

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

65-056

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 65-056

DRUG PRODUCT: Amoxicillin Tablets, USP

FIRM: TEVA Pharmaceuticals

DOSAGE FORM: Tablets **STRENGTH:** 500 and 875 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification provided on page 1973, Vol. 1.6. Acceptable EER dated 7/17/00.

BIO STUDY: The bio-study conducted on the applicant's product and Smithkline Beecham's Amoxil® capsules (875 mg) and the waiver for bio-study (500 mg) were found acceptable by the Division of Bioequivalence on 3/7/00.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are both USP. The applicant is using USP methods in testing the bulk drug and finished product. The firm is using in-house validated methods for identification and dissolution testing on the finished product.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date. Containers used in the stability studies were identical to those described in the container section.

LABELING: See "Approval Summary".

STERILIZATION VALIDATION (IF APPLICABLE): Not-applicable to this drug product.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): Exhibit batch #1034-7 (875 mg) used for stability and bio-studies and exhibit batch #1034-58 (500 mg) used for stability studies were manufactured with bulk drug substance from TEVA Pharmaceuticals USA (API Division). Both exhibit batches were

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): See above

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch size is
The manufacturing process described in the master production record is the same as that described in the exhibit batch record.

CHEMIST: Ruth Ganunis
SUPERVISOR: Richard Adams

DATE: 8/22/00
DATE: 8/23/00

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

ANDA Number: 65-056

Date of Submission: December 3, 1999

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin Tablets USP, 500 mg and 875 mg

Labeling Deficiencies:

1. CONTAINER: 500 mg and 875 mg – 100s and 500s
 - a. We encourage you to differentiate your drug product strengths by using contrasting colors, boxing or some other means.
 - b. Revise the "Each tablet contains ..." statement to read, "Each tablet contains ___ mg amoxicillin as the trihydrate.
 - c. To be consistent with the innovator's labels, we encourage you to revise the "Usual Dosage ..." statement to read " Usual Dosage: 1 tablet every 12 hours. See package ...".
 - d. Following the storage temperature recommendations delete the word, "between", replace the hyphens with the word "to" add the text, "[See USP]".

2. INSERT
 - a. We encourage you to add the legend "Rx only" to follow the Title.
 - b. General Comments
 - i. We encourage you to use the abbreviation, "mcg" for micrograms instead of "µg".
 - ii. We encourage you to delete the terminal zero following a decimal point, i.e., "3" instead of "3.0", when expressing a range of doses.
 - c. DESCRIPTION

Add the following as the last sentence of the first paragraph:

The structural formula is:
 - d. CLINICAL PHARMACOLOGY

Revise the first five paragraphs of this section to be in accord with the attached labeling of the reference listed drug, Amoxil®, with the following exceptions:

 - First paragraph

... investigated. The 875 mg formulation ... However, food effect ... the 500 mg formulation.
 - Second paragraph

Orally administered doses of 500 mg ...

- Delete the paragraph, "Amoxicillin chewable ... respectively".
- Delete the paragraph, "Oral administration of single doses of 400 mg ... data" and the associated table.

e. PRECAUTIONS

i. Drug Interactions

Revise this subsection to be in accord with the attached labeling of the reference listed drug, Amoxil®.

ii. Drug/Laboratory Test Interactions

Delete the text "(e.g., Tes-Tape®)".

f. DOSAGE AND ADMINISTRATION

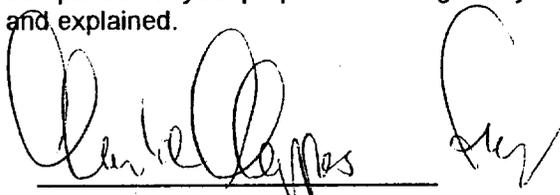
Revise this section to be in accord with the attached labeling of the reference listed drug, Amoxil®.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

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.

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/rd/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.



Robert L. West, M.S., R.Ph.
Director Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Portions of the Amoxil®'s package insert labeling.

1, 1

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

ANDA Number: 65-056

Date of Submission: December 3, 1999

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Amoxicillin Tablets USP, 500 mg and 875 mg

Labeling Deficiencies:

1. CONTAINER: 500 mg and 875 mg – 100s and 500s
 - a. We encourage you to differentiate your drug product strengths by using contrasting colors, boxing or some other means.
 - b. Revise the "Each tablet contains ..." statement to read, "Each tablet contains ___ mg amoxicillin as the trihydrate.
 - c. To be consistent with the innovator's labels, we encourage you to revise the "Usual Dosage ..." statement to read " Usual Dosage: 1 tablet every 12 hours. See package ...".
 - d. Following the storage temperature recommendations delete the word, "between", replace the hyphens with the word "to" add the text, "[See USP]".

2. INSERT
 - a. We encourage you to add the legend "Rx only" to follow the Title.
 - b. General Comments
 - i. We encourage you to use the abbreviation, "mcg" for micrograms instead of "µg".
 - ii. We encourage you to delete the terminal zero following a decimal point, i.e., "3" instead of "3.0", when expressing a range of doses.
 - c. DESCRIPTION

Add the following as the last sentence of the first paragraph:

The structural formula is:
 - d. CLINICAL PHARMACOLOGY

Revise the first five paragraphs of this section to be in accord with the attached labeling of the reference listed drug, Amoxil®, with the following exceptions:

 - First paragraph

... investigated. The 875 mg formulation ... However, food effect ... the 500 mg formulation.
 - Second paragraph

Orally administered doses of 500 mg ...

- Delete the paragraph, "Amoxicillin chewable ... respectively".
- Delete the paragraph, "Oral administration of single doses of 400 mg ... data" and the associated table.

e. PRECAUTIONS

i. Drug Interactions

Revise this subsection to be in accord with the attached labeling of the reference listed drug, Amoxil®.

ii. Drug/Laboratory Test Interactions

Delete the text "(e.g., Tes-Tape®)".

f. DOSAGE AND ADMINISTRATION

Revise this section to be in accord with the attached labeling of the reference listed drug, Amoxil®.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

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.

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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.

Robert L. West, M.S., R.Ph.
Director Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Portions of the Amoxil®'s package insert labeling.

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			
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			
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
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	
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	
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	

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?			
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 inactives ingredients differ from the RLD.	*		
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	
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?		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. *Same as 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. *Applicant does not propose the 400 mg dosage form. Therefore, text referencing this dosage form will be deleted. See FTR.	*		
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. Labeling model

Amoxil, by SmithKline Beecham Pharmaceuticals, approved 5/11/99 and issued 4/99

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components and composition statements.
[Vol. B1.3, 1829]

3. The firm's physical description/scoring of each tablet strength in the HOW SUPPLIED section is consistent with the firm's finished dosage form statements.
[Vol. B1.2, p. 2466 & 2482].

4. Manufacturing Facility

Teva Pharmaceuticals USA
New Jersey/Pennsylvania
[B1.3, 1968]

5. Patent and exclusivity –none pending

6. Package Sizes

RLD	-	500 mg	20s, 100s, 500s
	-	875 mg	20s, 100s, 500s
ANDA	-	500 mg	100s, 500s
	-	875 mg	100s, 500s

7. Container/Closure

500 mg – 100s & 500s:

- Bottle - High Density Polyethylene [natural colorant]
- Closure - nonchild-resistant cap

875 mg – 100s & 500s:

- Bottle - High Density Polyethylene [natural colorant]
- Closure - nonchild-resistant cap

[B1.2, 2237, 2257, 2275, 2453, 2454, 2322 & 2333]

8. Storage and/or Dispensing:

NDA - Store at or below 25°C (77°F). Dispense in a tight container.

ANDA - Store at controlled room temperature 15° to 30° C (59° to 86° F)
Dispense in a tight light-resistant container as defined in the USP, with a child-resistant closure (as required).

9. Tablet Scoring

NDA - 500 mg – none
- 875 mg – scored

ANDA - 500 mg – none
- 875 mg - scored

10. Bioavailability/Bioequivalence - pending

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

ANDA Number: 65-056
Date of Submission: June 30, 2000
Applicant's Name: Teva Pharmaceuticals USA
Established Name: Amoxicillin Tablets USP, 500 mg and 875 mg
Labeling Deficiencies:

1. INSERT

a. General Comment

Portion of your insert labeling require further revisions due to the approval of the reference listed drug, "Amoxil®" insert labeling on May 16, 2000.

b. CLINICAL PHARMACOLOGY (Microbiology)

To be consistent with the reference listed drug and to improve the promptness of locating a microorganism, we encourage you to list the microorganisms in a column instead of side-by-side.

c. ADVERSE REACTIONS

i. Liver

Revise this subsection to be consistent with the attached insert labeling of the reference listed drug, Amoxil®.

ii. Hemic and Lymphatic Systems

Revise this subsection to be consistent with the attached insert labeling of the reference listed drug, Amoxil®.

d. DOSAGE AND ADMINISTRATION (Adults and pediatric patients >3 months

Revise this subsection to be consistent with the attached insert labeling of the reference listed drug, Amoxil®.

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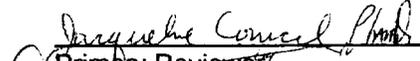
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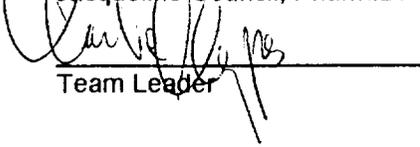
11. Labeling Issue:

CLINICAL PHARMACOLOGY section:

Currently the applicant does not propose to market the 125 mg, 200 mg, 250 mg and 400 mg dosage form. Therefore, text referencing these strengths will be deleted from the CLINICAL PHARMACOLOGY section. This is consistent with a similar decision for ANDAs not marketing the 400 mg and 875 mg dosage forms. In this case, ANDAs were requested to delete the text referencing both the 400 mg and the 875 mg dosage forms from the CLINICAL PHARMACOLOGY section.

Date of Review: 2/14/2000



Primary Reviewer
Jacqueline Council, Pharm.D.


Team Leader

2-29-2000

Date

7/3/00

Date

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.

William Peter Richman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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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
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Does the package proposed have any safety and/or regulatory concerns?		X	
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Labeling			
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