# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**64164**

# ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING #1

ANDA

Draft Container labels, Carton and Insert labeling

DATE OF REVIEW: October 26, 1995

AADA #: 64-156 (250 mg and 500 mg Capsules)
64-155 (375 mg/5 mL For Oral Suspension)
64-164 (250 mg/5 mL " " " )
64-165 (187 mg/5 mL " " " )
64-166 (125 mg/5 mL " " " )

NAME OF FIRM: Ranbaxy Laboratories Limited

NAME OF DRUG: Cefaclor Capsules USP and Cefaclor For Oral Suspension USP

DATE OF SUBMISSION: July 17, 1995 (AADA's 64-156 and 64-155) and September 27, 1995 (AADA's 64-155, 64-164, 64-165 and 64-166)

COMMENTS:

CONTAINER:

100s, 250s, 500s (250 mg and 500 mg) Capsules:

1. We encourage you to differentiate your product strengths by the use of boxing, contrasting colors, or some other means.

2. ...light-resistant... (add hyphen)

3. Revise "Usual dose" so that it reads "Usual Adult Dosage".

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

5. 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)".

6. Revise to read: Each capsule contains Cefaclor USP (monohydrate) equivalent to ____ mg of anhydrous cefaclor.

50 mL and 100 mL (187 mg/5 mL and 375 mg/5 mL);
75 mL and 150 mL (125 mg/5 mL and 250 mg/5 mL) For Oral Suspension:

1. See comments 4 and 5 under CONTAINER above.

2. 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).

3. Revise your storage recommendation to read as follows:

   Prior to mixing: Store ...

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

5. 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.

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

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

8. 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.

9. Decrease the prominence of "150 mL (when mixed)" to be

less than the primary expression of strength "125 mg/5 mL".

UNIT DOSE BLISTER: 10s (250 mg and 500 mg)

1. See comment 1 under CONTAINER.

2. Revise the established name to be singular (capsule).

UNIT DOSE CARTON: 10 X 10s

1. See comments under CONTAINER for capsules.

2. Add a comma after the word "tight" and before the word "light" in the dispensing statement.

3. Please include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be with a child resistant container, e.g.,:

   This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized. [Note: The second sentence optional]

4. Include the total net quantity (100 unit-dose capsules).

INSERT:

1. GENERAL COMMENT

   Please use "mcg" rather than "μg". 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).

7. HOW SUPPLIED

We note that both capsule strengths are identical in color. Please include any identifying markings that may appear on the capsules.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their container labels, unit dose labels, carton and insert labeling, then prepare and submit draft labels and labeling.

NOTE TO THE CHEMIST:

Please note comment 5 under CONTAINER for capsule and comment 7 under INSERT.

FOR THE RECORD:

1. Review based on the listed drug (Ceclor; Eli Lilly; Approved May 28, 1993; Revised February 12, 1993). The insert revised 2/12/93 supersedes the April 1993 approval of the insert that was revised December 1991.

2. Storage/dispensing

AADA: Store at a temperature not to exceed 25° C. Protect from moisture. Dispense in a tight, light-resistant container. Keep tightly closed. See comments under container for the capsule (2 & 6) and suspensions (3).

NDA: Store at CRT

USP: Preserve in tight containers.

3. Packages

Generic - Unit dose, 100s, 250s, 500s (capsules) and 50, 75, 100, and 150 mLs For Oral Suspension.

Listed drug - unit-dose, 15 (unit of use), 100s (capsules)and 50, 75, 100, and 150 ml (for Oral suspension).

Packages are bottles composed of HPDE (light-resistant). The suspensions have CRC closures.

4. The composition statement is found on page 1919. The DESCRIPTION section accurately reflects this statement.

5. The firm will be submitting the 125 mg , 187 and the 250 mg/ mL strengths as separate AADAs. We will include these AADAs in this review once they have been received. These AADA's were submitted with a letter date of September 27, 1995. The AADAs were inserted in this review cycle.

6. The applicant has a foreign address in accord with 21 CFR 201.1(i). We believe that when they are ready to market this product it will have a U.S. distributor. We will not

comment on the lack of a U.S. address (distributor) on the labels and labeling.

7. The PRECAUTIONS, General section now deletes
Previous we had been deleting only

Angela Payne

cc: AADA 64-156
64-155
64-164
64-165
64-166
Dup/Division File APayne 11/29/95
HFD-613/APayne/CHoppes/JPhillips (no cc)
HFD-600 CHoppes 11/29/95
11/20/95

JPhillips 11/30/95

# MEMORANDUM

DATE: September 5, 1997

FROM: Susan Rosencrance

SUBJECT: Ranbaxy's Cefaclor for Oral Suspension USP

TO: AADAs 64-155, 64-164, 64-165 & 64-166

Upon review at the Division level it was noted that 2 additional items needed revision/change. These items were communicated to the firm via telephone on 8/27/97. The firm's response dated 9/4/97 has adequately addressed the items of concern. The items are summarized as follows:

1) The components/composition statement did not include a total formula amount (per 5 mL). The revised statement provided in the 9/4/97 telephone amendment now contains a total weight of mL). Acceptable

2) The limits of % for individual and total related substances is higher than limits approved in other applications for this drug product (Re: 64-110, 64-070). The firm was asked to lower the total limit to NMT % and to lower the expiry date to 18 months. The firm has agreed to lower the limit and has provided a revised stability protocol in the 9/4/97 telephone amendment. With respect to the expiry date the firm has lowered only the 250 mg/5 mL strength to 18 months. Based on the 24 month data this is the only strength that exceeds the new % total limit. The other strengths (125 mg/5 mL, 187 mg/5 mL & 375 mg/5 mL) continue to maintain a 24 month expiry date. Acceptable

# APPROVAL SUMMARY
# REVIEW OF PROFESSIONAL LABELING
# DIVISION OF LABELING AND PROGRAM SUPPORT
# LABELING REVIEW BRANCH

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AADA Number: 64-155 (375 mg/5 mL For Oral Suspension)
64-164 (250 mg/5 mL " " " )
64-165 (187 mg/5 mL " " " )
64-166 (125 mg/5 mL " " " )

Date of Submission: May 28, 1997

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Cefaclor For Oral Suspension USP

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**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes
(6 in blue jackets - 6 in red jackets)

Container Labels: (50 mL and 100 mL) = 375mg 187mg ~~250mg~~ (75mL and 150mL) = 125mg 250mg
*Satisfactory as of May 28, 1997 submission.*
QUzzi 8/12/97

Professional Package Insert Labeling:
*Satisfactory as of May 28, 1997 submission.*

Revisions needed post-approval: NONE

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: CeClor®

NDA Number: 50-522

NDA Drug Name: CeClor® (Cefaclor For Oral Suspension USP)

NDA Firm: Lilly

Date of Approval of NDA Insert and supplement #: 9/24/96 (S-017)

Has this been verified by the MIS system for the NDA? No - MIS has last approved SLR as S-014 on 9-30-96 - but there is an approval letter dated 9-24-97 in the file for S-014 with labeling (draft) that we use as our model. S-014 includes the labeling changes from S-017.

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Labels on file

# REVIEW OF PROFESSIONAL LABELING CHECK LIST

| Established Name | Yes | No | N.A. |
|---|---|---|---|
| Different name than on acceptance to file letter? | | X | |
| Is this product a USP item? If so, USP supplement in which verification was assured. USP 23 | X | | |
| Is this name different than that used in the Orange Book? | | X | |
| If not USP, has the product name been proposed in the PF? | | | X |
| **Error Prevention Analysis** | | | |
| Has the firm proposed a proprietary name? NO. | | | |
| **Packaging** | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | X | |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | | X |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | | X | |
| Are there any other safety concerns? | | X | |
| **Labeling** | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
| Has applicant failed to clearly differentiate multiple product strengths? | | X | |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | | |

| Labeling (continued) | Yes | No | N.A. |
|---|---|---|---|
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | | X |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | X | |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | | X | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | X | | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | | X | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | X | | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | | |

FOR THE RECORD:

1. Review based on the listed drug (Ceclor; Eli Lilly; Approved September 24, 1996; Revised January 19, 1996 - draft).

2. Storage/dispensing

   AADA: Store at a temperature not to exceed 25° C. Protect from moisture. Dispense in a tight, light-resistant container. Keep tightly closed.
   NDA: Store at CRT

USP: Preserve in tight containers.

3. Packages

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4. The composition statement is found on page 1919. The DESCRIPTION section accurately reflects this statement.

5. The firm submitted the 125 mg , 187 and the 250 mg/ mL strengths as separate AADAs.

6. The applicant has a foreign address in accord with 21 CFR 201.1(i) and a U.S. distributor.

7. The PRECAUTIONS, General section deletes only

8. Bio - studies found acceptable, waiver granted - see review dated May 13, 1996.

9. These AADAs share an insert with AADA 64-156 Cefaclor Capsules and thus must be approved together.

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Date of Review: August 11, 1997 Date of Submission: 5/28/97

Primary Reviewer: Adolph Vezza /S/ Date: 8/12/97

Team Leader: John Grace /S/ Date: 8/12/97

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cc:

ANDA 64-155; 64-164; 64-165; 64-166
DUP/DIVISION FILE
HFD-613/AVezza/JGrace (no cc)

Review