CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-789

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-789

American Pharmaceutical Partners, Inc.
Attention: Toni A. Glinsey
Senior Regulatory Scientist
2045 North Cornell
Melrose Park, IL 60160

Dear Ms. Glinsey:

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: Tobramycin for Injection, USP

Review Priority Classification: Standard (S)

Date of Application: December 20, 2002

Date of Receipt: December 24, 2002

Our Reference Number: NDA 50-789

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2003 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 24, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Product
Attention: Division Document Room, HFD-520
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: Document Room
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call LTJG Raquel Peat, Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Frances LeSane
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Beth Duvall-Miller
2/19/03 05:14:47 PM
BDM acting for FVL

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
OPS, HFD-805 **Peter Cooney and Paul Stinavage**			**HFD-520, DAIDP** **Raquel Peat, S. Pagay and F. LeSane**	
DATE October 2, 2003	IND NO.	NDA NO. 50-789	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 20 December 2002
NAME OF DRUG Tobramycin for Injection	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG aminoglycosides	DESIRED COMPLETION DATE **October 10, 2003**

NAME OF FIRM: American Pharmaceuticals Partners, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Microbiology Sterility Review for the label. Please review "Preparation and Storage " section of the label. If the stability data support [redacted] hours at room temperature and [redacted] hours in refrigerator, is there a time limit for storage and dispensing the entire contents of the PBP from microbiology consideration"? There is a DRAFT guidance that requires the product be dispensed within 4 hours and restrictions with respect to - how the product is reconstituted and dispensed.

The PDUFA date is 10/24/03. If this is a deficiency, we need to contact the sponsor perhaps as a telecon. Attached is a copy of the sponsor's proposed label.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
R. Peat, LeSane and Pagay	X DFS-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

19 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative/Correspondence 1

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/s/

Frances LeSane
10/2/03 10:53:36 AM

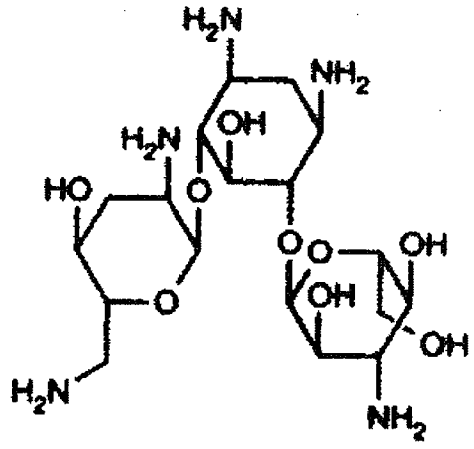
NDA FILEABILITY CHECKLIST

NDA Number: 50-789 Applicant: American Pharmaceuticals, Partners, Inc. Stamp Date: 12/31/02
Drug Name: Tobramycin for Injection, USP, 1.2 grams/15 mL fill in 50 mL Vial

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		The NDA is submitted as 505(b)(2) with reference drug - Nebcin-Lilly
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		EER submitted for all 5 facilities.
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		Section 4.A.I.4
8	Does the section contain controls for the drug product?	√		Section 4.A.II.6
9	Has stability data and analysis been provided to support the requested expiration date?	√		Section 4.A.II.7
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		NA	No IND for this NDA
11	Have draft container labels been provided?	√		Page 00088
12	Has the draft package insert been provided?	√		
13	Has an investigational formulations section been provided?		NA	No IND for this NDA
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		Portions of 4.A.II.5 section



Proposed Drug Product Composition (unit Dose)

Tobramycin sulfate USP [redacted]

[redacted]

Water for Injection, USP q.s.

[redacted]

The final product is a dry powder.

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.
Review Chemist: S.N. Pagay Date:
Acting Team Leader &
DNDCIII Deputy Director: Bonnie B. Dunn, Ph.D. Date:
cc:
Original NDA 50-789
HFD-520/Division File
HFD-520/Chem/Pagay
HFD-520/PM/Peat
HFD-830/DepDivDir/Chem/Dunn

Have all DMF References been Identified?

DMF Number	Holder	Description	LOA Included	Status
[redacted]			Yes	Not reviewed
			Yes	
			Yes	

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/s/

Shrikant Pagay
2/4/03 06:55:02 PM
CHEMIST

Bonnie Dunn
2/4/03 07:48:33 PM
CHEMIST

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
OPS, HFD-805 **Peter Cooney**	**HFD-520** **Raquel Peat**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 3, 2003		50-789	New NDA	20 December 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tobramycin for Injection		aminoglycosides	**ASAP**

NAME OF FIRM: American Pharmaceuticals Partners, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Microbiology Sterility Review

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
R. Peat, LeSane and Pagay	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Shrikant Pagay
1/15/03 10:37:37 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING REVIEW ISSUES IDENTIFIED

NDA 50-789

American Pharmaceutical Partners, Inc.
Attention: Toni A. Glinsey
Senior Regulatory Scientist
2045 North Cornell
Melrose Park, IL 60160

Dear Ms. Glinsey:

Please refer to your December 20, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tobramycin for Injection, USP.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 21, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call LTJG Raquel Peat, Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Janice Soreth
2/21/03 04:49:17 PM

Division of Anti-Infective Drug Products
PROJECT MANAGEMENT REVIEW
OF FINAL PRINTED LABELING (FPL)

Application Number: NDA 50-789/N-000 (AC)

Name of Drug: Tobramycin for Injection, USP

Sponsor: American Pharmaceutical Partners, Inc.

Material Reviewed:

Submission Date: January 12, 2004

Receipt Date: January 13, 2004

Background and Summary

New drug application for (NDA) 50-789/N-000 (AC) Tobramycin for Injection, USP, dated January 12, 2004, and received on January 13, 2004.

An approvable letter was issued on October 24, 2003 based on final draft labeling submitted October 17, 2003. Final printed labeling (FPL) was submitted in response to the approvable letter on January 13, 2004.

This review compares the final printed label submitted on January 13, 2004 to the applicant's draft labeling dated October 17, 2003 that was approved in the approvable letter on October 24, 2003.

Review

A comparison of the final printed labeling submitted on January 13, 2004 to the draft labeling that was approved in the October 24, 2003 approvable letter detected no discrepancies.

Conclusions

An approval letter should be issued for NDA 50-789 based on the final printed labeling submitted January 13, 2004.

LT Raquel A. Peat, M.S., M.P.H.
Senior Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Ms. Frances V. LeSane
Chief, Project Management Staff

CSO LABELING REVIEW

Enclosed: Labeling

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative/Correspondence 2

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/s/

Raquel Peat
7/6/04 01:49:27 PM
CSO
FPL Review

Frances LeSane
7/6/04 02:48:25 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-789

INFORMATION REQUEST LETTER

American Pharmaceutical Partners, Inc.
Attention: Toni Glinsey
Senior Regulatory Scientist
2045 North Cornell Avenue
Melrose Park, IL 60160-1002

Dear Ms. Glinsey:

Please refer to your December 20, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tobramycin for Injection, USP.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Provide a complete update on stability data for the following lots: R102-002 and R102-003. If available, also provide statistical analysis of the data

If you have any questions, call LTJG Raquel Peat, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely,

James Vidra, Ph.D.
Chemistry Team Leader for the
Division of Anti-Infective Drug Products, HFD-520
DNDC DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Jim Vidra
8/14/03 03:00:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-789

INFORMATION REQUEST LETTER

American Pharmaceutical Partners, Inc.
Attention: Toni Glinsey
Senior Regulatory Scientist
2045 North Cornell Avenue
Melrose Park, IL 60160-1002

Dear Ms. Glinsey:

Please refer to your December 20, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tobramycin for Injection, USP.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Submit the following information for the Drug Substance:

[redacted]

[redacted]

Submit the following information for the Drug Product:

6). The unit dose is defined as [redacted] and the vial size is 1.2 g. Please explain how the 2 values are related.

7). Based on the acceptance criteria fo: [redacted] in the drug product and the maximum daily dose, please provide mg/day exposure for

8). Although, batch records provide manufacturing procedure from a different perspective, please provide in detail, step-by-step manufacturing procedure to include all the unit operations starting from preparation of tobramycin solution to sealing the finished vials. Please identify critical process parameters for each of the unit operations for the manufacture of the finished dosage form and for the preparation of container closure components for the [redacted] 3 operations.

9). Submit the in-process pH test for the bulk solution.

10). Provide the upper and lower fill weight limits in terms of the lyophilized powder weight.

11). Submit the in-process test and data, [redacted]

12). The proposed acceptance criteria for impurities listed on page 1273 Vol. 1.5 is significantly wider than the data provided for lots listed in Tables 4 -30 to 4-32, page 1275 to 1277, Vol. 1.5.

[redacted]

13). Please identify the process impurities and degradants in the drug substance and drug product.

If you have any questions, call LTJG Raquel Peat, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely,

James Vidra, Ph.D.
Chemistry Team Leader for the
Division of Anti-Infective Drug Products, HFD-520
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Jim Vidra
9/24/03 04:01:18 PM

February 5, 2003

45 DAY MEETING CHECKLIST – NDA 50-789

Drug: A generic Tobramycin for Injection, USP product.

Note: Refer to the innovator's labeling, Eli Lilly's NEBCIN®, Tobramycin for Injection, USP

Applicant: American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue,
Melrose Park, Illinois 60160

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:

CLINICAL MICROBIOLOGY:

(1)	On its face, is the Clinical Microbiology section of the NDA organized in a manner to allow substantive review to begin?	YES
(2)	Is the Clinical Microbiology section of the NDA indexed and paginated in a manner to allow substantive review to begin?	YES
(3)	On its face, is the Clinical Microbiology section of the NDA legible so that substantive review can begin?	YES
(4)	On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains, and using necessary numbers of approved laboratories to meet current divisional standard of approvability of the submitted draft labeling?	N/A
(5)	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	N/A
(6)	Has the applicant submitted draft breakpoint and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	N/A
(7)	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	N/A

FILEABILITY (con't):

On initial overview of the NDA application:

CLINICAL MICROBIOLOGY:

(8) Has the applicant submitted draft labeling consistent with §201.56 and §201.57, current divisional policy, and the design of the development package? Yes

(9) From a **Clinical Microbiology** perspective, is this NDA fileable? **Yes**

Clinical Microbiologist's comment:

A Clinical Microbiology Review of the package insert labeling along with current Divisional Policy will determine whether the labeling remains like the innovator or made current.

Harold V. Silver
Clinical Microbiology Reviewer
DAIDP/HFD-520

Final Initialed 2/6/03 ATS
Albert T. Sheldon, Jr. Ph.D.
Team Leader Microbiology
DAIDP/HFD-520

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/s/

Harold Silver
2/6/03 02:59:31 PM
MICROBIOLOGIST

Sign off on the 45 Day Clinical Microbiology NDA
Fileable Checklist.

Albert Sheldon
2/9/03 12:31:26 PM
MICROBIOLOGIST

Lillian Gavrilovich
2/11/03 11:29:22 AM
MEDICAL OFFICER