepared by Saudi Prepared Media Laboratory (SPML), Riyadh, Saudi Arabia, and kanamycin-vancomycin laked blood agar plates, also prepared by SPML. The swabs were then placed in cooked meat medium containing vitamin K, sodium chloride, heme, tripticacein, and dextrose and incubated in anaerobic jars for 72 hours. For fungi, the specimen was inoculated into Sabouraud's dextrose agar plates and incubated for 4 days. The identification and characterization of the isolates were based on their cultural, morphologic, and biochemical characteristics.

RESULTS

A total of 102 patients were studied. Thirty-two (31%) were children under the age of 12 years. There were 111 isolates: 49 (44%) were pure cultures, 34 (33.3%) were mixed, and in 19 (18.6%) no growths were recorded.

Table 1 shows the various isolates. Eighty-two (74%) were aerobes, 28 (25%) were fungi, and only 1 (0.9%) was an anaerobe. *Pseudomonas aeruginosa*, in 25 (22.5%), was the most common bacterial isolate, followed by *Staphylococcus aureus* in 23

From the Department of Otolaryngology–Head and Neck Surgery, North West Armed Forces Hospital, Tabuk, Saudi Arabia.
CORRESPONDENCE — A. Olu Ibekwe, FRCS, Dept of ENT, North West Armed Forces Hospital, PO Box 100, Tabuk, Saudi Arabia.

TABLE 1. MICROBIOLOGIC ISOLATES FROM 102 EARS WITH CHRONIC SUPPURATIVE OTITIS MEDIA

	Total 111 Isolates		Pure Cultures 44%	
Isolates	*No.*	*%*	*No.*	*%*
Pseudomonas aeruginosa	25	22.5	21	18.9
Staphylococcus aureus	23	20.7	12	10.8
Streptococcus pneumoniae	12	10.8	1	0.9
Haemophilus influenzae	7	6.3		
Proteus mirabilis	4	3.6	3	2.7
Klebsiella	3	2.7		
Enterobacteriaceae	4	3.6		
Acinetobacter calcoaceticus	2	1.8		
Serratia ficaria	1	0.9		
Bacteroides sp (anaerobe)	1	0.9		
Aspergillus (fungus)	19	17.1	9	8.1
Candida (fungus)	9	8.1	3	2.7
No growth	19/102	18.6		
Total	111		49	44

Total number of patients was 102 (32 children were under 12 years of age)

(20.7%); there were fungi in 28 (25.2%). *Aspergillus* species (19 or 17.1%) made up the bulk of the fungi, and the rest (9 or 8.1%) were *Candida*.

DISCUSSION

The aerobic microbes isolated in this study correlate well with those in other studies, as illustrated in Table 2.[11,14-18] *Pseudomonas aeruginosa* was the most common microbe in most of the studies in Table 2, except those of Jokipii et al[14] and Ojala et al,[15] in which *S aureus* was the most common. In children, *S aureus* is usually the most predominant organism, probably because most CSOM in children follows poorly treated acute suppurative otitis media, in which *S aureus* is the most common pathogenic organism.[11,15]

It is generally accepted that anaerobes make up 20% to 50% of isolates in CSOM.[6-10] This high yield can be attributed to improved techniques of collection, transportation, and inoculation of specimens.[5] Our study did not confirm this finding. We only cultured 1 anaerobe from 102 specimens. An attempt will be made to find the cause for this poor yield.

Our specimens were collected from the middle ear through an aural speculum. We did not try to sterilize the ear canal, as advocated by Brook,[5] the reason being that other studies have shown that external ear cultures correlated well with middle ear cultures.[19,20] Our specimens were transported in commercially available transport media that allow for survival of anaerobic organisms. However, most of our patients were referred from primary health care physicians who first treated these patients with both systemic and topical antibiotics. The most common systemic antibiotics used were amoxicillin, Augmentin, and second-generation cephalosporins. The topical antibiotic was gentamicin ear drops. It is, therefore, possible that by the time these patients were seen, most of the anaerobes had been eliminated by antibiotic therapy. Another reason could be that perhaps we did not allow enough time for the slow-growing anaerobes to grow. Our cultures were for 72 hours, while Brook[5] recommends 14 days.

Although 20% to 50% of CSOM can be attributed[5] to anaerobes, their role in this infection is often questioned.[21] However, observations by numerous workers suggest that anaerobes play a pathogenic role in CSOM. Anaerobes always grow in mixed cultures; they are usually grown with aerobes. Experiments show that when anaerobes or aerobes are inoculated separately, no inflammation is produced, but together, they produce intense inflammation with production of pus.[22] This reaction is attributed to the synergistic relationship between aerobes and anaerobes.[5,20] The recovery of anaerobes in otogenic intracranial complications also points to their pathogenicity.[4] The production of β-lactamase by anaerobes and some aerobes and their ability to pass on their protective role to other organisms increase their pathogenicity in the mixed state.[5]

In our study, 25% of the isolates were fungi, espe-

TABLE 2 TYPES OF AEROBIC AND FUNGAL ISOLATES FROM VARIOUS STUDIES COMPARED WITH PRESENT STUDY

								Fungi	
Authors	*Year*	*No. of Ear Isolates*	Pseudomonas aeruginosa	Proteus sp	Escherichia coli	Klebsiella	Staphylococcus	Aspergillus	Candida
Palva and Hallstrom[16]	1965	100	24.0%	8.0%	4.0%	ND	13.0%	ND	
Jokipii et al[14]	1977	70	4.0%	8.0%	7.0%	ND	19.0%	ND	
Ojala et al[15]	1981	806	19.0%	12.9%	6.8%	3.7%	22.0%	ND	
Ibekwe and Okafor[11]	1983	62	45.2%	12.9%	ND	ND	29.0%	4.3%	1.6%
Sugita et al[17]	1981	62	7.8%	21.1%	ND	1.6%	6.3%	ND	ND
Fliss et al[18]	1992	170	84.0%	Enteric gram-negative bacilli 32%			20.0%	ND	ND
Present study		102	22.5%	3.6%	ND	2.7%	20.7%	17.1%	8.1%

ND — no data

cially *Aspergillus* species (17.1%). Some studies from hot and humid environments also grew fungi.[11-13] It is interesting to note that studies from identical geographic areas were different in their culture of fungi. Dincer et al,[13] in a study from Turkey, found 28.6% of the isolates were *Aspergillus* and *Candida*, while Erkan et al,[23] also from Turkey, did not report the growth of any fungi. Again, Ibekwe and Okafor,[11] in their study from Nigeria, reported about 6% of isolates to be due to fungi, while Rotimi et al,[24] also from Nigeria, did not report any fungal isolates. The possible explanation for this is that while one group looked for fungi, the other group did not. It is our belief that when looked for, fungi will invariably be isolated in ears with CSOM.

Fungal infections in otolaryngology are often associated with a decrease in immune function and are often regarded as colonization rather than invasion and therefore as not requiring treatment. This assertion is far from the truth. Gregson and La Touche[25] suggested that active fungal infection, predominantly by species of *Aspergillus* or *Candida*, may be more common than is recognized and may explain failure to obtain dry ears in many cases of otorrhea. In CSOM, the development of otalgia, itching, and the presence of hyphae indicate the presence of fungi.[11] Recent reports of *Aspergillus* involving certain areas in otorhinolaryngology, eg, paranasal sinuses with intracranial complications,[26-28] suggest that fungi can be pathogenic in ear infections as well. Fungi become pathogenic in an already inflamed mucosa, and unless they are treated when isolated in CSOM, a dry ear may not be achieved. We advocate that in investigating pathogenic organisms in CSOM, requests should include anaerobes and fungi.

ACKNOWLEDGMENTS — We thank the Research Committee of the North West Armed Forces Hospital for allowing us to carry out this study, and Linda Lacuesta for the secretarial work.

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TWENTIETH ANNUAL MEETING OF THE BÁRÁNY SOCIETY

The Twentieth Annual Meeting of the Bárány Society will be held in Würzburg, Germany, September 20-23, 1998. For more information, contact the Local Organizing Committee, Institute of the 4-G-F, Kurhausstrasse 12, D 97688 Bad Kissingen, Germany; telephone 0049/971-64832; fax 0049/ 971-68637.

DAIICHI

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November 18, 1997

Gary K. Chikami, M.D., Acting Director
Attention: Document Control Room
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA 20-799
FLOXIN® Otic
(Ofloxacin Otic Solution) 0.3%
Response to FDA Request for Information

Dear Dr. Chikami:

To follow-up our response submitted on November 17, 1997, please find attached the additional information requested during our November 6, 1997 discussions with FDA.

At the November 6, 1997 rehearsal meeting, we were requested to supply information on the distribution of MIC's to ofloxacin, neomycin and polymixin for pathogens isolated in the otitis externa protocols separately by protocol. The tables had previously been supplied on November 4, 1997 as combined data from the two protocols (Protocol 8280A-PRT002 entitled "A Multicenter, Randomized, Evaluator-Blind Study to Compare the Safety and Efficacy of Ofloxacin Otic Solution with that of Cortisporin® Otic Solution in the Treatment of Acute Otitis Externa in Adults" and Protocol 8280A-PRT003 entitled "A Multicenter, Randomized, Evaluator-Blind Study to Compare the Safety and Efficacy of Ofloxacin Otic Solution with that of Cortisporin® Otic Solution in the Treatment of Acute Otitis Externa in Pediatric Patients"). The requested tables, supplying data for the two protocols separately, are attached.

If you require further clarification of any data provided in this submission, please do not hesitate to contact my office.

This submission contains trade secret and commercial or financial information which is privileged or confidential and entitled to protection from disclosure and handling by the Food and Drug Administration under the agency's regulations in 21 CFR Part 20.

Sincerely,

Amy S. Domanowski, Ph.D.
Senior Director, Regulatory Affairs

ASD/ban
cc: Ms. Beth Duvall Miller, CSO, Project Management, 9201 Corporate Blvd.
Attachments

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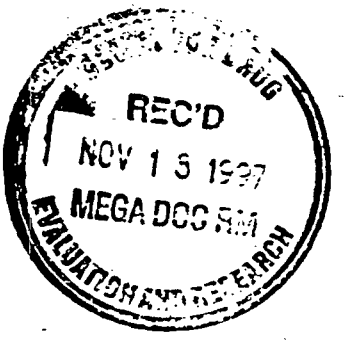

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Response to FDA Request for Information

Dear Dr. Chikami:

Further to discussions held at our November 6, 1997 meeting, we have collected preliminary additional data from the subjects in the current control arm of Protocol 8280A-PRT006, "A Multicenter, Prospective With Historical and Current Practice Control, Open-Label Study to Examine the Safety and Efficacy of Ofloxacin Otic Solution in the Treatment of Purulent Otorrhea (Draining Ear) in Adolescents and Adults with Chronic Perforation of Tympanic Membranes". The supplemental protocol is attached with information on the treatments received by the current control subjects.

We have also included information regarding monomicrobial and polymicrobial infections for each registration trial and on audiometric findings at 8,000 Hz, from 8280A-PRT008.

This submission contains trade secret and commercial or financial information which is privileged or confidential and entitled to protection from disclosure and handling by the Food and Drug Administration under the agency's regulations in 21 CFR Part 20.

Sincerely,

Amy S. Domanowski

Amy S. Domanowski, Ph.D.
Senior Director, Regulatory Affairs

ASD/ban
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