CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64164

CORRESPONDENCE

AADA 64-164

Ranbaxy Pharmaceuticals Inc.
Attention: Jim Sibert
U.S. Agent for: Ranbaxy Laboratories Limited
4600 Marriott Drive Suite 100
Raleigh, NC 27612

NOV 17 1995

Dear Sir:

We acknowledge the receipt of your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Cefaclor for Oral Suspension USP, 250 mg/5 mL

DATE OF APPLICATION: September 27,1995

DATE OF RECEIPT: September 29, 1995

We will correspond with you further after we have completed the review of your application.

Please be advised that during the AADA approval process, samples of the active and inactive ingredients, and the AADA exhibit batch(es) (which should be the same as the biobatch if a bioequivalence study was conducted) may be collected by the FDA district office staff and tested by FDA district or headquarters laboratory staff. Drug substance standards and manufacturer's documentation of the impurity profile should be made available. In addition, batch records, certificates of analysis and specifications and tests for the drug substance, drug product and inactive ingredients may be collected.

The subject product of an AADA must conform to the current official compendial monograph requirements and be compatible with the test and assay methods described in that monograph. You must submit adequate documentation and laboratory data in your AADA that prove that any non-official alternate procedures that you choose to use for the analytical control (release) of your product are equivalent to the official compendial procedures. If this information is not submitted, the review of the application will be delayed.

Please identify any communications concerning this application with the number shown above.

In addition we note you have provided a copy of your debarment certification and convictions statements. Please provide a revised certification/statement with an original signature.

Should you have questions concerning this application contact:

Mark Anderson
Consumer Safety Officer
(301) 594-0360

Sincerely yours,

/S/ 11/16/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-164
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett
HFD-473/Antimicrobial Drugs Branch

AADA Acknowledgement Letter!

AADA's 64-155 (375 mg/ 5mL)
64-164 (250 mg/ 5mL) ✓
64-165 (187 mg/ 5mL)
64-166 (125 mg/ 5mL)

Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Jim Sibert
4600 Marriott Drive Suite 100
Raleigh, NC 27612

FEB 7 1996

Dear Sir:

This is in reference to your abbreviated antibiotic applications dated July 7 and September 27, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Cefaclor for Oral Suspension USP.

Reference is also made to your amendments dated September 27, 1995.

The applications are deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Chem

B. Labeling Deficiencies

CONTAINER:

1. Please revise your Manufactured by statement to be consistent with that appearing in the insert labeling.

2. Revise your storage temperature to include a lower temperature range, not less than 15°C. Please note that the innovator cites: "Store at controlled room temperature 15° to 30° C (59° to 86° F)".

3. Revise the Usual dosage statement to read as follows:

   Usual dosage: ...day (40 mg..) (insert a space). In addition replace "3" with "three" (two occurrences).

4. Revise your storage recommendation to read as follows:

   Prior to mixing: Store ...

5. We encourage you to relocate "Shake Well Before Use" to the main panel.

6. Capitalize the "L "in "ml" and revise the "Each 5 mL contains" statement to read as follows:

   Each 5 mL (Approx. one teaspoonful) will then contain cefaclor monohydrate equivalent to ___mg anhydrous cefaclor.

7. Relocate the "Each 5 mL contains" statement so that immediately follows the "Directions for mixing" instructions.

8. We encourage you to bold "Directions for mixing" and the amount of water to be added to help the pharmacist.

9. Insert the following text so that it follows the Usual Dosage paragraph:

   Contains cefaclor monohydrate equivalent to ___ g cefaclor in a dry pleasantly flavored mixture.

10. Decrease the prominence of (when mixed)" to be less than the primary expression of strength "125 mg/5 mL".

INSERT:

1. GENERAL COMMENT

   Please use "mcg" rather than Revise throughout the insert.

2. TITLE

   Please revise to reflect the official established names:

   Cefaclor Capsules USP and Cefaclor For Oral Suspension USP

3. CLINICAL PHARMACOLOGY

   a. Revise the third sentence as follows:

      It has been reported that following administration...

   b. "in-vitro" should appear in italics. (two locations)

4. CONTRAINDICATIONS

   Make the section heading plural.

5. PRECAUTIONS

   a. General, sixth paragraph - ...tablet but not with Glucose Enzymatic Test Strip, USP. Delete

   b. Pediatric Use - ...for use in pediatric patients less than...

6. DOSAGE AND ADMINISTRATION

   Penultimate paragraph - ...(see PRECAUTIONS).

Please revise your container labels, and insert labeling, then prepare and submit final print. Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

In addition to responding to these deficiencies, please note and acknowledge the following in your responses:

1. The reference bulk antibiotic application has not yet been approved. Until it is approved, these applications will remain not approvable. You may independently seek to address all the deficiencies within your control.

2. Your bioavailability study data for the 375 mg/5 mL strength, and your request for a waiver of the requirement for a bioavailability study for the corresponding 125 mg/5 mL, 187 mg/5 mL and 250 mg/5mL strengths remains under consideration. We will correspond under separate cover if any comments are warranted.

The files on these applications are now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these applications. Your amendments should respond to all the deficiencies listed. Partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The responses to this letter will be considered as MAJOR amendments and should be so designated in your cover letters. You will be notified in a separate letter of any deficiencies in the bioequivalence portion of your applications. If you have substantial disagreement with our reasons for not approving these applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 2/7/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA's 64-155 (375 mg/5 mL)
64-164 (250 mg/5 mL)
64-165 (187 mg/5 mL)
64-166 (125 mg/5 mL)

Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Jim Sibert
4600 Marriott Drive Suite 100
Raleigh, NC 27612

APR 30 1997

Dear Sir:

This is in reference to your abbreviated antibiotic applications dated July 7 and September 27, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Cefaclor for Oral Suspension USP.

Reference is also made to your amendments dated September 27, 1995.

The following comments pertain to labeling issues only:

This letter is to inform you of changes in the labeling of the listed drug. Please revise your labeling at the time of next printing or within 180 days, whichever is sooner, using the labeling for Ceclor® Capsules and Oral Suspension (Eli Lilly; Approved 9/24/96; Revised 1/19/96).

On February 7, 1996 we issued a deficient letter that outlined chemistry and labeling issues. You will still make the changes as outlined in our February 7, 1996 correspondence in addition to the changes found in the latest approved labeling cited above. Please submit revise labels and labeling as described in our February 7, 1996 correspondence.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the listed drug labeling with all differences annotated and explained.

Sincerely yours,

/S/ for 4-30-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA 64-155
Division File
HFD-600/Reading File
HFD-610/JPhillips AVezza 3/21/97
HFD-613/APayne/AVezza/JGrace (no cc:)

Letter Out

AVezza 3/21/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

64-164

Public Health Service

Rockville MD 20857

Ranbaxy Pharmaceuticals, Inc.
Attention: Mr. Jim Sibert
4600 Marriott Drive - Suite 100
Raleigh, North Carolina 27612

MAR 27 1996

Reference Number: OGD 96-030

Dear Mr Sibert:

This letter is in response to your February 6, 1996, request that the Office of Generic Drugs (OGD) review your proposal for modifications of the formulations, for purposes of process validation, of Ranbaxy Pharmaceutical's, Inc., Cefaclor Oral Suspension [abbreviated antibiotic applications (AADA's) 64-155, 64-164, 64-165, and 64-166)}, and Cefaclor Capsules (AADA 64-156). The Office has reviewed your proposal and provides the remarks described below.

Regarding Cefaclor Oral Suspension, the proposal to delete the proposed flavoring and coloring component(s)(specified in the pending AADAs) and substitute an alternate flavor and color is considered a change in formulation which may not be representative of the proposed formulation for purposes of manufacturing process validation.

In reference to Cefaclor Capsules the proposal to delete the proposed capsule coloring components (specified in the pending AADA) and to substitute alternates is considered acceptable for purposes of manufacturing process validation, provided that the physical characteristics of the alternate hard gelatin capsule are unchanged.

If you have any questions, please call Mr. Robert West at (301) 594-0360. In future correspondence regarding this issue, please include a copy of this letter along with a copy of the firm's proposal.

Sincerely yours,

/S/ for

Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

AADAs 64-155
64-164
64-165
64-166

MAY 21 1996

Ranbaxy Pharmaceuticals Inc.
Attention: Jim Sibert
U.S. agent for Ranbaxy Laboratories Limited
4600 Marriott Drive Suite 100
Raleigh, NC 27612

Dear Sir:

Reference is made to your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act for Cefaclor for Oral Suspension USP, 375 mg/5 mL.

The Division of Bioequivalence has completed its review and has no further questions at this time.

In the future, data should be submitted on a computer diskette in ASCII format containing two separate files as follows:

A. SUBJ SEQ PER TRT AUCT AUCI C_{MAX}
B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

The fields should be delimited by one blank space, and missing values should be indicated by a period.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

RANBAXY
PHARMACEUTICALS INC.
4600 MARRIOTT DRIVE-SUITE 100 RALEIGH, NORTH CAROLINA 27612
PHONE : (919) 510 0949 FAX : (919) 510 0958.

labeling satisfactory for approval - review drafted 8/11/97 A. Uzzo

May 28, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AC

MAJOR
AMENDMENT

RE: Cefaclor for Oral Suspension USP

AADA 64-155 (375mg/5mL)
✓ AADA 64-164 (250mg/5mL)
AADA 64-165 (187mg/5mL)
AADA 64-166 (125mg/5mL)

Major Amendment Response to 2/7/96 FDA Letter

Dear Sir:

Reference is made to our pending Abbreviated Antibiotic Drug applications for Cefaclor for Oral Suspension, USP. This major amendment is in response to your letter of February 7, 1996 indicating that the above application is deficient and therefore not approvable.

The questions are responded to in the same order as in the letter. A copy of the FDA letter is attached at the end of the responses for your convenience.

Field Copy. We certify that a true copy of the technical section described in 21 CFR 314.50 (d) (1) of this submission has been provided to the Food and Drug Administration, Office of Generic Drugs.

If you have any questions regarding the submission, please call me at (919) 510-0949 ext. 224.

RECEIVED
JUN 0 2 1997
GENERIC DRUGS

Sincerely,

Jim Sibert

Jim Sibert
Executive Director, Regulatory Affairs, Ranbaxy Pharmaceuticals Inc.
U.S. Agent for Ranbaxy Laboratories Ltd.

H:\RCOLE\LTRS\MAJORA.DOC

RANBAXY
PHARMACEUTICALS INC.
4600 MARRIOTT DRIVE-SUITE 100 RALEIGH, NORTH CAROLINA 27612
PHONE: (919) 510 0949 **FAX**: (919) 510 0958.

September 4, 1997

TELEPHONE
AMENDMENT
N/AC

NDA ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: Cefaclor for Oral Suspension USP

AADA 64-155 (375mg/5mL)
AADA 64-164 (250mg/5mL) ✓
AADA 64-165 (187mg/5mL)
AADA 64-166 (125mg/5mL).

Telephone Amendment Response to 8/27/97 FDA Telephone Call

Dear Madam/Sir:

Reference is made to our pending Abbreviated Antibiotic Drug applications for Cefaclor for Oral Suspension, USP. This telephone amendment is in response to Florence Fang's telephone call of August 27, 1997 indicating that two (2) items need to be revised before approval can be given.

The 2 items requested for revision/change are:

1) **Original submission, page 1764, Quantitative Listing of All Ingredients**
   a. Unit Formula

   There needs to be Totals for the 5mL Quantities

   Response:
   The Quantitative Listings for all ingredients for the 5mL formulas have been revised and the Totals are also given. See Attachment 1.

2) **The Total Related Substance specification in Stability is too high. Change the specification to NMT % Total and lower the Expiry date to 18 months.**

Response:
Based on the 24-month Stability Data and the revised "NMT % Total" specification for Related Substances, we request the following Expiry Dates for the following drug products in the following AADAs:

	Strength	AADA	Expiry Date
Cefaclor for Oral Suspension USP	125mg\mL	64-166	24 months
Cefaclor for Oral Suspension USP	187mg\mL	64-165	24 months
Cefaclor for Oral Suspension USP	375mg\mL	64-155	24 months
Cefaclor for Oral Suspension USP	250mg\mL	64-164	18 months

Please note that these are individual AADAs.

The Revised Stability Protocol is in Attachment 2.

Field Copy. We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this submission has been provided to the Food and Drug Administration, Office of Generic Drugs.

If you have any further questions regarding the submission, please call me at (919) 510-0949 x224.

Sincerely,

Jim Sibert

Jim Sibert
Executive Director Regulatory Affairs, Ranbaxy Pharmaceuticals Inc.
U.S. Agent for Ranbaxy Laboratories Ltd.

RANBAXY
PHARMACEUTICALS INC.
4600 MARRIOTT DRIVE-SUITE 100 RALEIGH, NORTH CAROLINA 27612
PHONE : (919) 510 0949 FAX : (919) 510 0958.

10/30/95

September 27, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: Initial AADA Submission
Cefaclor for Oral Suspension, USP 250 mg/5 mL

Dear Sir:

Please refer to your letter of September 20, 1995 (attached) wherein you notified us that you were refusing to file our Abbreviated Antibiotic Drug Application dated July 7, 1995 for Cefaclor for Oral Suspension, USP 125, 187, 250, and 375 mg/5 mL, AADA 64-155 because oral suspensions with multiple strengths are not eligible to be condensed into a single application. In addition, please refer to the September 25, 1995 telephone conversation between Mr. Harvey Greenberg of the Agency and Mr. Jim Sibert of Ranbaxy wherein Mr. Greenberg agreed that we could amend AADA 64-155 with a revised Form FDA 356h to cover only the 375 mg/5 mL strength and that our separate applications for 125, 187 and 250 mg/ 5 mL strengths could consist of copies of Sections I through V and Sections VII through XXI of the July 7, 1995 submission and could reference AADA 64-155 for bioequivalence data (Section VI).

Submitted herewith please find an original Abbreviated Antibiotic Drug Application for Cefaclor Suspension, USP 250 mg/5 mL which consists of three volumes. This submission is based on the innovator product Ceclor® (cefaclor, USP) Suspension manufactured by Eli Lilly Industries, Inc, a subsidiary of Eli Lilly and Company.

One suspension strength (250 mg/5mL) is proposed in this AADA. A letter appointing Mr. Jim Sibert as U.S. agent for Ranbaxy Laboratories Limited is included. The bulk drug substance, cefaclor, USP is manufactured by Ranbaxy Laboratories Limited in accordance with the pending Abbreviated Antibiotic Drug Application, AADA 64-155.

A two way crossover bioequivalence study was conducted under fasted conditions in 26 normal volunteers comparing the proposed 375 mg/5mL suspension to the same strength innovator product (Ceclor® 375 mg/5 mL - Lilly). In addition, a three way crossover bioequivalence/bioavailability study was conducted under fed conditions in 16 normal volunteers comparing the proposed 375 mg/5 mL suspension to the same strength innovator (Ceclor® 375 mg/5 mL- Lilly) and comparing the bioavailability of the proposed 375 mg/5 mL suspension under fed and fasted conditions. The 375 mg/5 mL strength was shown to be bioequivalent to the innovator. Please refer to AADA 64-155 for bioequivalence data. The 250 mg/5 mL strength which is the subject of this application is proportionally similar to the 375 mg/5 mL strength.

The number of copies included are as follows:

FDA Archival Copy (full copy)	3 volumes, (Section I-XXI)
FDA Archival (Methods Validation Copy #2, #3, #4)	1 volume (Section XVI)
FDA Archival (Draft Labeling Copy #2, #3, #4)	1 volume (Section V)
FDA Review Copy, CMC	3 volumes (Sections I-V, VII-XXI)
FDA Review Copy, Bioequivalence	1 volumes (Sections I-VII)
Certified Field Copy District Office Review	3 volumes(Sections I-V and VII-XXI)

If you have any questions regarding this submission please do not hesitate to contact me at (919) 510-0949.

Sincerely,

Jim Sibert

Jim Sibert
Executive Director
Regulatory Affairs
Ranbaxy Pharmaceuticals Inc.
US Agent for:
Ranbaxy Laboratories, Limited