

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65115

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING DIVISION OF LABELING AND PROGRAM SUPPORT LABELING REVIEW BRANCH

ANDA Number: 65-115

Dates of Submission: - July 23, 2002
- August 6, 2002

Applicant's Name: Ranbaxy Pharmaceuticals Inc.

Established Name: Cefadroxil for Oral Suspension USP, 125 mg/5 mL,
250 mg/5 mL and 500 mg/5 mL

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container: 125 mg/5 mL – 100 mL
250 mg/5 mL - 100 mL
500 mg/5 mL - 75 mL and 100 mL

Satisfactory as of the August 6, 2002, submission. [Vol. 1.1]

Professional Package Insert Labeling:

Satisfactory as of the August 6, 2002, submission. Insert code: FDA3/ revised August 2002 [Vol. 1.1]

Revisions needed post-approval:

1. CONTAINER: 125 mg/5 mL – 100 mL/250 mg/5 mL - 100 mL/500 mg/5 mL - 75 mL and 100 mL
Side panel
 - i. First paragraph
Add the text "To Pharmacist" prior to the text, "DO NOT USE IF...".
 - ii. Last paragraph
Revise "100 mL CEFADROXIL FOR ORAL SUSPENSION USP" to read,
"100 mL (when mixed) CEFADROXIL FOR ORAL SUSPENSION USP"
as previously requested.

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: - Duracef®
NDA Number: NDA 50-527
NDA Drug Name: Cefadroxil monohydrate
NDA Firm: Bristol-Myers Squibb
Date of Approval of NDA Insert and supplement #COUNS-020 Approved 5.3.02. .
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Duricef
Basis of Approval for the Carton Labeling: Duricef

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letters?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. *USP 25	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?			
Error Prevention Analysis			
<i>PROPRIETARY NAME</i>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<i>PACKAGING</i> –See applicant's packaging configuration in FTR	-	-	-
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.			
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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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	
<i>LABELING</i>			
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	
Error Prevention Analysis: LABELING (Continued)	Yes	No	N.A.
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)		X	
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
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR	-	-	-
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		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? *[Some of the inactive ingredients differ from the RLD].	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? [see approval summary under future revisions & FTR]			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)	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? *See comments under CONTAINER above.	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. * Consistent with the RLD.	*		
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.			

NOTE/QUESTION TO THE CHEMIST

1. CONTAINER/PACKAGE sizes:

Ranbaxy's previously labeling contained the following container sizes:

CONTAINER: 125 mg/5 mL – 50 mL
250 mg/5 mL - 75 mL
500 mg/5 mL - 75 mL and 100 mL

In the amendment dated 8/6/02 Ranbaxy revised the container sizes as follows:

CONTAINER: 125 mg/5 mL – 100 mL
250 mg/5 mL - 100 mL
500 mg/5 mL - 75 mL and 100 mL

This information is provided in original application.

Did Ranbaxy provide any updated data supporting and/or informing you of their container size revisions? *OK*

2. INSERT

Ranbaxy revised "polysorbate" to read "polysorbate 80" in the DESCRIPTION section. Do you concur? *Inactive Ingredient "polysorbate 80" is the one provided in original application*

NOTE/QUESTION TO THE CHEMIST [Previous]

1. DOSAGE AND ADMINISTRATION section:

- a. The firm's volume of water for reconstitution differs from the reference listed drug. Is this difference acceptable? *Yes*
- b. Has the firm submitted data to support the volume of water specified in the labeling for reconstitution? *Yes*

Bottle Size	Amount of Water Required for Reconstitution
75 mL	53 mL
100mL	70 mL

- c. Has the firm submitted data to support the accuracy of the final concentration after reconstitution? *Yes*

-125 mg/5 mL
-250 mg/5 mL
-500 mg/5 mL

2. Has the firm submitted data to support the following storage statements?

After reconstitution, store in refrigerator. Keep tightly closed. Discard unused portion after 14 days.

Yes, Pages 2851-2868A (original application)

Y. Pan 2/5/03

FOR THE RECORD:

1. MODEL LABELING - Duricef® (NDA 50-527/S-020); Bristol-Myers Squibb Company; Approved 5/3/02.
2. PATENTS/EXCLUSIVITIES - None pending
3. STORAGE TEMPERATURE

Dry powder:

RLD - Store at controlled room temperature (15° - 30°C)

ANDA - Store at controlled room temperature 15° to 30°C
(59° to 86°F). [See USP].

USP - Preserve in tight containers.

After reconstitution:

RLD - After reconstitution, store in refrigerator. Keep tightly closed. Discard unused portion after 14 days.

ANDA - same as RLD

4. PACKAGING CONFIGURATIONS

NDA

125 mg/5 mL - 50 mL, 100 mL

250 mg/5 mL - 50 mL, 100 mL

500 mg/5 mL - 50 mL, 75 mL and 100 mL

ANDA

125 mg/5 mL - 100 mL

250 mg/5 mL - 100 mL

500 mg/5 mL - 75 mL and 100 mL

5. CONTAINER/CLOSURE

125 mg/5 mL - 50 mL *100 mL*

250 mg/5 mL - 75 mL *100 mL*

500 mg/5 mL - 75 mL and 100 mL

-Each of the above - natural translucent HDPE with CRC

[Vol. 1.3, p. 2425, 2426]

6. The firm's physical description of each drug product in the HOW SUPPLIED section is consistent with the finished dosage form statements.
[Vol. B1.4, p. 2843, 2844 & 2845 and Vol B1.3, p. 2495, 2498, 2503 & 2508]
7. Manufacturer: Ranbaxy, India, [Vol.B1.2, p.1999]
8. Future revisions:

INSERT: PRECAUTIONS/Geriatric Use

Revise "... treatment for pharyngitis ..." to read "treatment of pharyngitis...".

9. Ranbaxy, per our request plans to submit a letter informing us that once the container label is pulled from the "perforated pull tab" there is no other label beneath it and that this portion of the bottle remains bare. [Note: Ranbaxy's bottle retains a smaller label containing the established drug name and the storage recommendations.] The bare space is intended to be used by the Pharmacist to affix the patient's label. I was informed that this is consistent with other approved container labels in the market place.

10. Bioavailability/Bioequivalence:

- Fasting and fed *in vivo* bioequivalence studies were reviewed.
- The insert labeling contains a minimum amount of pharmacokinetics data and does not contain a pharmacokinetic subsection.

Fasting study

	ANDA	NDA	500 mg – 1000 mg INSERT*
Cmax (mcg/mL)	13.59	13.28	16 - 28

*NOTE: There is no indication if this value was obtained under fasting or fed conditions.

Fed study

	ANDA	NDA	500 mg – 1000 mg INSERT*
Cmax (mcg/mL)	11.57	11.54	16 - 28

*NOTE: There is no indication if this value was obtained under fasting or fed conditions.

- The Cmax results are comparable to the insert labeling.
- The other ANDA pharmacokinetic parameters from the fasting and fed bioequivalence studies were comparable to the NDA.
- The bioequivalence studies are acceptable from a labeling point of view.
- The Division of Bioequivalence found the fasting and food studies acceptable in May 2002. However, the dissolution study was found to be unacceptable in November 2002.

Date of Review: 1/27/03

Dates of Submission: - July 23, 2002
August 6, 2002

JS/
Primary Reviewer
Jacqueline Council, Pharm.D.

1/27/03
Date

JS/
Acting Team Leader
Captain Lillie Golson

1/30/03
Date

cc:

ANDA: 65115
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)

Review

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 65-115
Date of Submission: December 17, 2001
Applicant's Name: Ranbaxy Pharmaceuticals Inc.
Established Name: Cefadroxil for Oral Suspension USP, 125 mg/5 mL,
250 mg/5 mL and 500 mg/5 mL

Labeling Deficiencies:

1. CONTAINER: 125 mg/5 mL – 50 mL
250 mg/5 mL - 75 mL
500 mg/5 mL - 75 mL and 100 mL
 - a. General Comment

We note that did not provide annotation nor explanation of all differences between your product and the reference listed drug. Please provide. We refer you to 21 CFR 314.94(a)(8)(iv).
 - b. You submitted a 125 mg/5 mL – 100 mL container label. However, this package size is *not* listed in your HOW SUPPLIED section. Please comment.
 - c. You submitted a 250 mg/5 mL –100 container label. However, this package size is *not* listed in your HOW SUPPLIED section. Please comment.
 - d. You did not submit a 125 mg/5 mL – 50 mL container label, which is listed in your HOW SUPPLIED section. Please submit and/or comment.
 - e. You did not submit a 250 mg/5 mL –75 mL container label, which is listed in your HOW SUPPLIED section. Please submit and/or comment.
 - f. The reference listed drug includes a statement indicating, "DO NOT USE IF... MISSING OR BROKEN". Please propose a similar statement.
 - g. Your total water for reconstitution is not consistent with your DOSAGE AND ADMINISTRATION section on your 500 mg/5 mL – 100 mL container label. Please correct and/or comment.
 - h. Revise "teaspoon" to read "teaspoonful".
 - i. Revise "100 mL CEFADROXIL FOR ORAL SUSPENSION USP" to read, "100 mL (when mixed) CEFADROXIL FOR ORAL SUSPENSION USP".
 - j. Following the text, "...in refrigerator" add the statement, "Shake well before using".

2. INSERT:

a. General Comments

- i. Use "mcg" instead of "µg" for the abbreviation of micrograms.
- ii. Delete the terminal zero following a decimal point, [i.e., "4" instead of "4.0"].

b. TITLE

Revise the title to be consistent with the USP official monograph for this drug product, "Cefadroxil for Oral Suspension, USP".

c. DESCRIPTION

- i. Revise the last paragraph to read, "Each 5 mL of reconstituted suspension for oral administration contains cefadroxil monohydrate equivalent to ___ mg, ___ mg or ___ of cefadroxil. In addition, Cefadroxil for Oral Suspension contains the following inactive ingredients..."
- ii. To be consistent with your components statement, revise "polysorbate" to read "polysorbate 80" and/or comment.

d. PRECAUTIONS

i. General

In the first and second paragraphs revise "cefadroxil" to read "cefadroxil monohydrate".

ii. Geriatric Use

Add this "Geriatric Use" as the last subsection. [See Attachment].

e. DOSAGE AND ADMINISTRATION

- i. Throughout this section unless otherwise instructed revise "cefadroxil" to read "cefadroxil monohydrate".

ii. First Table

Revise the title to read, "DAILY DOSAGE OF CEFADROXIL FOR ORAL SUSPENSION".

- iii. Add the subsection title "Renal Impairment" immediately prior to the paragraph, "In patients with renal impairment, ...".

iv. Reconstitution Directions for Oral Suspension

A) We note that you omitted reconstitution directions for your package size of 50 mL. Please revise and/or comment.

B) Start a new paragraph with the text, "Method: ...".

f. HOW SUPPLIED

- i. The ___ mg per 5 mL of reconstituted suspension contains cefadroxil monohydrate equivalent to ___ mg
- ii. Provide a physical description for each strength of your drug product.
- iii. In your storage recommendations replace "0" with the symbol for degrees, "°".

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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 your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letters?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. *USP 25	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?			
Error Prevention Analysis			
<i>PROPRIETARY NAME</i>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<i>PACKAGING</i> –See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.			
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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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	
<i>LABELING</i>			
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	
Error Prevention Analysis: LABELING (Continued)	Yes	No	N.A.
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)		X	
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
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR	-	-	-
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		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? *[Some of the inactive ingredients differ from the RLD].	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? [see approval summary under future revisions & FTR]			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)	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? *See comments under CONTAINER above.	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. * Consistent with the RLD.	*		
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.			

NOTE/QUESTION TO THE CHEMIST

1. **DOSAGE AND ADMINISTRATION section:**

- a. The firm's volume of water for reconstitution differs from the reference listed drug. Is this difference acceptable?
- b. Has the firm submitted data to support the volume of water specified in the labeling for reconstitution?

Bottle Size	Amount of Water Required for Reconstitution
75 mL	53 mL
100mL	70 mL

- c. Has the firm submitted data to support the accuracy of the final concentration after reconstitution?

- 125 mg/5 mL
- 250 mg/5 mL
- 500 mg/5 mL

2. Has the firm submitted data to support the following storage statements?

After reconstitution, store in refrigerator. Keep tightly closed. Discard unused portion after 14 days.

FOR THE RECORD:

1. MODEL LABELING - Duricef® (NDA 50-527/S-020); Bristol-Myers Squibb Company; Approved 5/3/02.

2. PATENTS/EXCLUSIVITIES - None pending

3. STORAGE TEMPERATURE

Dry powder:

RLD - Store at controlled room temperature (15° - 30°C)

ANDA - Store at controlled room temperature 15° to 30°C (59° to 86°F). [See USP].

USP - Preserve in tight containers.

After reconstitution:

RLD - After reconstitution, store in refrigerator. Keep tightly closed. Discard unused portion after 14 days.

ANDA - same as RLD

4. PACKAGING CONFIGURATIONS

NDA

125 mg/5 mL - 50 mL, 100 mL

250 mg/5 mL - 50 mL, 100 mL

500 mg/5 mL - 50 mL, 75 mL and 100 mL

ANDA

125 mg/5 mL - 50 mL

250 mg/5 mL - 75 mL

500 mg/5 mL - 75 mL and 100 mL

5. CONTAINER/CLOSURE

125 mg/5 mL - 50 mL

250 mg/5 mL - 75 mL

500 mg/5 mL - 75 mL and 100 mL

-Each of the above - natural translucent HDPE with CRC

[Vol. 1.3, p. 2425, 2426]

6. The firm's physical description of each drug product in the HOW SUPPLIED section is consistent with the finished dosage form statements.

[Vol. B1.4, p. 2843, 2844, 2845]

7. Manufacturer: Ranbaxy, India, [Vol. B1.2, p. 1999]

Date of Review: 7/10/02

Date of Submission: 12/17/01

Primary Reviewer

Date

Jaqueline Council, Pharm.D.

Acting Team Leader

Date

Captain Lillie Golson

cc:

ANDA: 65018

DUP/DIVISION FILE

HFD-613/JWhite/CHoppes (no cc)

Review