CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

65-080

Trade Name:	DisperMox
Generic Name:	Amoxicillin Tablets for Oral Suspension, 200mg and 400mg
Sponsor:	Ranbaxy Pharmaceuticals, Inc.
Approval Date:	August 11, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 65-080

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-080

APPROVAL LETTER

ANDA 65-080

AUG 11 2003

Ranbaxy Pharmaceuticals, Inc.
Attention: Abha Pant
U.S. Agent for: Ranbaxy Laboratories Limited
600 College Road East
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 29, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for DisperMox™ (Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated March 19, 2001; May 30, August 6, November 1, November 5, November 21, and December 9, 2002; and June 5, June 18, July 11, and July 31, 2003. Reference is also made to the suitability petition submitted under Section 505(j)(2)(C) of the Act and approved on June 13,2000, permitting you to file this ANDA for a drug product that differs in dosage form from the reference listed drug product (RLD). Specifically, your ANDA provides for a tablet for oral suspension in contrast to the RLD, which is an oral suspension (powder for reconstitution).

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. DisperMox™ (Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg) can be expected to have the same therapeutic effect as that of the reference listed drug product upon which the agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 8/11/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

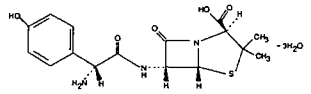
APPLICATION NUMBER:

65-080

FINAL PRINTED LABELING(S)

DisperMox™
(amoxicillin tablets for oral suspension)
Rx only

DESCRIPTION
Amoxicillin tablets for oral suspension contain amoxicillin, a semisynthetic anti-biotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically it is (2*S*, 5*R*, 6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid trihydrate. The structural formula is:



The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$, and the molecular weight is 419.45.

Amoxicillin tablets for oral suspension are intended for oral administration.

Tablets for Oral Suspension: Each amoxicillin tablet for oral suspension contains amoxicillin trihydrate equivalent to amoxicillin anhydrous 200 mg or 400 mg. Inactive ingredients: aspartame•, colloidal silicon dioxide, croscarmellose sodium, FD&C Red no. 40 aluminum lake, magnesium stearate, microcrystalline cellulose and strawberry guarana flavor.

• See **PRECAUTIONS**

CLINICAL PHARMACOLOGY
Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The effect of food on the absorption of amoxicillin from conventional amoxicillin tablets and conventional amoxicillin suspension has been partially investigated. The 400-mg and 875-mg formulations have been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200-mg and 500-mg formulations. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound.

Orally administered doses of 250 mg and 500 mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 mcg/mL to 5 mcg/mL and 5.5 mcg/mL to 7.5 mcg/mL, respectively.

Mean amoxicillin pharmacokinetic parameters from an open, two-part, single-dose crossover bioequivalence study in 27 adults comparing 875 mg conventional tablets of amoxicillin with 875 mg conventional tablets of amoxicillin/clavulanate potassium showed that the 875-mg conventional tablet of amoxicillin produces an $AUC_{0-\infty}$ of 35.4 ± 8.1 mcg.hr./mL and a C_{max} of 13.8 ± 4.1 mcg/mL. Dosing was at the start of a light meal following an overnight fast.

Conventional amoxicillin chewable tablets, 125 mg and 250 mg, produced blood levels similar to those achieved with corresponding doses of conventional amoxicillin oral suspensions. Orally administered doses of conventional amoxicillin suspension, 125 mg/5 mL and 250 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 1.5 mcg/mL to 3 mcg/mL and 3.5 mcg/mL to 5 mcg/mL, respectively.

Oral administration of single doses of 400-mg conventional amoxicillin chewable tablets and 400-mg/5 mL conventional suspension to 24 adult volunteers yielded comparable pharmacokinetic data:

Dose†	$AUC_{0-\infty}$ (mcg.hr./mL)	C_{max} (mcg/mL)‡
amoxicillin	amoxicillin (±SD)	amoxicillin (±SD)
400 mg (5 mL of suspension)	17.1 (3.1)	5.92 (1.62)
400 mg (one chewable tablet)	17.9 (2.4)	5.18 (1.64)

† Administered at the start of a light meal.
‡ Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Following a 1-gram dose and utilizing a special skin window technique to determine levels of the antibiotic, it was noted that therapeutic levels were found in the interstitial fluid. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

The following pharmacokinetic data is from Ranbaxy's study of DisperMox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL.
The dispersed mixture of DisperMox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspensions. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg DisperMox tablets result in average peak blood levels 1 to 2 hours after administration in the range of 3.2 mcg/mL to 11.5 mcg/mL.

Oral administration of single doses of 400-mg DisperMox tablets and 400-mg/5 mL conventional suspension to 24 adult volunteers yielded comparable pharmacokinetic data:

Dose¶	In $AUC_{0-\infty}$ (mcg.hr./mL)	C_{max} (mcg/mL)††
amoxicillin	amoxicillin	amoxicillin
400 mg (5 mL of suspension)	18.5	8.4
400 mg (one tablet for oral suspension)	17.9	7.5

¶ Dosing was following an overnight fast.
†† Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Microbiology
Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms:
Enterococcus faecalis
Staphylococcus spp.† (β-lactamase-negative strains only)
Streptococcus pneumoniae
Streptococcus spp. (α- and β-hemolytic strains only)
† Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

Aerobic gram-negative microorganisms:
Escherichia coli (β-lactamase-negative strains only)
Haemophilus influenzae (β-lactamase-negative strains only)
Neisseria gonorrhoeae (β-lactamase-negative strains only)
Proteus mirabilis (β-lactamase-negative strains only)

Helicobacter:
Helicobacter pylori

DisperMox™
(amoxicillin tablets for oral suspension)
Rx only

Susceptibility tests
Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentratio (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs shou be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth agar) or equivalent with standardized inoculum concentrations and standardized concentrations of **ampicillin** powd Ampicillin is sometimes used to predict susceptibility of *Streptococcus pneumoniae* to amoxicillin; however, sor intermediate strains have been shown to be susceptible to amoxicillin. Therefore, *Streptococcus pneumoniae* susce tibility should be tested using amoxicillin powder. The MIC values should be interpreted according to the followi criteria:

For gram-positive aerobes:
Enterococcus

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
≥ 16	Resistant (R)

Staphylococcus[a]

MIC (mcg/mL)	Interpretation
≤ 0.25	Susceptible (S)
≥ 0.5	Resistant (R)

Streptococcus (except *S. pneumoniae*)

MIC (mcg/mL)	Interpretation
≤ 0.25	Susceptible (S)
0.5 to 4	Intermediate (I)
≥ 8	Resistant (R)

S. pneumoniae[b]
(**Amoxicillin** powder should be used to determine susceptibility.)

MIC (mcg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1	Intermediate (I)
≥ 2	Resistant (R)

For gram-negative aerobes:
Enterobacteriaceae

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

H. influenzae[c]

MIC (mcg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

a. Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as res tant to amoxicillin.
b. These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjus Mueller-Hinton broth with 2-5% lysed horse blood.
c. These interpretive standards are applicable only to broth microdilution test with *Haemophilus influenzae* us *Haemophilus* Test Medium (HTM).[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiol ically concentrated or in situations where high dosage of drug can be used. This category also provides a bu zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A rep of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the bl reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the te nical aspects of the laboratory procedures. Standard **ampicillin** powder should provide the following MIC value:

Microorganism	MIC (mcg/mL)
E. coli ATCC 25922	2 to 8
E. faecalis ATCC 29212	0.5 to 2
H. influenzae ATCC 49247[d]	2 to 8
S. aureus ATCC 29213	0.25 to 1

Using **amoxicillin** to determine susceptibility:

Microorganism	MIC Range (mcg/mL)
S. pneumoniae ATCC 49619[e]	0.03 to 0.12

d. This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution pro dure using HTM.[1]
e. This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by the broth microdilution prc dure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide rep ducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized proced requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 r ampicillin to test the susceptibility of microorganisms, except *S. pneumoniae*, to amoxicillin. Interpretation invol correlation of the diameter obtained in the disk test with the MIC for **ampicillin**.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-mcg ampicillin d should be interpreted according to the following criteria:

For gram-positive aerobes:
Enterococcus

Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)
≤ 16	Resistant (R)

Staphylococcus[f]

Zone Diameter (mm)	Interpretation
≥ 29	Susceptible (S)
≤ 28	Resistant (R)

β-hemolytic streptococci

Zone Diameter (mm)	Interpretation
≥ 26	Susceptible (S)
19 to 25	Intermediate (I)
≤ 18	Resistant (R)

NOTE: For streptococci (other than β-hemolytic streptococci and *S. pneumoniae*), an ampicillin MIC should be de mined.

S. pneumoniae
S. pneumoniae should be tested using a 1-mcg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are sus tible to amoxicillin. An amoxicillin MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone size ≤ 19 mm.

For gram-negative aerobes:
Enterobacteriaceae

Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)
14 to 16	Intermediate (I)
≤ 13	Resistant (R)

H. influenzae[g]

Zone Diameter (mm)	Interpretation
≥ 22	Susceptible (S)
19 to 21	Intermediate (I)
≤ 18	Resistant (R)

f. Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as re tant to amoxicillin.
g. These interpretive standards are applicable only to disk diffusion susceptibility tests with *H. influenzae* u *Haemophilus* Test Medium (HTM).[2]
Interpretation should be as stated above for results us ng dilution techniques.

As with standard dilution techniques, disk diffusion susceptibility test procedures require the use of laboratory cor microorganisms. The 10-mcg **ampicillin** disk should provide the following zone diameters in these laboratory

Susceptibility tests

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of **ampicillin** powder. Ampicillin is sometimes used to predict susceptibility of *Streptococcus pneumoniae* to amoxicillin; however, some intermediate strains have been shown to be susceptible to amoxicillin. Therefore, *Streptococcus pneumoniae* susceptibility should be tested using amoxicillin powder. The MIC values should be interpreted according to the following criteria:

For gram-positive aerobes:

Enterococcus

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
≥ 16	Resistant (R)

Staphylococcus[a]

MIC (mcg/mL)	Interpretation
≤ 0.25	Susceptible (S)
≥ 0.5	Resistant (R)

Streptococcus (except *S. pneumoniae*)

MIC (mcg/mL)	Interpretation
≤ 0.25	Susceptible (S)
0.5 to 4	Intermediate (I)
≥ 8	Resistant (R)

S. pneumoniae[b]

(**Amoxicillin** powder should be used to determine susceptibility.)

MIC (mcg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1	Intermediate (I)
≥ 2	Resistant (R)

For gram-negative aerobes:

Enterobacteriaceae

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

H. influenzae[c]

MIC (mcg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

a. Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

b. These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

c. These interpretive standards are applicable only to broth microdilution test with *Haemophilus influenzae* using *Haemophilus* Test Medium (HTM).[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard **ampicillin** powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
E. coli ATCC 25922	2 to 8
E. faecalis ATCC 29212	0.5 to 2
H. influenzae ATCC 49247[d]	2 to 8
S. aureus ATCC 29213	0.25 to 1

Using **amoxicillin** to determine susceptibility:

Microorganism	MIC Range (mcg/mL)
S. pneumoniae ATCC 49619[e]	0.03 to 0.12

d. This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[1]

e. This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by the broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg ampicillin to test the susceptibility of microorganisms, except *S. pneumoniae*, to amoxicillin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for **ampicillin**.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-mcg ampicillin disk should be interpreted according to the following criteria:

For gram-positive aerobes:

Enterococcus

Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)
≤ 16	Resistant (R)

Staphylococcus[f]

Zone Diameter (mm)	Interpretation
≥ 29	Susceptible (S)
≤ 28	Resistant (R)

β-hemolytic streptococci

Zone Diameter (mm)	Interpretation
≥ 26	Susceptible (S)
19 to 25	Intermediate (I)
≤ 18	Resistant (R)

NOTE: For streptococci (other than β-hemolytic streptococci and *S. pneumoniae*), an ampicillin MIC should be determined.

S. pneumoniae

S. pneumoniae should be tested using a 1-mcg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to amoxicillin. An amoxicillin MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤ 19 mm.

For gram-negative aerobes:

Enterobacteriaceae

Zone Diameter (mm)	Interpretation
≥ 17	Susceptible (S)
14 to 16	Intermediate (I)
≤ 13	Resistant (R)

H. influenzae[g]

Zone Diameter (mm)	Interpretation
≥ 22	Susceptible (S)
19 to 21	Intermediate (I)
≤ 18	Resistant (R)

f. Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

g. These interpretive standards are applicable only to disk diffusion susceptibility tests with *H. influenzae* using *Haemophilus* Test Medium (HTM).[2]

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, disk diffusion susceptibility test procedures require the use of laboratory control microorganisms. The 10-mcg **ampicillin** disk should provide the following zone diameters in these laboratory test

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	16 to 22
H. influenzae ATCC 49247[h]	13 to 21
S. aureus ATCC 25923	27 to 35

Using 1-mcg **oxacillin** disk:

Microorganism	Zone Diameter (mm)
S. pneumoniae ATCC 49619[i]	8 to 12

h. This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using HTM.[2]

i. This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller- Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Susceptibility testing for *Helicobacter pylori*

In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MICs) and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms.

Culture and susceptibility testing should be obtained in patients who fail triple therapy. If clarithromycin resistance is found, a non-clarithromycin-containing regimen should be used.

INDICATIONS AND USAGE

Amoxicillin is indicated in the treatment of infections due to susceptible (ONLY β-lactamase-negative) strains of the designated microorganisms in the conditions listed below:

Infections of the ear, nose, and throat due to *Streptococcus* spp. (α- and β-hemolytic strains only), *Streptococcus pneumoniae*, *Staphylococcus* spp., or *H. influenzae*

Infections of the genitourinary tract due to *E. coli*, *P. mirabilis*, or *E. faecalis*

Infections of the skin and skin structure due to *Streptococcus* spp. (α- and β-hemolytic strains only), *Staphylococcus* spp., or *E. coli*

Infections of the lower respiratory tract due to *Streptococcus* spp. (α- and β-hemolytic strains only), *Streptococcus pneumoniae*, *Staphylococcus* spp., or *H. influenzae*

Gonorrhea, acute uncomplicated (ano-genital and urethral infections) due to *N. gonorrhoeae* (males and females) Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin.

Indicated surgical procedures should be performed.

H. pylori eradication to reduce the risk of duodenal ulcer recurrence

Triple therapy: Amoxicillin/clarithromycin/lansoprazole

Amoxicillin, in combination with clarithromycin plus lansoprazole as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**.)

Dual therapy: Amoxicillin/lansoprazole

Amoxicillin, in combination with lansoprazole delayed-release capsules as dual therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.** (See the clarithromycin package insert, **MICROBIOLOGY**.) Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**.)

CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

Phenylketonurics: Each 200 mg Amoxicillin Tablet for Oral Suspension contains 5.6 mg phenylalanine; each 400 mg Amoxicillin Tablet for Oral Suspension contains 5.6 mg phenylalanine.

Laboratory Tests: As with any potent drug, periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy.

All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with amoxicillin should have a follow-up serologic test for syphilis after 3 months.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin. This has been demonstrated *in vitro*; however, the clinical significance of this interaction is not well documented.

Drug/Laboratory Test Interactions: High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted however, the following information is available from tests on a 4:1 mixture of amoxicillin and potassium clavulanate Mixture of amoxicillin and potassium clavulanate was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Mixture of amoxicillin and potassium clavulanate was weakly positive in the mouse lymphom assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Mixture of amoxicillin and potassium clavulanate was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micro-nucleus test, and was negative in each of these assays. In a multigeneration reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen doses up to 500 mg/kg (approximately 3 times the human dose in mg/m^2).

Pregnancy: *Teratogenic Effects. Pregnancy Category B.* Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs show that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions but moderately increased the height and duration of contractions. However, it is not known whether use of amoxicillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

Pediatric Use: Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of amoxicillin should be modified in pediatric patients 12 weeks or younger (≤ 3 months). (See **DOSAGE AND ADMINISTRATION** - Neonates and infants.)

Information for Patients:
A Patient Information Sheet is provided with the drug product.

ADVERSE REACTIONS
As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of penicillins:

Gastrointestinal: nausea, vomiting, diarrhea, and hemorrhagic/pseudomembranous colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See **WARNINGS**.)

Hypersensitivity Reactions: Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson Syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hypersensitivity vasculitis and urticaria have been reported.

NOTE: These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis, and acute cytolytic hepatitis have been reported.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, and/or dizziness have been reported rarely.

Combination therapy with clarithromycin and lansoprazole
In clinical trials using combination therapy with amoxicillin plus clarithromycin and lansoprazole, and amoxicillin plus lansoprazole, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with amoxicillin, clarithromycin, or lansoprazole.

Triple therapy: amoxicillin/clarithromycin/lansoprazole
The most frequently reported adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%). No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual therapy: amoxicillin/lansoprazole
The most frequently reported adverse events for patients who received amoxicillin t.i.d. plus lansoprazole t.i.d. dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with amoxicillin t.i.d. plus lansoprazole t.i.d. dual therapy than with lansoprazole alone.

For more information on adverse reactions with clarithromycin or lansoprazole, refer to their package inserts, **ADVERSE REACTIONS**.

OVERDOSAGE
In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison-control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[3]

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin. Amoxicillin may be removed from circulation by hemodialysis.

DOSAGE AND ADMINISTRATION
Amoxicillin may be given without regard to meals.

Direction for Amoxicillin Tablets for Oral Suspension: Dissolve one tablet in a glass with a suitable amount of water (2 teaspoonfuls to 2 oz of water). Be sure to drink the entire mixture. Rinse the glass with an additional 4 to 8 oz of water and drink the contents to assure the whole dose is taken. Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.

The tablet is not recommended to be mixed with any liquid other than water, as studies have only been conducted using water.

ALL RECOMMENDED DOSAGES FOR AMOXICILLIN ARE INCLUDED IN THIS SECTION FOR INFORMATIONAL PURPOSES ONLY. THE 200 mg TABLET FOR ORAL SUSPENSION IS APPROPRIATE ONLY FOR A 200 mg DOSE AND THE 400 mg TABLET FOR ORAL SUSPENSION IS APPROPRIATE ONLY FOR A 400 mg DOSE.

Neonates and infants aged ≤ 12 weeks (≤ 3 months)
Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended upper dose of amoxicillin is 30 mg/kg/day divided q12h.

Adults and pediatric patients > 3 months

Infection	Severity‡	Usual Adult Dose	Usual Dose for Children > 3 months§
Ear/nose/throat	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every 8 hours
Lower respiratory tract	Mild/Moderate or Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every 8 hours
Skin/skin structure	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every 8 hours
Genitourinary tract	Mild/Moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every 8 hours
Gonorrhea Acute, uncomplicated ano-genital and urethral infections in males and females		3 grams as single oral dose	Prepubertal children: 50 mg/kg amoxicillin, combined with 25 mg/kg probenecid as a single dose **NOTE: SINCE PROBENECID IS CONTRAINDICATED IN CHILDREN UNDER 2 YEARS, DO NOT USE THIS REGIMEN IN THESE CASES.**

‡ Dosing for infections caused by less susceptible organisms should follow the recommendation for severe infections.
§ The children's dosage is intended for individuals whose weight is less than 40 kg. Children weighing 40 kg or more should be dosed according to the adult recommendations.

All patients with gonorrhea should be evaluated for syphilis. (See **PRECAUTIONS** - Laboratory Tests.)

Larger doses may be required for stubborn or severe infections.

General: It should be recognized that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy. Except for gonorrhea, treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by *Streptococcus pyogenes* to prevent the occurrence of acute rheumatic fever.

H. pylori eradication to reduce the risk of duodenal ulcer recurrence
Triple therapy: Amoxicillin/*clarithromycin*/*lansoprazole*
The recommended adult oral dose is 1 gram amoxicillin, 500 mg clarithromycin, and 30 mg lansoprazole, all given twice daily (q12h) for 14 days. (See **INDICATIONS AND USAGE**.)

Dual therapy: Amoxicillin/*lansoprazole*
The recommended adult oral dose is 1 gram amoxicillin and 30 mg lansoprazole, each given three times daily (q8h) for 14 days. (See **INDICATIONS AND USAGE**.)
Please refer to clarithromycin and lansoprazole full prescribing information for **CONTRAINDICATIONS** and **WARNINGS**, and for information regarding dosing in elderly and renally impaired patients.

Dosing recommendations for adults with impaired renal function:
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of < 30 mL/minute should not receive the 875-mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

There are currently no dosing recommendations for pediatric patients with impaired renal function.

HOW SUPPLIED

Amoxicillin Tablets for Oral Suspension:
Each tablet for oral suspension contains 200 mg or 400 mg amoxicillin as the trihydrate.

200-mg Tablet for Oral Suspension
200 mg light pink colored, strawberry flavored, circular, biconvex, unscored, mottled tablets, debossed with "RX565" on one side and plain on the other.

NDC 63304-565-20	Bottles of 20
NDC 63304-565-60	Bottles of 60
NDC 63304-565-10	Bottles of 1000
NDC 63304-565-80	Unit dose pack of 100s

400-mg Tablet for Oral Suspension
400 mg light pink colored, strawberry flavored, circular, biconvex, unscored, mottled tablets, debossed with "RX567" on one side and plain on the other.

NDC 63304-567-20	Bottles of 20
NDC 63304-567-60	Bottles of 60
NDC 63304-567-05	Bottles of 500
NDC 63304-567-80	Unit dose pack of 100s

The product is also available as:

Amoxicillin Capsules:
Each capsule contains 250 mg or 500 mg amoxicillin as the trihydrate.

250-mg Capsule
250 mg yellow opaque cap and yellow opaque body, size 2, printed "RX654" on both cap and body.

NDC 63304-654-30	bottles of 30
NDC 63304-654-01	bottles of 100
NDC 63304-654-05	bottles of 500
NDC 63304-654-80	unit-dose 100s

500-mg Capsule
500 mg maroon opaque cap and yellow opaque body, size 0-el, printed "RX655" on both cap and body.

NDC 63304-655-30	bottles of 30
NDC 63304-655-01	bottles of 100
NDC 63304-655-05	bottles of 500
NDC 63304-655-80	unit-dose 100s

Amoxicillin Tablets :
Each tablet contains 500 mg or 875 mg amoxicillin as the trihydrate.

500-mg Tablet
500 mg pink colored, film coated, capsule shaped tablets; debossed with "RX762" on one side.

NDC 63304-762-82	bottles of 12
NDC 63304-762-13	bottles of 120
NDC 63304-762-01	bottles of 100
NDC 63304-762-05	bottles of 500

875-mg Tablet
875 mg pink colored, film coated, capsule shaped tablets; debossed with "RX763" on one side and scored on reverse side.

NDC 63304-763-82	bottles of 12
NDC 63304-763-13	bottles of 120
NDC 63304-763-01	bottles of 100
NDC 63304-763-05	bottles of 500

Amoxicillin Chewable Tablets :
Each chewable tablet contains 125 mg, 200 mg, 250 mg or 400 mg amoxicillin as the trihydrate.

125-mg Tablet
125 mg pink colored, strawberry flavored, oval, biconvex tablets, with mottled appearance; debossed with "RX514" on one side.

NDC 63304-514-01	bottles of 100
NDC 63304-514-05	bottles of 500

200-mg Tablet
200 mg light pink colored, strawberry flavored, circular, flat faced, bevelled edge tablets, with mottled appearance; debossed with "RX760" on one side.

NDC 63304-760-20	bottles of 20
NDC 63304-760-01	bottles of 100
NDC 63304-760-05	bottles of 500

250-mg Tablet
250 mg pink colored, strawberry flavored, circular, flat faced, bevelled edge tablets, with mottled appearance; debossed with "RX515" on one side.

NDC 63304-515-01	bottles of 100
NDC 63304-515-04	bottles of 250

400-mg Tablet
400 mg light pink colored, strawberry flavored, circular, flat faced, bevelled edge tablets, with mottled appearance; debossed with "RX761" on one side.

NDC 63304-761-20	bottles of 20
NDC 63304-761-01	bottles of 100
NDC 63304-761-05	bottles of 500

Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).
Dispense in a tight container.

CLINICAL STUDIES
H. pylori eradication to reduce the risk of duodenal ulcer recurrence
Randomized, double-blind clinical studies performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of lansoprazole in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy, or in combination with amoxicillin capsules as dual 14-day therapy, for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy: amoxicillin 1 gram b.i.d./clarithromycin 500 mg b.i.d./lansoprazole 30 mg b.i.d.

‡ Dosing for infections caused by less susceptible organisms should follow the recommendation for severe infections.
§ The children's dosage is intended for individuals whose weight is less than 40 kg. Children weighing 40 kg or more should be dosed according to the adult recommendations.

All patients with gonorrhea should be evaluated for syphilis. (See **PRECAUTIONS** - Laboratory Tests.)

Larger doses may be required for stubborn or severe infections.

General: It should be recognized that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy. Except for gonorrhea, treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by *Streptococcus pyogenes* to prevent the occurrence of acute rheumatic fever.

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Please refer to clarithromycin and lansoprazole full prescribing information for **CONTRAINDICATIONS** and **WARNINGS**, and for information regarding dosing in elderly and renally impaired patients.

Dosing recommendations for adults with impaired renal function:
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of < 30 mL/minute should not receive the 875-mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

There are currently no dosing recommendations for pediatric patients with impaired renal function.

HOW SUPPLIED

Amoxicillin Tablets for Oral Suspension:
Each tablet for oral suspension contains 200 mg or 400 mg amoxicillin as the trihydrate.

200-mg Tablet for Oral Suspension
200 mg light pink colored, strawberry flavored, circular, biconvex, unscored, mottled tablets, debossed with "RX565" on one side and plain on the other.

NDC 63304-565-20	Bottles of 20
NDC 63304-565-60	Bottles of 60
NDC 63304-565-10	Bottles of 1000
NDC 63304-565-80	Unit dose pack of 100s

400-mg Tablet for Oral Suspension
400 mg light pink colored, strawberry flavored, circular, biconvex, unscored, mottled tablets, debossed with "RX567" on one side and plain on the other.

NDC 63304-567-20	Bottles of 20
NDC 63304-567-60	Bottles of 60
NDC 63304-567-05	Bottles of 500
NDC 63304-567-80	Unit dose pack of 100s

The product is also available as:

Amoxicillin Capsules:
Each capsule contains 250 mg or 500 mg amoxicillin as the trihydrate.

250-mg Capsule
250 mg yellow opaque cap and yellow opaque body, size 2, printed "RX654" on both cap and body.

NDC 63304-654-30	bottles of 30
NDC 63304-654-01	bottles of 100
NDC 63304-654-05	bottles of 500
NDC 63304-654-80	unit-dose 100s

500-mg Capsule
500 mg maroon opaque cap and yellow opaque body, size 0-el, printed "RX655" on both cap and body.

NDC 63304-655-30	bottles of 30
NDC 63304-655-01	bottles of 100
NDC 63304-655-05	bottles of 500
NDC 63304-655-80	unit-dose 100s

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Each tablet contains 500 mg or 875 mg amoxicillin as the trihydrate.

500-mg Tablet
500 mg pink colored, film coated, capsule shaped tablets; debossed with "RX762" on one side.

NDC 63304-762-82	bottles of 12
NDC 63304-762-13	bottles of 120
NDC 63304-762-01	bottles of 100
NDC 63304-762-05	bottles of 500

875-mg Tablet
875 mg pink colored, film coated, capsule shaped tablets; debossed with "RX763" on one side and scored on reverse side.

NDC 63304-763-82	bottles of 12
NDC 63304-763-13	bottles of 120
NDC 63304-763-01	bottles of 100
NDC 63304-763-05	bottles of 500

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Each chewable tablet contains 125 mg, 200 mg, 250 mg or 400 mg amoxicillin as the trihydrate.

125-mg Tablet
125 mg pink colored, strawberry flavored, oval, biconvex tablets, with mottled appearance; debossed with "RX514" on one side.

NDC 63304-514-01	bottles of 100
NDC 63304-514-05	bottles of 500

200-mg Tablet
200 mg light pink colored, strawberry flavored, circular, flat faced, bevelled edge tablets, with mottled appearance; debossed with "RX760" on one side.

NDC 63304-760-20	bottles of 20
NDC 63304-760-01	bottles of 100
NDC 63304-760-05	bottles of 500

250-mg Tablet
250 mg pink colored, strawberry flavored, circular, flat faced, bevelled edge tablets, with mottled appearance; debossed with "RX515" on one side.

NDC 63304-515-01	bottles of 100
NDC 63304-515-04	bottles of 250

400-mg Tablet
400 mg light pink colored, strawberry flavored, circular, flat faced, bevelled edge tablets, with mottled appearance; debossed with "RX761" on one side.

NDC 63304-761-20	bottles of 20
NDC 63304-761-01	bottles of 100
NDC 63304-761-05	bottles of 500

Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).
Dispense in a tight container.

CLINICAL STUDIES

H. pylori eradication to reduce the risk of duodenal ulcer recurrence
Randomized, double-blind clinical studies performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of lansoprazole in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy, or in combination with amoxicillin capsules as dual 14-day therapy, for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy: amoxicillin 1 gram b.i.d./clarithromycin 500 mg b.i.d./lansoprazole 30 mg b.i.d.

Dual therapy: amoxicillin 1 gram t.i.d./lansoprazole 30 mg t.i.d.

All treatments were for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4 to 6 weeks following the end of treatment. Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

***H. pylori* Eradication Rates - Triple Therapy**
(amoxicillin/clarithromycin/lansoprazole)
Percent of Patients Cured
[95% Confidence Interval]
(Number of Patients)

Study	Triple Therapy Evaluable Analysis†	Triple Therapy Intent-to-Treat Analysis‡
Study 1	92 § [80-97.7] (n=48)	86 § [73.3-93.5] (n=55)
Study 2	86‖ [75.7-93.6] (n=66)	83‖ [72-90.8] (n=70)

† This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, (Delta West Ltd., Bentley, Australia), histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.
‡ Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.
§ ($p < 0.05$) versus lansoprazole/amoxicillin and lansoprazole/clarithromycin dual therapy.
‖ ($p < 0.05$) versus clarithromycin/amoxicillin dual therapy.

***H. pylori* Eradication Rates - Dual Therapy**
(amoxicillin/lansoprazole)
Percent of Patients Cured
[95% Confidence Interval]
(Number of Patients)

Study	Dual Therapy Evaluable Analysis¶‖	Dual Therapy Intent-to-Treat Analysis††
Study 1	77‡‡ [62.5-87.2] (n=51)	70‡‡ [56.8-81.2] (n=60)
Study 2	66§§ [51.9-77.5] (n=58)	61§§ [48.5-72.9] (n=67)

¶‖ This analysis was based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.
†† Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.
‡‡ ($p < 0.05$) versus lansoprazole alone.
§§ ($p < 0.05$) versus lansoprazole alone or amoxicillin alone.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fourth Edition; Approved Standard. NCCLS Document M7-A4, Vol. 17, No. 2. NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition; Approved Standard. NCCLS Document M2-A6, Vol. 17, No. 1. NCCLS, Wayne, PA, January 1997.
3. Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than six years of age. *Vet Hum Toxicol* 1988; 30: 66-67.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540, USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India

November 2002

Patient Information Sheet
DisperMox™
(amoxicillin tablets for oral suspension)

PATIENT'S DIRECTIONS FOR USE

Dissolve the Dispermox tablet in water before you take it.
1. Remove one tablet from the bottle.
2. Place the tablet in a glass with a suitable amount of water (2 teaspoonfuls to 2 oz of water).
3. Swirl or stir until the tablet is completely dissolved.
4. Drink the mixture immediately after mixing. (The mixture is pink colored and has a strawberry flavor.)
5. Be sure to drink the entire mixture.
6. Rinse the glass with an additional 4 to 8 oz of water and drink the contents to assure the whole dose is taken.

DO NOT CHEW or SWALLOW the Dispermox tablets whole. The tablets will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

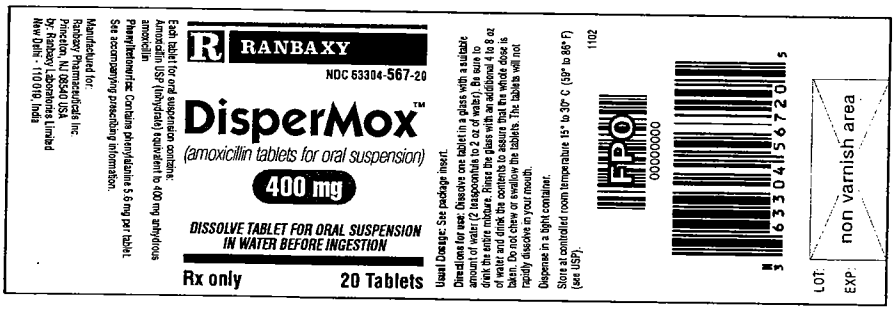
Do not mix Dispermox with any liquid other than water.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

Issued: November 2002

FDA-5

USA Label Size 60cc = 1 1/2" x 4 5/8"



APPROVE

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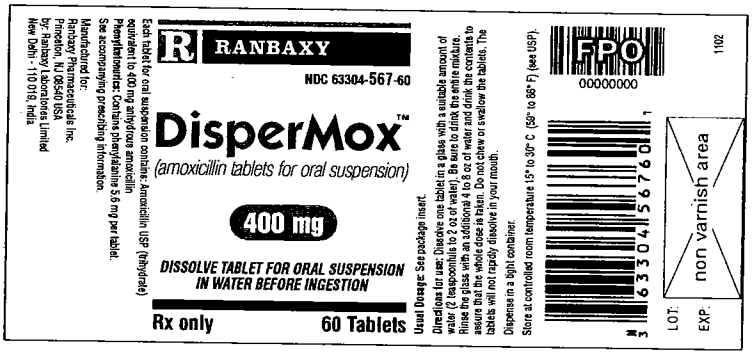

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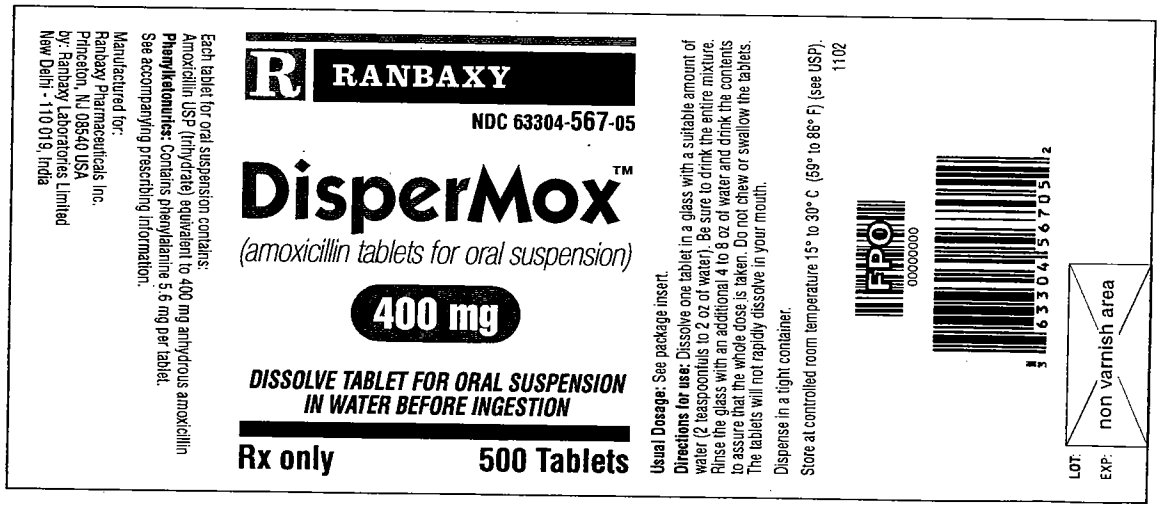
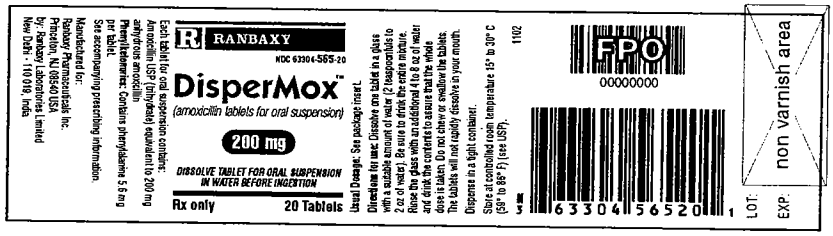
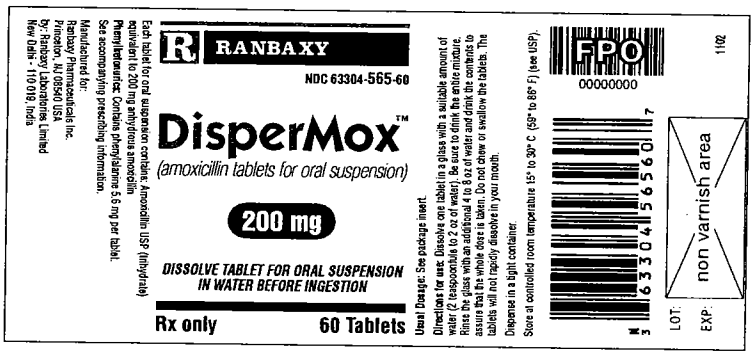


INDIA Label Size 40cc = 1 1/8" x 4 1/4"

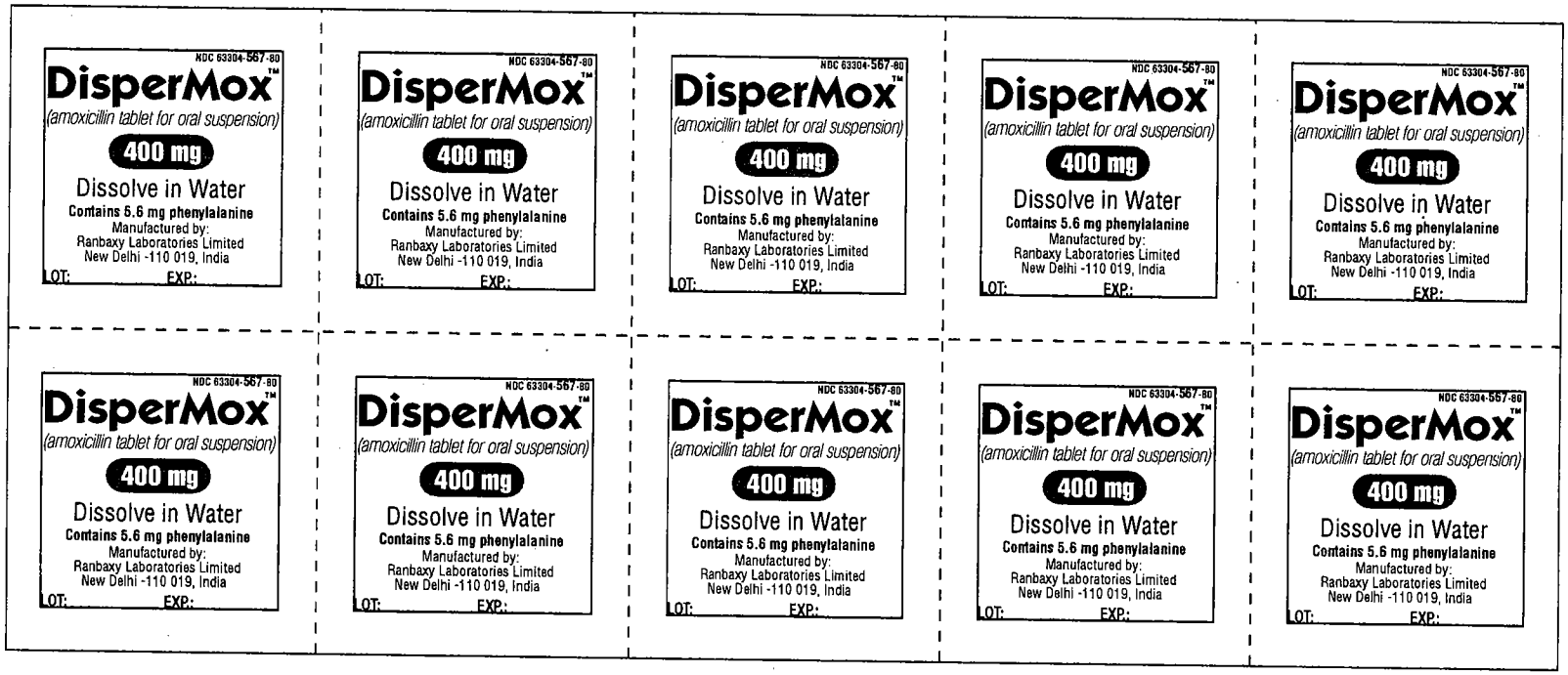


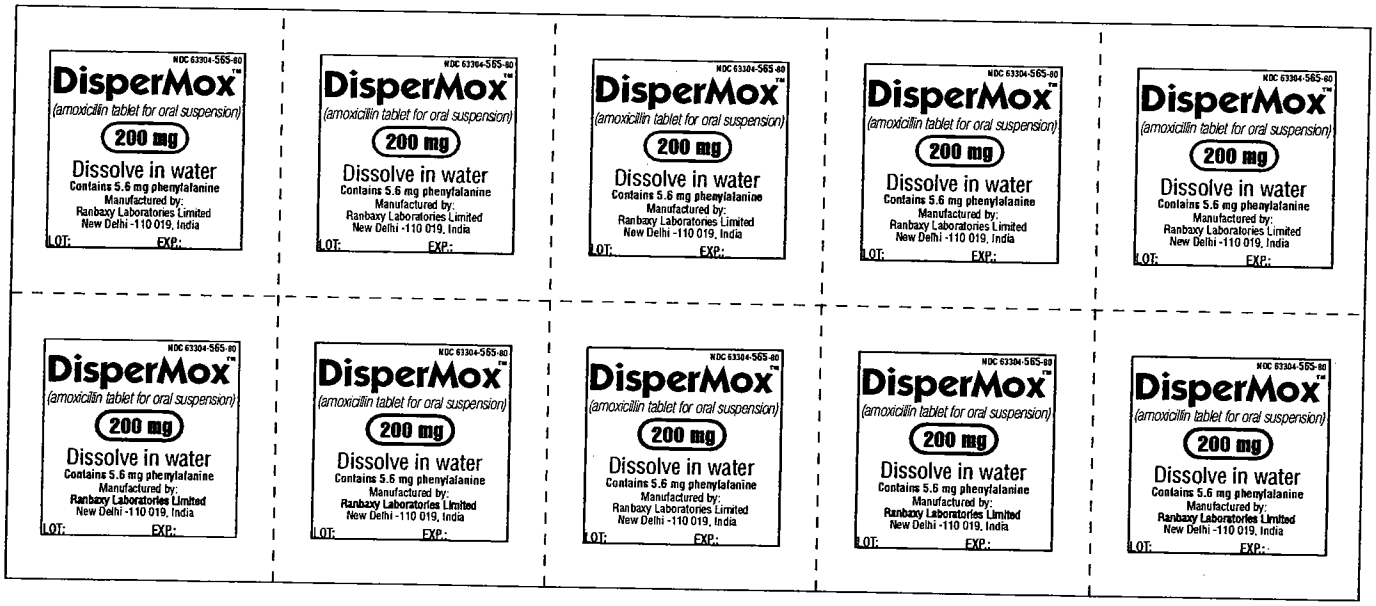
APPROVED

INDIA Label Size 75cc = 3 7/8" x 1 3/4"

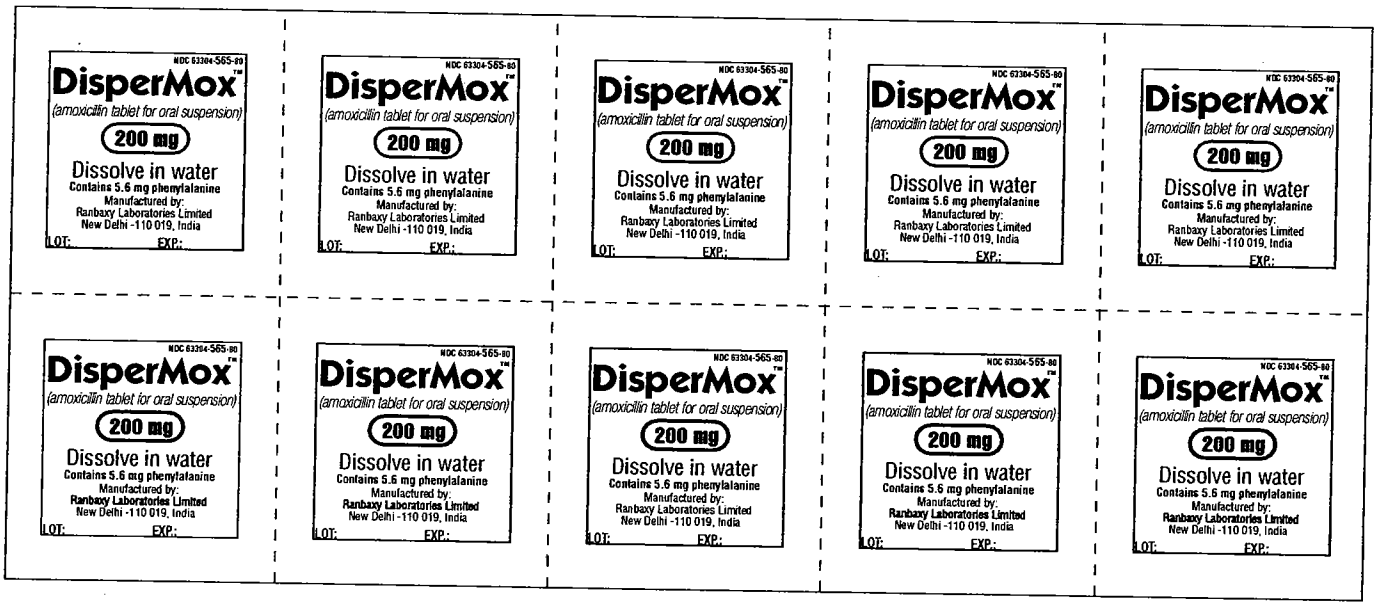


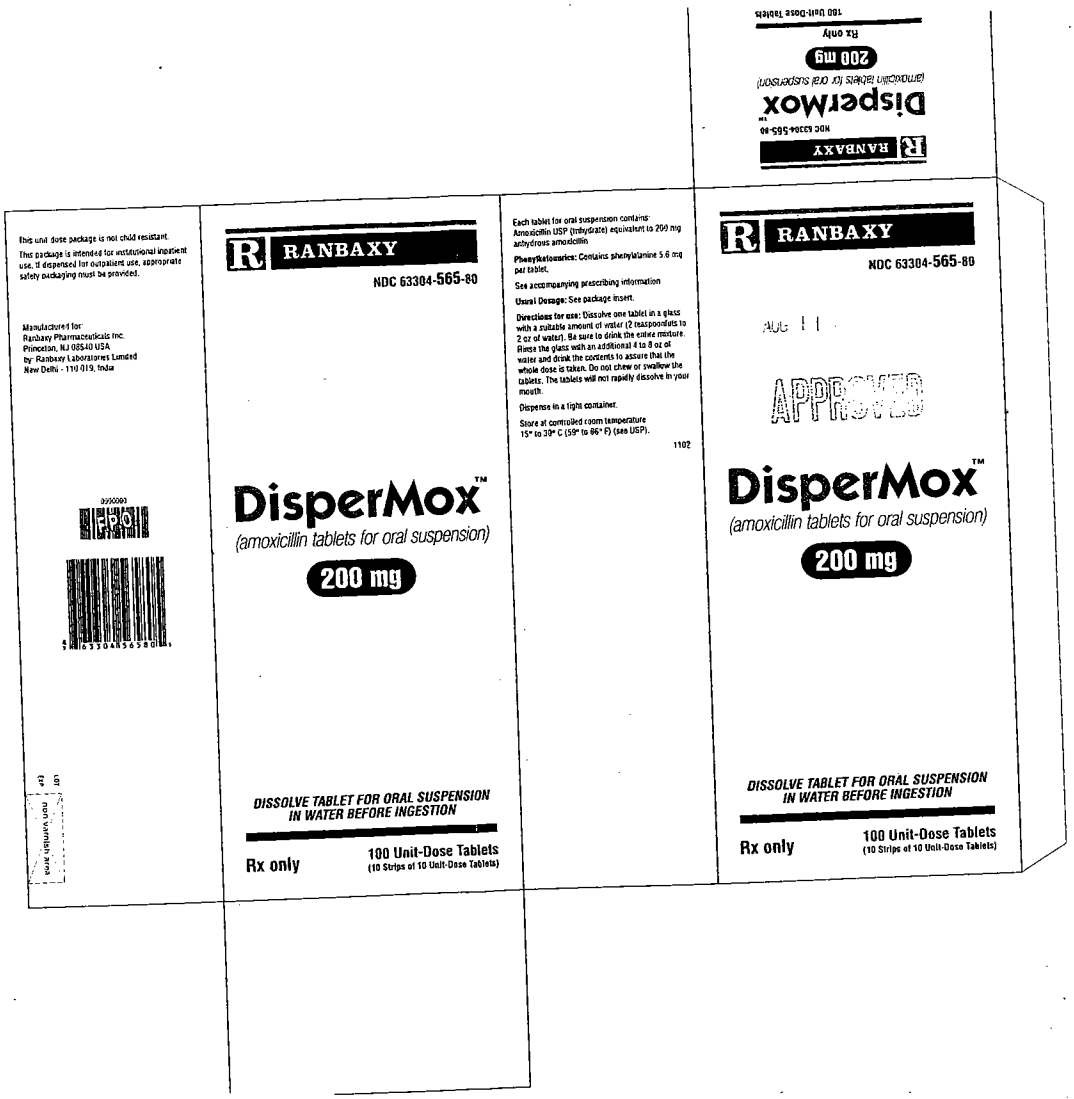
INDIA Label Size 1300cc = 2.5" x 6"


NDC 63304-567-80
DisperMox™
(amoxicillin tablet for oral suspension)
400 mg
Dissolve in Water
Contains 5.6 mg phenylalanine
Manufactured by:
Ranbaxy Laboratories Limited
New Delhi -110 019, India
LOT:
EXP:


NDC 63304-565-80
DisperMox™
(amoxicillin tablet for oral suspension)
200 mg
Dissolve in water
Contains 5.6 mg phenylalanine
Manufactured by:
Ranbaxy Laboratories Limited
New Delhi -110 019, India
LOT:
EXP:

APPROVED


NDC 63304-565-80
DisperMox™
(amoxicillin tablet for oral suspension)
200 mg
Dissolve in water
Contains 5.6 mg phenylalanine
Manufactured by:
Ranbaxy Laboratories Limited
New Delhi -110 019, India
LOT:
EXP.:



This unit dose package is not child resistant.

This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

R RANBAXY

NDC 63304-565-80

DisperMox™

(amoxicillin tablets for oral suspension)

200 mg

DISSOLVE TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only

100 Unit-Dose Tablets
(10 Strips of 10 Unit-Dose Tablets)

Each tablet for oral suspension contains: Amoxicillin USP (trihydrate) equivalent to 200 mg anhydrous amoxicillin.

Phenylketonurics: Contains phenylalanine 5.6 mg per tablet.

See accompanying prescribing information

Usual Dosage: See package insert.

Directions for use: Dissolve one tablet in a glass with a suitable amount of water (2 teaspoonfuls to 2 oz of water). Be sure to drink the entire mixture. Rinse the glass with an additional 4 to 8 oz of water and drink the contents to assure that the whole dose is taken. Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.

Dispense in a tight container.

Store at controlled room temperature 15° to 30° C (59° to 86° F) (see USP).

1102

AUG 11

APPROVED

R RANBAXY

NDC 63304-565-80

DisperMox™

(amoxicillin tablets for oral suspension)

200 mg

DISSOLVE TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only

100 Unit-Dose Tablets
(10 Strips of 10 Unit-Dose Tablets)

This unit-dose package is not child resistant.

This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

RANBAXY

NDC 63304-567-80

DisperMox™

(amoxicillin tablets for oral suspension)

400 mg

DISSOLVE TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only

100 Unit-Dose Tablets
(10 Strips of 10 Unit-Dose Tablets)

Each tablet for oral suspension contains:
Amoxicillin USP (trihydrate) equivalent to 400 mg anhydrous amoxicillin

Phenylketonurics: Contains phenylalanine 5.6 mg per tablet.
See accompanying prescribing information

Usual Dosage: See package insert.

Directions for use: Dissolve one tablet in a glass with a suitable amount of water (2 teaspoonfuls to 2 oz of water). Be sure to drink the entire mixture. Rinse the glass with an additional 4 to 8 oz of water and drink the contents to assure that the whole dose is taken. Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.

Dispense in a tight container.

Store at controlled room temperature
15° to 30° C (59° to 86° F) (see USP)

1102

RANBAXY

RANBAXY

NDC 63304-567-80

APPROVED

DisperMox™

(amoxicillin tablets for oral suspension)

400 mg

DISSOLVE TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only

100 Unit-Dose Tablets
(10 Strips of 10 Unit-Dose Tablets)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-080

CSO LABELING REVIEW(S)

THIS APPROVAL SUMMARY SUPERSEDES THE APPROVAL SUMMARY FOR THE FIRM'S SUBMISSIONS DATED November 1, 2002, November 5, 2002 and November 21, 2002.

APPROVAL SUMMARY

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

ANDA Number: 65-080

Date of Submission: July 11, 2003

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg

Proprietary Name: Dispermox™

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 Labels: 200 mg - 20s, 60s, 1000s and 400 mg – 20s, 60s, 500s
Satisfactory as of the July 11, 2003, submission. [Volume 6.1]

Unit Dose Blister Label: 200 mg and 400 mg
Satisfactory as of the July 11, 2003, submission. [Volume 6.1]

Unit Dose Carton Label:
200 mg/100s - Satisfactory as of the July 11, 2003, submission. [Volume 6.1]
400 mg/100s – Satisfactory as of the July 11, 2003, submission. [Volume 6.1]

Professional Package Insert Labeling:
Satisfactory as of the July 11, 2003, submission. [Volume 6.1]
[Insert code#:FDA-6 (Issued, July 2003)]

Patient Information Sheet
Satisfactory as of the July 11, 2003, submission. [Volume 6.1]

Revisions needed post-approval:
1. CONTAINER:
Increase the prominence of the established name.
2. CARTON:
See comment under CONTAINER.
3. INSERT
DESCRIPTION
Revise the flavor of your drug product to be consistent with your DESCRIPTION section.
4. Double check on additional package sizes not in original submissions.

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Amoxil® for Oral Suspension
ANDA Number: 62-226
ANDA Drug Name: Amoxil® (amoxicillin trihydrate) for Oral Suspension
ANDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 5/16/00 (S-002)[NDA 50-754]
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: RLD
Basis of Approval for the Carton Labeling: RLD

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 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?		X	
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 OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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)		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?		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	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.			

NOTE TO BIO. REVIEWER:

The firm's revised the CLINICAL PHARMACOLOGY section reads as follows:

The following pharmacokinetic data is from Ranbaxy's study of Dispermox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL. The dispersed mixture of Dispermox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspension. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg Dispermox tablets result in average peak blood levels 1 to 2 hours after administration in the range of
3.2 mcg/mL to [redacted]
Oral administration of singe doses of 400 mg DisperMox tablets and 400 mg/5 mL conventional suspension to 24 adult volunteers yield comparable pharmacokinetic data:

Dose*	AUC (mcg.hr/mL)	Cmax (mcg/mL)**
Amoxicillin	Amoxicillin	Amoxicillin
400 mg (5 mL of suspension)	18.6	8.4
400 mg (one dispersible tablet)	17.9	7.5

*Dosing was following an overnight fast
**Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

-Previously you informed me that "The range noted for Dispermox tablet should read as "3.2 mcg/ml to 11.5 mcg/ml" instead of [redacted] Before I request this revision. Do you concur with all of the pharmacokinetic data listed above?

-Is the firm's average peak blood level 1 to 2 hours or approximately [redacted] ? [See conflicting text above].

Bio. reviewer response:
The pharmacokinetic parameters are not accurate. [C.K.]

Additional question [new]

The Cmax listed in the insert labeling of the innovator for the amoxicillin suspension dosage form [Amoxil] is reported to be 5.92 mcg/mL.
Ranbaxy's insert labeling reports the Cmax for the innovator's amoxicillin suspension dosage form [Amoxil] to be 8.4 mcg/mL. Is this difference acceptable?

Thanks for your assistance.

NOTE TO THE CHEMIST:

DOSAGE AND ADMINISTRATION section

The firm revised their Directions which previously read, "..[redacted] to read "[redacted]

Did Ranbaxy provide additional data to support their revised directions?

Chemist response:

[Ganunis, Ruth M] This change in dispersion volume is ok, since a suspension and not a solution is formed.

Jackie -

To be more specific about the actual data submitted - in the chemistry section the data covered the range 50 ml to 120 ml. However, the bio-study review says that the tablets were dispersed in 10 ml for administration. I believe that 1 tablespoon is 15 ml, so we know that the tablets do disperse over the revised range.

Ruth

FOR THE RECORD:

1. Reference Listed drug: Amoxil (amoxicillin for oral suspension)/NDA 50-542/S-017, approved 5/16/2000
   NOTE: The most recent approved labeling for NDA 50-542/S-016/approved 4/10/02 is not currently available. After numerous attempts to obtain a hard copy and/or electronic copy from the Division of Anti-Infective Drug Products, we were informed that neither is available. Therefore, an Office decision was made to continue to use the approved insert labeling from S-017 as the labeling model for this drug product.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer: Ranbaxy, India.

4. Package Size:

   Both strengths will be available in UD 100s. The 200 mg tablets will be available in 1000s and the 400 mg tablets will be available in 500s.

   In the submission dated May 22, 2001, the firm added a package size of 20s for the 200 mg and 400 mg drug product.

5. Storage/dispensing recommendations

   RLD: Store at or below 70° C (68° F)

   ANDA: Store at controlled room temperature 15° to 30° C (59° to 86° F)(see USP). Dispense in a tight container. [The firm has been requested to revise this statement].

6. I was not able to verify the tablet descriptions as seen in the HOW SUPPLIED section.

7. The firm was asked that all information in the CLINICAL PHARMACOLOGY section not relating to this drug product be replaced by product specific information.

8. After discussion with J. Lee and C. Kim of BIO, it was determined that despite the fact that there are food references in the Amoxicillin RLD insert BIO has a policy stating that no food studies will be requested of any generic Amoxicillin applicant no matter what the dosage form. [Noted from previous review].

9. Container/Closure:

Strength	*Package size*	*Bottle type*	*Closure*
200 mg	20s	HDPE	CRC
200 mg	1000s	HDPE	Non CRC
200 mg	100s unit dose	Aluminum foil/laminate	
400 mg	20s	HDPE	CRC
400 mg	500s	HDPE	Non CRC
400 mg	100s unit dose	Aluminum foil/laminate	

[Vol. B2.1, p. 26-29]

10. Unit dose blisters container labels and carton labeling are satisfactory in printer's proof, providing the proposed established and proprietary names are found acceptable.

11. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement.
[Vol. B1.2, p. 1037]

12. The firm's physical description of each [redacted] tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor.
[Vol. B1.4, p. 2106, 2107]

13. A meeting was held to discuss the conditions of use of this ANDA. The Regulatory Branch informed us that since this drug product was found to be acceptable for filing under a petition, the drug product is not required to meet all the same conditions of use as the reference listed drug. Therefore, the dispersible tablet labeling can differ from the reference listed drug and should include statements that indicate that their drug product use is limited due to the dispersible tablet dosage form.

We have requested the firm to add the following statement as the first paragraph of the DOSAGE AND ADMINISTRATION section.

> All recommended dosages for amoxicillin are included in this section for informational purposes only. The 200 mg [redacted] tablet is appropriate only for a 200 mg dose and the 400 mg [redacted] tablet is appropriate only for a 400 mg dose.

14. We previously asked the firm the following:

> We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

Firm's response:

If the amoxicillin [redacted] tablet is inadvertently chewed it will form a soft mass. The drug product if chewed will not behave any differently from the dispersed mixture or if swallowed whole.

15. In the February 13, 2002, submission the firm's indicates, "that per their last telephone communications with the USP [January 2002] the drug product established name as proposed to the USP and the inclusion of the Amoxicillin [redacted] Tablets as a USP monograph is still in process and has not as yet been published in the Pharmaceutical Forum".

16. Previous NOTES TO BIO/CHEMIST:

NOTE TO CHEMIST

The firm's dosage form contains strawberry flavor. They indicate in their proposed patient package insert that "strawberry flavor can be taken by patients that are allergic to strawberries. Please refer to page 004 and attachment 3 in their February 13, 2002, submission.

Do you concur with firm's statement or do you know how we can verify this?

> ***[Ganunis, Ruth M]*** The supplier of Artificial Strawberry-Guarana Flavor [redacted], provides a statement that "to the best of our knowledge and belief, the above referenced product does not contain strawberries or derivatives of strawberries (attachment 2, 2/13/02 amendment)." Since we accept supplier certifications for other things (such as absence of solvents or compatibility of container closure systems), I believe that we can accept it here.

NOTE TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section read as follows:

The following pharmacokenetic data is from Ranbaxy's study of Dispermox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL. The dispersed mixture of Dispermox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspension. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg Dispermox tablets result in average peak blood levels 1 to 2 hours after administration in the range of 3.2 mcg/mL to [redacted]

Is the information provided in firm's revised paragraph accurate?
[Note, previously the firm included a range of "3.9 mcg/mL to 11.5 mcg/mL and 3.3 mcg/mL to 7 mcg/mL" for amoxcillin suspension and a range of "3.6 mcg/mL to [redacted] L and 3.2 mcg/mL to 7 mcg/mL" for the [redacted], tablet].

Thanks for your assistance.

Bio Comment

The range noted for amoxicillin suspension is correct.
The range noted for Dispermox tablet should read as "3.2 mcg/ml to 11.5 mcg/ml" instead of "3.2 mcg/ml ot [redacted]

Thanks
Carol

17. Patient Package Insert

- The Labeling Review Branch requested Ranbaxy to provide a PPI. The proposed PPI was forwarded to the Division of Anti-Infective Drug Products. The Division decided not to respond to the consult because they did not have an approved NDA for this new proposed "dosage form".

- The Office of Drug Safety also requested that firm provide separate instructions for the patient.

- An Office decision was made to request Ranbaxy to provide a "Patient Information Sheet" with "Directions for Use" instead of a "Patient Package Insert". The text for the "Directions for Use" was reviewed by Dr. Hixon in response to the Labeling Consult. In addition, it was agreed to replace ".. [redacted] ." with "... a glass of water...".
[See consult response].

18. DOSAGE AND ADMINISTRATION section

The updated text requested in this review is from Dr. Hixon's response to the Labeling Consult [See consult response].

19. The labeling review of the firm's May 30, 2003, submission was based on decisions made in a meeting on June 10, 2003, between OGD and the Office of Counter-Terrorism and Pediatric Drug Development (HFD-950). See labeling revisions below and related e-mails in the file folder.

The following decisions effects the labeling:

- Cephalexin and cefaclor are to be scored.
- Amoxicillin sholud not to be scored.
- Update the bolded statements "... for informational purposes ... to reflect with the 1/2 tablet wording. [Cephalexin and cefaclor]
- Amount of water: 2 teaspoonfuls
- Include the statement, "Entire amount should be swallowed".
- Keep the statement "only mix with water"

The firm has been requested the following:

a. Revise the "Directions for Use" to read:

Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

b. Replace " [redacted] " throughout your labeling.

c. PATIENT INFORMATION SHEET

PATIENT'S DIRECTIONS FOR USE

[redacted] Dispermox tablet in water before you take it.

1. Remove one tablet from the bottle
2. Place the tablet in a small amount of water (approximately 2 teaspoonfuls).
3. Swirl or stir until [redacted]
4. Drink the mixture immediately after mixing. (The mixture is pink colored and has a strawberry flavor.)
5. Be sure to drink the entire mixture.
6. Rinse the [redacted] water and drink the contents to assure the whole dose is taken.

DO NOT CHEW or SWALLOW the Dispermox tablets whole. The tablets will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

Do not mix Dispermox with any liquid other than water.

20. The proposed proprietary name was re-evaluated and ok'd 8/8/03.

Date of Review: 7/21/03

Date of Submission: 7/11/03

Primary Reviewer:
Jacqueline Council, Pharm.D. Date:

Team Leader:
Captain Lillie Golson /s/ Date: 8/8/03

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cc: ANDA: 65-080
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
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Review

APPROVAL SUMMARY

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

ANDA Number: 65-080

Date of Submission: - November 1, 2002
- November 5, 2002
- November 21, 2002

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg

Proprietary Name: DisperMox™

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 Labels: 200 mg - 20s, 60s, 1000s and 400 mg – 20s, 60s, 500s
Satisfactory as of the November 1, 2002, submission. [Volume 5.1]

Unit Dose Blister Label: 200 mg and 400 mg
Satisfactory as of the November 1, 2002, submission. [Volume 5.1]

Unit Dose Carton Label:
200 mg/100s - Satisfactory as of the November 21, 2002, submission. [Volume 5.1]
400 mg/100s – Satisfactory as of the November 21, 2002, submission. [Volume 5.1]

Professional Package Insert Labeling:
Satisfactory as of the November 1, 2002, submission. [Volume 5.1]
[Insert code#:FDA-5 (Issued, November 2002)]

Patient Information Sheet
Satisfactory as of the November 1, 2002, submission. [Volume 5.1]

Revisions needed post-approval:

1. CONTAINER:
   Increase the prominence of the established name.
2. CARTON:
   See comment under CONTAINER.
3. INSERT
   a. DESCRIPTION
      Revise the flavor of your drug product to be consistent with your DESCRIPTION section.
   b. DOSAGE AND ADMINISTRATION
      In the second paragraph correct the spelling of the word "teaspoonfuls". [Note, previous spelling was correct.]

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Amoxil® for Oral Suspension
ANDA Number: 62-226
ANDA Drug Name: Amoxil® (amoxicillin trihydrate) for Oral Suspension
ANDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 5/16/00 (S-002)[NDA 50-754]
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: RLD
Basis of Approval for the Carton Labeling: RLD

APPEARS THIS WAY
ON ORIGINAL

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 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?		X	
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 OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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)		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?		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	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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? Yes. If so, was a food study done? No. See FTR#7		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. Yes. See FTR#13	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 TO THE CHEMIST

1. The firm submitted a new package of 60's with the amendment dated 11/1/02. Is the closure a child resistant cap?

Yes. Information in Telephone Amendments 12/9/02 & 12/10/02 demostrates that the same C/C System (components in CRC caps) is used on the 60's size.

MS 12/12/02

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Reference Listed drug: Amoxil (amoxicillin for oral suspension)/NDA 50-760/S-001, approved 5/16/2000.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer: Ranbaxy, India.

4. Package Size:

   Both strengths will be available in UD 100s. The 200 mg tablets will be available in 1000s and the 400 mg tablets will be available in 500s.

   In the firm's submission dated May 22, 2001, the firm added package sizes of 20s for the 200 mg and 400 mg drug product.

   In the firm's submission dated November 1, 2002, the firm added package sizes of 60s for the 200 mg and 400 mg drug product.

5. Storage/dispensing recommendations

   Store at controlled room temperature 15° to 30°C (59° to 86°F)(see USP). Dispense in a tight container.

6. The firm was asked that all information in the CLINICAL PHARMACOLOGY section not relating to this drug product be replaced by product specific information. Ranbaxy has complied.

7. After discussion with J. Lee and C. Kim of BIO, it was determined that despite the fact that there are food references in the Amoxicillin RLD insert BIO has a policy stating that no food studies will be requested of any generic Amoxicillin applicant no matter what the dosage form. [Noted from previous review].

8. Container/Closure:

Strength	***Package size***	***Bottle type***	***Closure***
200 mg	20s	HDPE	CRC
200 mg	1000s	HDPE	Non CRC
200 mg	100s unit dose	Aluminum foil/laminate	
400 mg	20s	HDPE	CRC
400 mg	500s	HDPE	Non CRC
400 mg	100s unit dose	Aluminum foil/laminate	

   [Vol. B2.1, p. 26-29]

9. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement.
   [Vol. B1.2, p. 1037]

10. The firm's physical description of each dispersible tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor.
    [Vol. B1.4, p. 2106, 2107]

11. A meeting was held to discuss the conditions of use of this ANDA. The Regulatory Branch informed us that since this drug product was found to be acceptable for filing under a petition, the drug product is not required to meet all the same conditions of use as the reference listed drug. Therefore, the dispersible tablet labeling can differ from the reference listed drug and should include statements that indicate that their drug product use is limited due to the dispersible tablet dosage form.

    We have requested the firm to add the following statement as the first paragraph of the DOSAGE AND ADMINISTRATION section.

All recommended dosages for amoxicillin are included in this section for informational purposes only. The 200 mg [redacted] tablet is appropriate only for a 200 mg dose and the 400 mg [redacted] tablet is appropriate only for a 400 mg dose.

12. We previously asked the firm the following:

> We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

Firm's response:

If the amoxicillin dispersible tablet is inadvertently chewed it will form a soft mass. The drug product if chewed will not behave any differently from the dispersed mixture or if swallowed whole.

13. The firm submitted a copy of the recently published Pharmacopeial Forum for July-August 2002, which coins the name "Amoxiclin Tablets for Oral Suspension". This is the name proposed as the official USP established name for the USP 26/Supplement 1.

14. Previous NOTES TO BIO/CHEMIST:

NOTE TO CHEMIST

The firm's dosage form contains strawberry flavor. They indicate in their proposed patient package insert that "strawberry flavor can be taken by patients that are allergic to strawberries. Please refer to page 004 and attachment 3 in their February 13, 2002, submission.

Do you concur with firm's statement or do you know how we can verify this?

> ***[Ganunis, Ruth M]*** The supplier of Artificial Strawberry-Guarana Flavor [redacted] provides a statement that "to the best of our knowledge and belief, the above referenced product does not contain strawberries or derivatives of strawberries (attachment 2, 2/13/02 amendment)." Since we accept supplier certifications for other things (such as absence of solvents or compatibility of container closure systems), I believe that we can accept it here.

NOTE TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section to read as follows:

> The following pharmacokinetic data is from Ranbaxy's study of Dispermox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL. The dispersed mixture of Dispermox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspension. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg Dispermox tablets result in average peak blood levels 1 to 2 hours after administration in the range of 3.2 mcg/mL to [redacted]

Is the information provided in firm's revised paragraph accurate?
[Note, previously the firm included a range of " [redacted] for amoxcillin suspension and a range of " [redacted] for the [redacted] tablet].

Thanks for your assistance.

Bio Comment

The range noted for amoxicillin suspension is correct.
The range noted for Dispermox tablet should read as "3.2 mcg/ml to 11.5 mcg/ml" instead of '

Thanks
Carol

15. Patient Package Insert

- The Labeling Review Branch requested Ranbaxy to provide a PPI. The proposed PPI was forwarded to the Division of Anti-Infective Drug Products. The Division decided not to respond to the consult because they did not have an approved NDA for this new proposed "dosage form".

- The Office of Drug Safety also requested that firm provide separate instructions for the patient.

- An Office decision was made to request Ranbaxy to provide a "Patient Information Sheet" with "Directions for Use" instead of a "Patient Package Insert". The text for the "Directions for Use" was reviewed by Dr. Hixon in response to the Labeling Consult. In addition, it was agreed to replace ".. ' with "... a glass of water...".
[See consult response].

- The "Patient Information Sheet" submitted with the firm's November 1, 2002, contains further revisions which were found to be acceptable by our Office.

16. DOSAGE AND ADMINISTRATION section

The updated text requested in this review is from Dr. Hixon's response to the Labeling Consult
[See consult response].
[See FTR#15]

17. The firm submitted a "new product launch" letter with the 11/5/02 submission. This letter should be submitted to the DDMAC by the firm. This letter also informs the Pharmacist ot the Patient Information Sheet.

18. Bioavailability/Bioequivalence:

- The firm's pharmacokinetic parameters from the fasting bioequivalence study was comparable to the reference listed drug.

- The firm's pharmacokinetic parameters listed in the insert labeling are comparable to the bioequivalence study results.

- The bioequivalence fasting study is acceptable from a labeling point of view.

- *The reported pharmacokinetic parameters from the fasting bioequivalence study was found to be within acceptable limits by the Division of Bioequivalence.
*However, the Division of Bioequivalence recommends deleting the word " from the 7th paragraph. ("...peak blood levels..." instead of ".
[To be further discussed]

Dose	AUC (mcg.hr/mL)	Cmax (mcg/mL)	Tmax(hr)
Amoxicillin	Amoxicillin	Amoxicillin	
400 mg (5 mL of suspension)-insert	18.5	8.4	~1
400 mg (one tablet)-insert	17.9	7.5	~1
ANDA	17.83-18.15	7.76	1.16
RLD	18.49-18.82	8.6	1.02

Date of Review: 11/21/02

Date of Submission: 11/01/02, 11/05/02, 11/21/02

Primary Reviewer: /S/
Jacqueline Council, Pharm.D. Date: 12/4/02

Acting Team Leader: /S/
Captain Lillie Golson Date: 12/4/02

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cc: ANDA: 65-080
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSNZ\RANBAXY\LTRS&REV\65080ap.lL.doc
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number:	65-080
Date of Submission:	May 30, 2002
Applicant's Name:	Ranbaxy Laboratories Limited
Established Name:	Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg
Proprietary Name:	Dispermox™

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Please comment on the status of your communications with the USP regarding your proposed drug product established name.

   b. After review of the your appeal regarding your proposed proprietary name, the Office of Drug Safety (ODS) still does not recommend the use of your proposed proprietary name [redacted] for reasons listed below.

   Please note, although ODS does not recommend the use of the [redacted] modifier, you may propose another modifier for review.

I. RESPONSE TO THE SPONSOR'S APPEAL:

A. [redacted]

Sponsor's Comments:

OPDRA has also noted that the mark [redacted] contains the medical abbreviation [redacted] which indicates that the drug product is dosed [redacted] A review of the Trademark Office records indicates that there are in excess of 25 registrations for trademarks for pharmaceuticals which incorporate the suffix " [redacted] Copies of these registrations are attached to this response. Many of these products, like [redacted] can be dosed more than [redacted] depending on patient and disease conditions. This group includes the mark MACROBID, one of the marks cited by OPDRA in its deficiency letter.

DMETS Comments:

DMETS has evaluated the sponsor's arguments and agrees with the sponsor that medication errors caused by the [redacted] ending in " [redacted] " may be low.

B. [redacted]

Sponsor's Comments:

Ranbaxy has reviewed OPDRA's comments regarding the suffix "[redacted] as it is used as part of the mark [redacted], and respectfully requests OPDRA to reconsider its conclusions. Clearly, the abbreviation "[redacted] is not a medical abbreviation. Accordingly, the only circumstance under which the misinterpretation referred to by OPDRA could occur is a circumstance under which the letters are misread. Since the letters are a part of the trademark [redacted] and will always appear in conjunction with the word [redacted] it is difficult to understand the circumstances under which such a misinterpretation or the suggested effect of that misinterpretation could occur. Ranbaxy believes the risk of interpreting the [redacted], as [redacted] is low. The

name [redacted] contains the letters [redacted] which is interpreted as [redacted]. The prescriptions for [redacted] are written by a physician and should clearly state the dosing requirements per day. Regarding the misinterpretation of [redacted] for [redacted], this is also extremely low since the product is not intended for ophthalmic use and the product packaging does not include any instructions for use as an ophthalmic product. As for the comments regarding the study conducted by OPDRA, Ranbaxy intends to instruct its detail people to refer to the product as [redacted] and teach prescribers to order the medicine in this fashion. If prescribers are taught to prescribe the product using the whole trademark, we expect that a similar post introduction survey would show universal use of the entire product name by prescribers.

DMETS Comments:

According to *Medical Abbreviations: 14,000 Conveniences at the Expense of Communications and Safety*[1], "[redacted]" is an abbreviation for [redacted] and so on. The practitioner may misinterpret [redacted] to mean "[redacted]. This would cause the patient to be overdosed, causing an increased potential risk of side effects such as nausea, vomiting, and diarrhea. However, [redacted] is not commonly used in writing prescriptions to convey a dose.

The [redacted] modifier can also be misinterpreted as "QD" depending on how [redacted] is scripted. Even though [redacted] contains [redacted], meaning [redacted], practitioners may not make a cognitive link that the [redacted] in the [redacted] name means [redacted] A prescription written as [redacted] use as directed, #28" may be interpreted as "[redacted] use as directed. #28" ([redacted] take [redacted] as directed, #28). If the patient only takes the [redacted], then the patient would be underdosed and would not be treated adequately for his or her disease state. Regarding the possible misinterpretation of [redacted] as [redacted], DMETS agrees with the sponsor that the risk of putting a tablet in the eye would be low. However, misinterpretation of [redacted] is possible as indicated in the DMETS study (verbal) for [redacted] where 2 respondents interpreted [redacted] as [redacted] If [redacted] was intended to be given, for example, three times a day, the [redacted] may lead the practitioner to believe that it is prescribed as twice a day, especially when the directions on the prescription are written as "use as directed". Also, in a DMETS study for another Ranbaxy proprietary name ([redacted], ODS Consult 01-0206-1), one respondent interpreted [redacted] as "ll" and returned a response of [redacted] Another respondent in that study interpreted [redacted] as [redacted]. In the DMETS study for [redacted] (ODS Consult 01-0052-1), 7 (8%) out of 87 respondents interpreted [redacted] as [redacted], and [redacted] Even though these DMETS studies involve a small sample number, the misinterpretations found in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. These studies prove that the [redacted] modifier can be misinterpreted as [redacted] or any other misleading abbreviations.

Regarding the issue of prescribers omitting the [redacted] on a [redacted] prescription, the sponsor states that the prescribers will be instructed to order the prescription as [redacted] to ensure that the [redacted] not omitted. DMETS does recognize and agrees with the sponsor that if the prescriber includes the [redacted] modifier along with the proprietary name [redacted] in a prescription, there would be a decrease in the potential risk of medication errors occurring between [redacted] and other proprietary names mentioned in DMETS' review. However, DMETS is somewhat concerned that in certain situations such as in the knowledge that [redacted] is not available in another formulation where it needs to be distinguished with a modifier or in a hurried environment, a prescriber may leave off the modifier [redacted] when writing

[1] Neil M. Davis. Medical Abbreviations: 14,000 Conveniences at the Expense of Communications and Safety, 1999.

the prescription. Leaving off the [redacted] modifier may lead to an increased risk of confusion between the name '[redacted]' (without the [redacted] modifier) and another proprietary name that is in the existing U.S. market such as *Macrobid*. It has been reported to the Agency that physicians sometimes leave off the modifier in writing a prescription. One report (ISR #3779865-2) stated that there was a possibility of confusion between *Aciphex* and *Adipex-P* due to the sound-alike qualities. It states that "although the product name is actually *Adipex-P*, physicians only write for *Adipex*." However, DMETS acknowledges that a modifier may be needed to distinguish its product from the rest of all the amoxicillin tablet formulations and does not object to the use of a modifier.

C. DISPERDOSE

Sponsor's Comments:

Finally, the OPDRA letter notes that the expert panel expressed concerns that [redacted] could be confused with the currently available PCE DISPERTAB. We would agree with OPDRA that similarity in '[redacted]and DISPERTAB should not lead to name confusion because prescribers will most likely order these products using the proprietary names PCE and [redacted], not the name of the dosage formulation. OPDRA's concern, however is that the practitioner may be confused on how the dosage form is administered and that the practitioner may tell the patient to swallow the [redacted] tablet as a whole without dissolving it in water. The labeling and patient information leaflet clearly states to "Dissolve the tablets in water before ingestion". To the extent that this may occur, swallowing the [redacted] tablet whole will have no negative effect upon the patient and the dose will still be effective with no toxic effects. In addition, '[redacted] is related to its tradename and not the type of technology, for example, Eli Lilly's use of the word PULVULE in place of capsule. In addition, the product will not be prescribed using the DISPERTAB terminology.

DMETS Comments:

DMETS concurs that '[redacted] would not be confused with *PCE Dispertab*. However, having '[redacted]' and '[redacted]' as part of the tradename seems redundant. DMETS is still concerned, however, that the patient may still try to swallow the [redacted] formulation, which may become a problem if the patient cannot swallow or cannot swallow adequately. Even though the patient leaflet contains instructions on how to take the tablet, the patient (or practitioner) may not read or may not even be given the patient leaflet. Along with the instructions in the patient leaflet, DMETS, as stated in the November 16, 2001 " [redacted] review, recommends that the statement **"DISSOLVE TABLETS IN WATER BEFORE INGESTION"** be on the main panel of the container labels and carton labeling.

D. SOUND-ALIKE/LOOK-ALIKE DRUG PRODUCTS

1. *Sponsor's Maxifed and Maxifed DM Comments:*

Ranbaxy believes that the potential risk of a medication error occurring between either of these existing products and Ranbaxy's [redacted] is extremely low. While this is contrary to OPDRA's initial conclusion, Ranbaxy respectfully requests OPDRA to consider the following additional information.

First, OPDRA has concluded that MAXIFED and MAXIFED DM look and sound similar to '[redacted] and [redacted]. Ranbaxy respectfully requests that OPDRA reconsider the forgoing conclusion in view of the fact that Ranbaxy does not propose to sell a product named [redacted] but only a product named [redacted]. We note that this difference in Ranbaxy's mark may not have been considered by OPDRA in making its comparison because the writing sample contained in OPDRA's letter did not include the [redacted] suffix. Ranbaxy believes that the addition of the letters '[redacted] to the name '[redacted] creates a

product name [redacted] which is clearly distinguishable from the product names MAXIFED and MAXIFED DM both in sound and appearance. While Ranbaxy recognizes that there remains the possibility that the prescription writer may omit the [redacted] portion of the mark in writing the prescription, that is a separate issue that is discussed below. The point to be made here is that the product names, when compared in their entirety are easily distinguished because of the addition of the letters [redacted] the word [redacted]

Second, both MAXIFED and MAXIFED DM are offered in single strength tablets of Guaifenesin 700 mg/Pseudoephedrine 30 mg and 550 mg Guaifenesin/30 mg Dextromethorphan/60 mg Pseudoephedrine respectively. This dosage strength differs from the tablet strength of [redacted] which is offered in strengths of 200 and 400 mg. Therefore, so long as tablet strengths are included in the prescription of any of the products, there will be no possible medication errors caused by confusion among the three products. OPDRA has raised concerns, however, that a prescriber of [redacted] may fail to include a dosage strength and the MAXIFED and MAXIFED DM product may be used to fill the prescription. While it is not stated explicitly in the OPDRA letter, there also appears to be a concern that a doctor prescribing [redacted] may fail to include the letters [redacted] as part of the product name and may also forget to include the dosage strength.

As noted above, the name under which Ranbaxy will be selling the product is [redacted]. Even if the dosage strength is not included in the prescription, the differences between the marks will avoid MAXIFED being substituted for [redacted]. Likewise, the differences in the suffixes will avoid MAXIFED DM being substituted for [redacted] particularly where, as here, the suffix "DM" identifies, within the industry, the additional ingredient dextromethorphan.

As for the second hypothetical fact pattern, it seems highly unlikely that any prescriber would eliminate both the suffix from the product name and the strength of the tablet when prescribing [redacted]. Frankly, a prescriber would have to be very careless to omit the tablet strength because he would have to indicate the strength of the tablet in order to determine the proper dosing of the product. Any pharmacist, particularly in an age where prescription for a product lacking a formulation strength would question the prescription unless the product name was entirely clear.

Therefore, because of differences between Ranbaxy's mark [redacted] and MAXIFED and MAXIFED DM as well as differences in tablet strengths, Ranbaxy believes that the risk of a medication error occurring between [redacted] and these two products is extremely low.

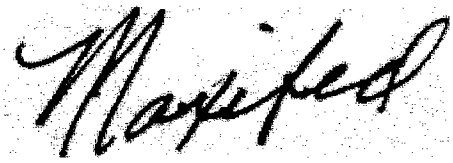
DMETS Comments:

DMETS agrees with the sponsor that when evaluating the proprietary name [redacted] in its entirety, the [redacted] modifier may decrease the potential risk of a medication error occurring between [redacted] and *Maxifed*. DMETS also recognizes that if a prescriber includes the strength of [redacted] in the prescription, the potential risk of confusion between [redacted] and *Maxifed* would decrease since there are no overlapping strengths (200 mg and 400 mg vs. 80 mg/700 mg). However, as stated in section B "Modifier [redacted] prescribers may omit the [redacted] modifier in writing a [redacted] prescription due to the knowledge that [redacted] is not available in any other dosage form or releasing mechanism. In regards to strength omission, it is careless for a prescriber to omit the strength on a prescription; however, in reality, prescribers may sometimes leave off the strength when writing a prescription due to a variety of factors from too many patients to a hectic environment. Even though the prescriber needs to know the strength of the drug product before deciding the correct dosage regimen, a prescriber may have already formulated the correct dosage regimen before writing the prescription. This would not prevent the prescriber from omitting the strength on a prescription. If a prescription was sent

to the pharmacy stating "... ———, use as directed" where the strength as well as the modifier was not included, a pharmacist may not question the prescription if he or she believes that it is "Maxifed #14, use as directed". Since *Maxifed* is only available in one strength, the strength does not need to be indicated on the prescription. The writing sample below shows " ——" written as " —— since a prescriber may leave off the — modifier when writing a prescription. ". DMETS agrees with the sponsor that the omission of the — modifier and strength are two different issues and that one omission may happen without the other. However, it is possible for both omissions to happen simultaneously for different reasons (omitting the "— due to the knowledge that it is the only amoxicillin dispersible tablet and omitting the strength due to carelessness).

Writing Sample:

———



—

Maxifed

———can also look similar to *Maxifed DM*. As discussed above, — ' can look similar to *Maxifed*. Even though — ; not exactly the same as "DM" visually and both have different meanings, they only differ by <u>one</u> letter. The "DM" may be mistaken for — and, in turn, have —— ' mistaken for *Maxifed DM*, especially during the early phase of marketing where practitioners will not be familiar with the " —— ' name. Like *Maxifed*, *Maxifed DM* is only available in one strength. If a prescription was sent to the pharmacy as ———— , use as directed" where the strength was not included, a pharmacist may not question the prescription if he or she believes that it is "Maxifed DM #14, use as directed". Again, since *Maxifed DM* is only available in one strength, the strength does not need to be indicated on the prescription.

2. <u>*Sponsor's Amoxapine Comments*</u>:

Ranbaxy believes that the potential risk of medication error occurring between ———and AMOXAPINE is extremely low, both because of differences in the marks as well as differences in tablet strength. While this is contrary to OPDRA's initial conclusion, we would ask OPDRA to consider the following arguments.

In Ranbaxy's opinion, the marks ——and AMOXAPINE are sufficiently different to avoid confusion even if there were no differences between the products themselves. First, we think it is unlikely that a prescriber would call in a prescription using the language suggested in OPDRA's letter. It is much more likely that the prescriber would say "I am calling in a prescription for AMOXAPINE" or I am calling in a prescription for ——— In addition, the marks share similarity and not identity only in the middle syllable of the name. Certainly, the suffix "pine" is easily distinguished from the suffix — and, in most instances, the letter "a" appearing as the first letter in AMOXAPINE would distinguish the names in both the visual and oral form of communication. Finally, the suffix —would further distinguish Ranbaxy's product from AMOXAPINE making the potential risk of medication error occurring between these two drug products extremely unlikely.

Look at the products themselves, as noted by OPDRA, there are no overlapping tablet strengths. OPDRA has suggested that a pharmacist may substitute two 100 mg tablets of AMOXAPINE for a single tablet of ——— but this would be an improper product substitution and would never be done by a pharmacist

without checking with the prescriber. Accordingly, because of differences in the marks as well as the fact that there are no overlapping pill strengths eliminates any potential risk of a medication error occurring between these two drug products.

DMETS Comments:

DMETS agrees with the sponsor that when evaluating the proprietary name [redacted] in its entirety, the [redacted] modifier may decrease the potential risk of a medication error occurring between [redacted] and *Amoxapine*. However, according to section B of this review, it is possible that a prescriber may omit the [redacted] modifier when writing a prescription for [redacted]. Regarding as to how a prescription is called into the pharmacy, there is no standard, official way for a physician to call in a prescription. DMETS does recognize that a prescription can be called in as "I am calling in a prescription for *Amoxapine*" or "I am calling in a prescription for [redacted] It is also possible for a prescriber to say, "I am calling in a [redacted] prescription." When the suffix "pine" of *Amoxapine* is pronounced "peene", then *Amoxapine* would sound different than "[redacted]" However, some practitioners may pronounce *Amoxapine* differently even though it may be the wrong pronunciation. Some may pronounce the "pine" as a "pin" so that the *Amoxapine* would sound like "Amoxapin". The "A" in *Amoxapine* may not distinguish the proprietary names *Amoxapine* and "[redacted]". When pronouncing the proprietary name, *Amoxapine*, the "m" is more pronounced than the first "a", which may render the "a" sound inaudible. Practitioners may just hear the word "Moxapin", which sounds like "[redacted]". DMETS agrees that *Amoxapine* and [redacted] do not look or sound alike.

Even though there are no overlapping strengths between *Amoxapine* (100 mg) and [redacted] (200 mg and 400 mg), it is possible that a pharmacist may dispense 2 tablets of *Amoxapine* (2 x 100 mg) if he or she misinterprets [redacted] 200 mg" as "Amoxapine 200 mg". A pharmacist does not need to contact the prescriber to obtain permission to give enough of the lower strength to equal the amount of the intended dose. In fact, *Amoxapine* can be given 200 mg to 300 mg per day; therefore, it is not uncommon to see a prescription for *Amoxapine* 200 mg.

3. *Sponsor's Maxaquin Comments:*

It is unlikely, in Ranbaxy's opinion, that there is any risk of a medication error occurring between MAXAQUIN and [redacted] because of differences in the marks. The only portions of the marks that are similar (not identical) are the prefixes [redacted] v. "maxa"). They share this similarity with several of the other pharmaceutical products noted by OPDRA in this deficiency letter. The repeated use on numerous pharmaceutical products requires both prescribers and pharmacists to rely upon other components of the respective brand names to distinguish the products from each other. In this case, the suffixes are completely different ("quin" v. [redacted]) and serve to distinguish the products from each other. While we recognize that the Committee may recommend against the use of a mark even where, as in the Celebrex case, there is a difference in suffix, those cases typically involve a prefix which is distinctive. In this case, because the prefix "maxi" or "maxa" is weak, both prescribers and pharmacists must look to the more distinctive portions of the mark to distinguish the products from one another even if the distinctive portion is the suffix rather than prefix.

In addition, as noted in arguments above, Ranbaxy's mark includes the suffix [redacted] This suffix further distinguishes the mark [redacted] from MAXAQUIN and eliminates the risk of a medication error occurring between these two drug products.

DMETS Comments:

DMETS agrees with the sponsor that when evaluating the proprietary name [redacted] in its entirety, the [redacted] modifier may decrease the potential risk of a medication error occurring between [redacted] and *Maxaquin*. However, after examining the information supplied by the sponsor and reevaluation of the *Maxaquin* name, DMETS agrees with the sponsor that the potential risk of a medication error between [redacted] and *Maxaquin* is low.

4. *Sponsor's Macrobid Comments:*

Reviewing the facts presented and the conclusions reached by OPDRA regarding MACROBID, we agree that the situation is analogous to the concerns expressed by OPDRA regarding simultaneous use of the marks [redacted] and AMOXAPINE and Ranbaxy believes that there is virtually no potential risk of a medical error occurring between these two products for the same reason discussed in the section of this response letter directed to AMOXAPINE.

Specifically, there is no risk of a medication error because differences in the marks, particularly when the marks are considered in their entirety, and the lack of any overlapping tablet strength will avoid any likelihood of medication error.

Considering first the product names, the prefix "macro" and the prefix [redacted] are considerably different in appearance, sound and meaning even when the word is written in script form. While they do share the syllable [redacted] the [redacted] product also includes the suffix [redacted] which does not appear in the writing sample. Ranbaxy believes that the addition of the [redacted] suffix further distinguishes the marks and avoids any risk of medication error.

In addition to differences in the marks serving as a barrier to a medication error, the lack of overlapping dosage would make in even less likely for a medication error to occur. While we imagine it is hypothetically possible for a pharmacist to confuse an order calling for a 200 mg capsule twice a day to be two 100 mg capsules twice a day, it does not seem likely that this situation could ever occur in view of the differences between the product names. To the contrary, in any circumstance where a party could mistakenly substitute MACROBID for [redacted], the dosage differences would likely cause the pharmacist to question the prescription with the prescriber.

Because of the differences between the product names [redacted] and MACROBID, as well as a lack of overlapping dosage amounts, Ranbaxy believes the potential risk of a medication error occurring between these two drug products is extremely low.

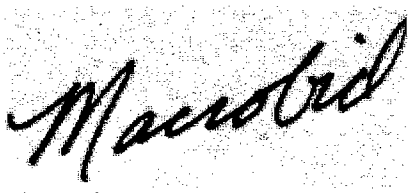
DMETS Comments:

DMETS agrees with the sponsor that when evaluating the proprietary name [redacted] in its entirety, the [redacted] modifier may decrease the potential risk of a medication error occurring between [redacted] and *Macrobid*. However, according to section B of this review, it is possible that a prescriber may omit the [redacted] modifier when writing a prescription for [redacted]. Without the [redacted] modifier, *Macrobid* and [redacted] can sound and look similar. *Macrobid* and [redacted] sound similar since both contain 3 syllables, begin with the "m" sound, have an internal "k" sound ("makro-" vs. "moksi-"), and have the same suffix ("-[redacted]. They also share the same route of administration (oral) and have the same dosage schedule (twice a day). *Macrobid* may also look similar to [redacted] (see below). Even though there are no overlapping strength, DMETS agrees with the sponsor that it is "possible for a pharmacist to confuse an order calling for a 200 mg capsule twice a day to be two 100 mg capsules twice a day." Also, the total daily dose of a nitrofurantoin product is 400 mg while [redacted] may also be given as a total daily dose of 400 mg. As stated in the *Amoxapine* comment, a pharmacist does not need to contact the prescriber to obtain permission to give

enough of the lower strength to equal the amount of the intended dose. Even though the proprietary name is [redacted], the proprietary name in the writing sample below is written as " [redacted] since a prescriber may omit the [redacted] modifier due to a variety of reasons as mentioned in section B "Modifier [redacted]

Writing Sample:

[redacted]



Macrobid

In summary, DMETS does not agree with the sponsor's choice of the modifier [redacted] since it can be misinterpreted as another abbreviation. The sponsor may choose to use a different modifier that would address this concern. However, use of any modifier will not address DMETS concerns pertaining to potential name confusion between [redacted] without the strength and/or modifier and Maxifed (DM), Amoxapine, or Macrobid. Therefore, DMETS does not recommend the use of the proprietary name [redacted]

2. CONTAINER: 200 mg – 20s and 1000s
   400 mg – 20s and 500s

   a. Differentiate the text, "DISSOLVE ... INGESTION" from the other bolded text on the front panel by using bold italic print and/or a different color. In addition, revise "TABLET" to read "TABLET FOR ORAL SUSPENSION".

   b. Left side panel

      Revise "Each tablet ..." to read "Each tablet for oral suspension".

   c. Right side panel

      Revise "Directions" to read as follows:

      Directions for Use

      [redacted]

3. CARTON: 200 mg and 400 mg – 100s unit dose

   See comments under CONTAINER.

4. INSERT

   a. CLINICAL PHARMACOLOGY

      Your pharmaockinetic data listed in your insert labeling is not consistent with the data from your pharmacokinetic studies. Please explain and revise accordingly.

   b. DOSAGE AND ADMINISTRATION

      i. Add the following as the first sentence:

         Amoxicillin may be given without regard to meals.

ii. Directions for Amoxicillin Tablets for Oral Suspension:

Revise this subsection to read as follows.

Dissolve one tablet in [redacted] drink the entire [redacted] Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.

ii. After further review we request that you provide a "Patient Information Sheet" with "Directions for Use" instead of a "Patient Package Insert".

PATIENT'S DIRECTIONS FOR USE

Dissolve the Dispermox tablet in water before you take it.

1. Remove one tablet from the bottle
2. Place the tablet in a glass with [redacted] of water.
3. Swirl or stir until the tablet is completely dissolved.
4. Drink the mixture immediately after mixing. (The mixture is pink colored and has a strawberry flavor.)
5. Be sure to drink the entire mixture.
6. Rinse the glass with [redacted] water [redacted]

DO NOT CHEW or SWALLOW the Dispermox tablets whole. The tablets will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

Do not mix Dispermox with any liquid other than water.

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.

/S/

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

APPEARS THIS WAY
ON ORIGINAL

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

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 500s (400 mg) and 1000s (200 mg)

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Amoxil® for Oral Suspension
ANDA Number: 62-226
ANDA Drug Name: Amoxil® (amoxicillin trihydrate) for Oral Suspension
ANDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 5/16/00 (S-002)[NDA 50-754]
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:
Basis of Approval for the Carton Labeling:
Other Comments: The RLD is an ANDA but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

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 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?		X	
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 OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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)		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?		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	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.			

APPEARS THIS WAY
ON ORIGINAL

NOTE TO BIO. REVIEWER:

The firm's revised the CLINICAL PHARMACOLOGY section reads as follows:

The following pharmacokinetic data is from Ranbaxy's study of Dispermox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL. The dispersed mixture of Dispermox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspension. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg Dispermox tablets result in average peak blood levels 1 to 2 hours after administration in the range of
3.2 mcg/mL to [redacted]
Oral administration of singe doses of 400 mg DisperMox tablets and 400 mg/5 mL conventional suspension to 24 adult volunteers yield comparable pharmacokinetic data:

Dose*	AUC (mcg.hr/mL)	Cmax (mcg/mL)**
Amoxicillin	Amoxicillin	Amoxicillin
400 mg (5 mL of suspension)	18.6	8.4
400 mg (one dispersible tablet)	17.9	7.5

*Dosing was following an overnight fast
**Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

-Previously you informed me that "The range noted for Dispermox tablet should read as "3.2 mcg/ml to 11.5 mcg/ml" instead of "3.2 mcg/ml to [redacted] Before I request this revision. Do you concur with all of the pharmacokinetic data listed above?

-Is the firm's average peak blood level 1 to 2 hours or approximately [redacted]. [See conflicting text above].

Bio. reviewer response:
The pharmacokinetic parameters are not accurate. [C.K.]

Additional question [new]

The Cmax listed in the insert labeling of the innovator for the amoxicillin suspension dosage form [Amoxil] is reported to be 5.92 mcg/mL.
Ranbaxy's insert labeling reports the Cmax for the innovator's amoxicillin suspension dosage form [Amoxil] to be 8.4 mcg/mL. Is this difference acceptable?

Thanks for your assistance.

NOTE TO THE CHEMIST:

DOSAGE AND ADMINISTRATION section

The firm revised their Directions which previously read, ".. [redacted] to read "[redacted]

[redacted]. Do not chew or swallow the tablets.

Did Ranbaxy provide additional data to support their revised directions?

Chemist response:

[Ganunis, Ruth M] This change in dispersion volume is ok, since a suspension and not a solution is formed.

Jackie -

To be more specific about the actual data submitted - in the chemistry section the data covered the range 50 ml to 120 ml. However, the bio-study review says that the tablets were dispersed in 10 ml for administration. I believe that 1 tablespoon is 15 ml, so we know that the tablets do disperse over the revised range.

Ruth

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Reference Listed drug: Amoxil (amoxicillin for oral suspension)/NDA 50-542/S-017, approved 5/16/2000
   NOTE: The most recent approved labeling for NDA 50-542/S-016/approved 4/10/02 is not currently available. After numerous attempts to obtain a hard copy and/or electronic copy from the Division of Anti-Infective Drug Products, we were informed that neither is available. Therefore, an Office decision was made to continue to use the approved insert labeling from S-017 as the labeling model for this drug product.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer: Ranbaxy, India.

4. Package Size:

   Both strengths will be available in UD 100s. The 200 mg tablets will be available in 1000s and the 400 mg tablets will be available in 500s.

   In the submission dated May 22, 2001, the firm added a package size of 20s for the 200 mg and 400 mg drug product.

5. Storage/dispensing recommendations

   Store at controlled room temperature 15o to 30oC (59o to 86oF)(see USP). Dispense in a tight container.

6. I was not able to verify the tablet descriptions as seen in the HOW SUPPLIED section.

7. The firm was asked that all information in the CLINICAL PHARMACOLOGY section not relating to this drug product be replaced by product specific information.

8. After discussion with J. Lee and C. Kim of BIO, it was determined that despite the fact that there are food references in the Amoxicillin RLD insert BIO has a policy stating that no food studies will be requested of any generic Amoxicillin applicant no matter what the dosage form. [Noted from previous review].

9. Container/Closure:

Strength	***Package size***	***Bottle type***	***Closure***
200 mg	20s	HDPE	CRC
200 mg	1000s	HDPE	Non CRC
200 mg	100s unit dose	Aluminum foil/laminate	
400 mg	20s	HDPE	CRC
400 mg	500s	HDPE	Non CRC
400 mg	100s unit dose	Aluminum foil/laminate	

[Vol. B2.1, p. 26-29]

10. Unit dose blisters container labels and carton labeling are satisfactory in printer's proof, providing the proposed established and proprietary names are found acceptable.

11. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement.
[Vol. B1.2, p. 1037]

12. The firm's physical description of each dispersible tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor.
[Vol. B1.4, p. 2106, 2107]

13. A meeting was held to discuss the conditions of use of this ANDA. The Regulatory Branch informed us that since this drug product was found to be acceptable for filing under a petition, the drug product is not required to meet all the same conditions of use as the reference listed drug. Therefore, the dispersible tablet labeling can differ from the reference listed drug and should include statements that indicate that their drug product use is limited due to the dispersible tablet dosage form.

We have requested the firm to add the following statement as the first paragraph of the DOSAGE AND ADMINISTRATION section.

> All recommended dosages for amoxicillin are included in this section for informational purposes only. The 200 mg dispersible tablet is appropriate only for a 200 mg dose and the 400 mg dispersible tablet is appropriate only for a 400 mg dose.

14. - CONTAINER:

- 200 mg – 20s and 100s
- 400 mg - 20s and 500s

  Satisfactory in draft as of the October 15, 2001, submission.
  [NOTE: Pending OPDRA recommendations].
- Unit dose blister

  Satisfactory in draft as of the May 22, 2001, submission.
  [NOTE: Pending OPDRA recommendations].

- CARTON: 100s unit dose

  Satisfactory in draft as of the October 15, 2001, submission.
  [NOTE: Pending OPDRA recommendations].

15. We previously asked the firm the following:

> We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

Firm's response:

If the amoxicillin dispersible tablet is inadvertently chewed it will form a soft mass. The drug product if chewed will not behave any differently from the dispersed mixture or if swallowed whole.

16. In the February 13, 2002, submission the firm's indicates, "that per their last telephone communications with the USP [January 2002] the drug product established name as proposed to the USP and the inclusion of the Amoxicillin Dispersible Tablets as a USP monograph is still in process and has not as yet been published in the Pharmaceutical Forum".

17. Previous NOTES TO BIO/CHEMIST:

NOTE TO CHEMIST

The firm's dosage form contains strawberry flavor. They indicate in their proposed patient package insert that "strawberry flavor can be taken by patients that are allergic to strawberries. Please refer to page 004 and attachment 3 in their February 13, 2002, submission.

Do you concur with firm's statement or do you know how we can verify this?

> ***[Ganunis, Ruth M]*** The supplier of Artificial Strawberry-Guarana Flavor [redacted] provides a statement that "to the best of our knowledge and belief, the above referenced product does not contain strawberries or derivatives of strawberries (attachment 2, 2/13/02 amendment)." Since we accept supplier certifications for other things (such as absence of solvents or compatibility of container closure systems), I believe that we can accept it here.

NOTE TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section read as follows:

> The following pharmacokenetic data is from Ranbaxy's study of Dispermox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL. The dispersed mixture of Dispermox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspension. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg Dispermox tablets result in average peak blood levels 1 to 2 hours after administration in the range of 3.2 mcg/mL to [redacted]

Is the information provided in firm's revised paragraph accurate?
[Note, previously the firm included a range of "3.9 mcg/mL to 11.5 mcg/mL and 3.3 mcg/mL to 7 mcg/mL" for amoxcillin suspension and a range of [redacted] for the dispersible tablet].

Thanks for your assistance.

Bio Comment

The range noted for amoxicillin suspension is correct.
The range noted for Dispermox tablet should read as "3.2 mcg/ml to 11.5 mcg/ml" instead of "3.2 mcg/ml ot [redacted]

Thanks
Carol

18. Patient Package Insert

- The Labeling Review Branch requested Ranbaxy to provide a PPI. The proposed PPI was forwarded to the Division of Anti-Infective Drug Products. The Division decided not to respond to the consult because they did not have an approved NDA for this new proposed "dosage form".

- The Office of Drug Safety also requested that firm provide separate instructions for the patient.

- An Office decision was made to request Ranbaxy to provide a "Patient Information Sheet" with "Directions for Use" instead of a "Patient Package Insert". The text for the "Directions for Use" was reviewed by Dr. Hixon in response to the Labeling Consult. In addition, it was agreed to replace ".. [redacted] ..." with "... a glass of water...".
[See consult response].

19. DOSAGE AND ADMINISTRATION section

The updated text requested in this review is from Dr. Hixon's response to the Labeling Consult [See consult response].

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 7/8/02 [Updated 10/3/02]

Date of Submission: 5/30/02

Primary Reviewer:
Jacqueline Council, Pharm.D. /S/ Date: 10-10-02

Acting Team Leader:
Captain Lillie Golson /S/ Date: 10/11/02

cc: ANDA: 65-080
DUP/DIVISION FILE
HFD-613/JCouncil/CHoppes (no cc)
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Review

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

ANDA Number:	65-080
Date of Submission:	May 30, 2002
Applicant's Name:	Ranbaxy Laboratories Limited
Established Name:	Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg
Proprietary Name:	Dispermox™

Labeling Deficiencies:

1. GENERAL COMMENT

Upon further review and in consultation with the Office of Counter-Terrorism and Pediatric Drug Development (HFD-950), please make the following changes to your labels and labeling:

a. Revise the "Directions for Use" to read:

[redacted] **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

b. Replace "dissolve" with '[redacted] throughout your labeling.

c. PATIENT INFORMATION SHEET

PATIENT'S DIRECTIONS FOR USE

[redacted] Dispermox tablet in water before you take it.

1. Remove one tablet from the bottle
2. Place the tablet in [redacted] water [redacted]
3. Swirl or stir until [redacted]
4. Drink the mixture immediately after mixing. (The mixture is pink colored and has a strawberry flavor.)
5. Be sure to drink the entire mixture.
6. Rinse the [redacted] with an additional [redacted] of water and drink the contents to assure the whole dose is taken.

DO NOT CHEW or SWALLOW the Dispermox tablets whole. The tablets will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

Do not mix Dispermox with any liquid other than water.

In addition, please revise your storage temperature recommendation to read: "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

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

APPEARS THIS WAY
ON ORIGINAL

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

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 500s (400 mg) and 1000s (200 mg)

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Amoxil® for Oral Suspension
ANDA Number: 62-226
ANDA Drug Name: Amoxil® (amoxicillin trihydrate) for Oral Suspension
ANDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 5/16/00 (S-002)[NDA 50-754]
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:
Basis of Approval for the Carton Labeling:
Other Comments: The RLD is an ANDA but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

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 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?		X	
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 OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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)		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?		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	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.			

NOTE TO BIO. REVIEWER:

The firm's revised the CLINICAL PHARMACOLOGY section reads as follows:

The following pharmacokinetic data is from Ranbaxy's study of Dispermox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL. The dispersed mixture of Dispermox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspension. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg Dispermox tablets result in average peak blood levels 1 to 2 hours after administration in the range of 3.2 mcg/mL to [redacted]
Oral administration of singe doses of 400 mg DisperMox tablets and 400 mg/5 mL conventional suspension to 24 adult volunteers yield comparable pharmacokinetic data:

Dose*	AUC (mcg.hr/mL)	Cmax (mcg/mL)**
Amoxicillin	Amoxicillin	Amoxicillin
400 mg (5 mL of suspension)	18.6	8.4
400 mg (one dispersible tablet)	17.9	7.5

*Dosing was following an overnight fast
**Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

-Previously you informed me that "The range noted for Dispermox tablet should read as "3.2 mcg/ml to 11.5 mcg/ml" instead of "3.2 mcg/ml to [redacted] . Before I request this revision. Do you concur with all of the pharmacokinetic data listed above?

-Is the firm's average peak blood level 1 to 2 hours or approximately 1 hour? [See conflicting text above].

Bio. reviewer response:
The pharmacokinetic parameters are not accurate. [C.K.]

Additional question [new]

The Cmax listed in the insert labeling of the innovator for the amoxicillin suspension dosage form [Amoxil] is reported to be 5.92 mcg/mL.
Ranbaxy's insert labeling reports the Cmax for the innovator's amoxicillin suspension dosage form [Amoxil] to be 8.4 mcg/mL. Is this difference acceptable?

Thanks for your assistance.

NOTE TO THE CHEMIST:

DOSAGE AND ADMINISTRATION section

The firm revised their Directions which previously read, "... [redacted] to read ' [redacted]

Did Ranbaxy provide additional data to support their revised directions?

Chemist response:
[Ganunis, Ruth M] This change in dispersion volume is ok, since a suspension and not a solution is formed.

Jackie -

To be more specific about the actual data submitted - in the chemistry section the data covered the range 50 ml to 120 ml. However, the bio-study review says that the tablets were dispersed in 10 ml for

administration. I believe that 1 tablespoon is 15 ml, so we know that the tablets do disperse over the revised range.

Ruth

FOR THE RECORD:

1. Reference Listed drug: Amoxil (amoxicillin for oral suspension)/NDA 50-542/S-017, approved 5/16/2000
   NOTE: The most recent approved labeling for NDA 50-542/S-016/approved 4/10/02 is not currently available. After numerous attempts to obtain a hard copy and/or electronic copy from the Division of Anti-Infective Drug Products, we were informed that neither is available. Therefore, an Office decision was made to continue to use the approved insert labeling from S-017 as the labeling model for this drug product.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer: Ranbaxy, India.

4. Package Size:

   Both strengths will be available in UD 100s. The 200 mg tablets will be available in 1000s and the 400 mg tablets will be available in 500s.

   In the submission dated May 22, 2001, the firm added a package size of 20s for the 200 mg and 400 mg drug product.

5. Storage/dispensing recommendations

   RLD: Store at or below 70° C (68° F)

   ANDA: Store at controlled room temperature 15° to 30° C (59° to 86° F)(see USP). Dispense in a tight container. [The firm has been requested to revise this statement].

6. I was not able to verify the tablet descriptions as seen in the HOW SUPPLIED section.

7. The firm was asked that all information in the CLINICAL PHARMACOLOGY section not relating to this drug product be replaced by product specific information.

8. After discussion with J. Lee and C. Kim of BIO, it was determined that despite the fact that there are food references in the Amoxicillin RLD insert BIO has a policy stating that no food studies will be requested of any generic Amoxicillin applicant no matter what the dosage form. [Noted from previous review].

9. Container/Closure:

Strength	*Package size*	*Bottle type*	*Closure*
200 mg	20s	HDPE	CRC
200 mg	1000s	HDPE	Non CRC
200 mg	100s unit dose	Aluminum foil/laminate	
400 mg	20s	HDPE	CRC
400 mg	500s	HDPE	Non CRC
400 mg	100s unit dose	Aluminum foil/laminate	

[Vol. B2.1, p. 26-29]

10. Unit dose blisters container labels and carton labeling are satisfactory in printer's proof, providing the proposed established and proprietary names are found acceptable.

11. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement.
[Vol. B1.2, p. 1037]

12. The firm's physical description of each dispersible tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor.
[Vol. B1.4, p. 2106, 2107]

13. A meeting was held to discuss the conditions of use of this ANDA. The Regulatory Branch informed us that since this drug product was found to be acceptable for filing under a petition, the drug product is not required to meet all the same conditions of use as the reference listed drug. Therefore, the dispersible tablet labeling can differ from the reference listed drug and should include statements that indicate that their drug product use is limited due to the dispersible tablet dosage form.

We have requested the firm to add the following statement as the first paragraph of the DOSAGE AND ADMINISTRATION section.

> All recommended dosages for amoxicillin are included in this section for informational purposes only. The 200 mg dispersible tablet is appropriate only for a 200 mg dose and the 400 mg dispersible tablet is appropriate only for a 400 mg dose.

14. We previously asked the firm the following:

> We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

Firm's response:

If the amoxicillin dispersible tablet is inadvertently chewed it will form a soft mass. The drug product if chewed will not behave any differently from the dispersed mixture or if swallowed whole.

15. In the February 13, 2002, submission the firm's indicates, "that per their last telephone communications with the USP [January 2002] the drug product established name as proposed to the USP and the inclusion of the Amoxicillin Dispersible Tablets as a USP monograph is still in process and has not as yet been published in the Pharmaceutical Forum".

16. Previous NOTES TO BIO/CHEMIST:

NOTE TO CHEMIST

The firm's dosage form contains strawberry flavor. They indicate in their proposed patient package insert that "strawberry flavor can be taken by patients that are allergic to strawberries. Please refer to page 004 and attachment 3 in their February 13, 2002, submission.

Do you concur with firm's statement or do you know how we can verify this?

[Ganunis, Ruth M] The supplier of Artificial Strawberry-Guarana Flavor [redacted] provides a statement that "to the best of our knowledge and belief, the above referenced product does not contain strawberries or derivatives of strawberries (attachment 2, 2/13/02 amendment)." Since we accept supplier certifications for other things (such as absence of solvents or compatibility of container closure systems), I believe that we can accept it here.

NOTE TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section read as follows:

The following pharmacokenetic data is from Ranbaxy's study of Dispermox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL. The dispersed mixture of Dispermox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspension. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg Dispermox tablets result in average peak blood levels 1 to 2 hours after administration in the range of 3.2 mcg/mL to [redacted]

Is the information provided in firm's revised paragraph accurate?
[Note, previously the firm included a range of "3.9 mcg/mL to 11.5 mcg/mL and 3.3 mcg/mL to 7 mcg/mL" for amoxcillin suspension and a range of [redacted] for the dispersible tablet].

Thanks for your assistance.

Bio Comment

The range noted for amoxicillin suspension is correct.
The range noted for Dispermox tablet should read as "3.2 mcg/ml to 11.5 mcg/ml" instead of "3.2 mcg/ml ot [redacted]

Thanks
Carol

17. Patient Package Insert

- The Labeling Review Branch requested Ranbaxy to provide a PPI. The proposed PPI was forwarded to the Division of Anti-Infective Drug Products. The Division decided not to respond to the consult because they did not have an approved NDA for this new proposed "dosage form".

- The Office of Drug Safety also requested that firm provide separate instructions for the patient.

- An Office decision was made to request Ranbaxy to provide a "Patient Information Sheet" with "Directions for Use" instead of a "Patient Package Insert". The text for the "Directions for Use" was reviewed by Dr. Hixon in response to the Labeling Consult. In addition, it was agreed to replace ".. [redacted] .." with "... a glass of water...".
[See consult response].

18. DOSAGE AND ADMINISTRATION section

The updated text requested in this review is from Dr. Hixon's response to the Labeling Consult [See consult response].

19. The labeling review of the firm's May 30, 2003, submission was based on decisions made in a meeting on June 10, 2003, between OGD and the Office of Counter-Terrorism and Pediatric Drug Development (HFD-950). See labeling revisions below and related e-mails in the file folder.

The following decisions effects the labeling:

- Cephalexin and cefaclor are to be scored.
- Amoxicillin sholud not to be scored.
- Update the bolded statements "... for informational purposes ... to reflect with the 1/2 tablet wording. [Cephalexin and cefaclor]
- Amount of water: 2 teaspoonfuls
- Include the statement, "Entire amount should be swallowed".
- Keep the statement "only mix with water"

The firm has been requested the following:

a. Revise the "Directions for Use" to read:

[redacted] **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

b. Replace "dissolve" with "mix" throughout your labeling.

c. PATIENT INFORMATION SHEET

PATIENT'S DIRECTIONS FOR USE

[redacted] Dispermox tablet in water before you take it.

1. Remove one tablet from the bottle
2. Place the tablet in a [redacted] water [redacted]
3. Swirl or stir until [redacted]
4. Drink the mixture immediately after mixing. (The mixture is pink colored and has a strawberry flavor.)
5. Be sure to drink the entire mixture.
6. Rinse the [redacted] with an additional [redacted] of water and drink the contents to assure the whole dose is taken.

DO NOT CHEW or SWALLOW the Dispermox tablets whole. The tablets will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

Do not mix Dispermox with any liquid other than water.

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 6/30/03

Date of Submission: 5/30/02

/S/

Primary Reviewer:
Jacqueline Council, Pharm.D.

Date: 2-12-03

Team Leader:
Captain Lillie Golson

Date:

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cc: ANDA: 65-080
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSNZ\RANBAXY\LTRS&REV\65080na7.l.doc
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number:	65-080
Date of Submission:	February 13, 2002
Applicant's Name:	Ranbaxy Laboratories Limited
Established Name:	Amoxicillin Tablets USP, [Dispersible] 200 mg and 400 mg
Proprietary Name:	Dispermox™

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Your appeal for your proposed proprietary name ... [redacted] submitted with this amendment has been forwarded to the Office of Drug Safety for their review and comment. We will inform you of their findings when available.

   b. We acknowledge your comments regarding the status of your communications with the USP in reference to your proposed drug product's established name.

   c. We acknowledge that you plan to provide one patient package insert on the top of each bottle of 20s and five in each unit dose carton of 100s. Also, that you plan to consult with our Office regarding the addition of the Patient Package Inserts to your package sizes of 500s and 1000s prior to marketing.

   d. We acknowledge your plans to provide a Dear Pharmacist letter to introduce your new dispersible tablet delivery system and to provide the pharmacist with a Patient Package Insert as well as a contact number for re-ordering.

   e. Your proposed Patient Package Insert has been forwarded to the Division of Anti-Infective Drug Products for their review and comment. We will inform you of their findings when available.

2. CONTAINER: 200 mg – 20s and 1000s
   400 mg – 20s and 500s

   Directions

   Revise to read, "... of water in a glass, [redacted]

3. CARTON: 200 mg and 400 mg – 100s unit dose

   See comment under CONTAINER.

4. INSERT

   a. GENERAL COMMENTS

      i. Improve the readability of your insert.

      ii. Delete the [redacted] following a decimal point, [i.e., "3" instead of "[redacted]

   b. CLINICAL PHARMACOLOGY

      i. We encourage the inclusion of the following as the second paragraph for informational and comparative purposes for health care providers:

Orally administered doses of 250 mg and 500 mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 mcg/mL to 5 mcg/mL and 5.5 mcg/mL to 7.5 mcg/mL, respectively.

ii. Relocate the paragraph, "Mean amoxicillin pharmacokinetic ... fast" to appear immediately prior to the paragraph, "Conventional amoxicillin chewable ... respectively".

iii. Revise the paragraph, "Mean amoxicillin pharmacokinetic ... fast" to read, "Mean amoxicillin pharmacokinetic ... 875 mg conventional tablet of ... fast".

c. PRECAUTIONS - Information for Patients

i. We note that you have added two new paragraphs [without an explanation], which are not listed in the insert labeling of the reference listed drug. In addition, the second sentence of the first paragraph refers to patients treated with cephalosporins. Delete these paragraphs and/or comment.

ii. Include a statement indicating that a "Patient Package Insert" is provided with your drug product. We refer you to 21 CFR 201.57 (f)(2).

d. DOSAGE AND ADMINISTRATION

We acknowledge that you deleted the text, [redacted] Therefore, we encourage you to add a statement that water is the only recommended liquid for dispersion, since amoxicillin suspension may be given in other liquids, formula, milk, fruit juice, ginger ale and cold drinks."

Please revise insert labeling, as instructed above, and submit in draft. We will not request final printed labeling until resolution of the established name issue and your proposed patient information.

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

APPEARS THIS WAY
ON ORIGINAL

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

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 500s (400 mg) and 1000s (200 mg)

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Amoxil® for Oral Suspension
ANDA Number: 62-226
ANDA Drug Name: Amoxil® (amoxicillin trihydrate) for Oral Suspension
ANDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 5/16/00 (S-002)[NDA 50-754]
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:
Basis of Approval for the Carton Labeling:
Other Comments: The RLD is an ANDA but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

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? 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 OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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)		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?		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	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.			

NOTE/QUESTION TO CHEMIST

The firm's dosage form contains strawberry flavor. They indicate in their proposed patient package insert that "strawberry flavor can be taken by patients that are allergic to strawberries. Please refer to page 004 and attachment 3 in their February 13, 2002, submission.

Do you concur with firm's statement or do you know how we can verify this?

NOTE/QUESTION TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section read as follows:

> The following pharmacokenetic data is from Ranbaxy's study of Dispermox tablets and conventional amoxicillin oral suspension, 400 mg/5 mL. The dispersed mixture of Dispermox tablets, 400 mg, produced blood levels similar to those achieved with the corresponding doses of conventional amoxicillin oral suspension. Orally administered doses of conventional amoxicillin suspension, 400 mg/5 mL, result in average peak blood levels 1 to 2 hours after administration in the range of 3.3 mcg/mL to 11.5 mcg/mL. Orally administered doses of 400 mg Dispermox tablets result in average peak blood levels 1 to 2 hours after administration in the range of 3.2 mcg/mL to [redacted]

Is the information provided in firm's revised paragraph accurate?
[Note, previously the firm included a range of "3.9 mcg/mL to 11.5 mcg/mL and 3.3 mcg/mL to 7 mcg/mL" for amoxcillin suspension and a range of " [redacted] for the dispersible tablet].

Thanks for your assistance.

NOTE TO THE CHEMIST: [from previous review]

DOSAGE AND ADMINISTRATION section

The firm revised their Directions which previously read, ". [redacted] to read "

Did Ranbaxy provide additional data to support their revised directions?

NOTE TO BIO. [previous]

The firm revised the CLINICAL PHARMACOLOGY section of their insert labeling. Is the revised text in the second and fourth paragraphs accurate?

Is data in Table 2 accurate as well as, the text immediately prior to Table 2 and immediately following Table 2?

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. The RLD is an ANDA (Amoxil® for Oral Suspension) but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer: Ranbaxy, India.

4. Package Size:

   Both strengths will be available in UD 100s. The 200 mg tablets will be available in 1000s and the 400 mg tablets will be available in 500s.

   In the submission dated May 22, 2001, the firm added a package size of 20s for the 200 mg and 400 mg drug product.

5. Storage/dispensing recommendations

   Store at controlled room temperature 15o to 30oC (59o to 86oF)(see USP). Dispense in a tight container.

6. I was not able to verify the tablet descriptions as seen in the HOW SUPPLIED section.

7. The firm was asked that all information in the CLINICAL PHARMACOLOGY section not relating to this drug product be replaced by product specific information.

8. After discussion with J. Lee and C. Kim of BIO, it was determined that despite the fact that there are food references in the Amoxicillin RLD insert BIO has a policy stating that no food studies will be requested of any generic Amoxicillin applicant no matter what the dosage form. [Noted from previous review].

10. In the submission dated May 22, 2001, the firm has revised a combined insert to include the conventional tablet and the chewable tablet dosage forms.

11. Ranbaxy acknowledged the following comments in their submission dated May 22, 2001.

    - Your proposed proprietary name ([redacted]) and your dose form trademark ([redacted]) have been forwarded to the Office of Post-Marketing Drug Risk Assessment for their review and comment. We will inform you of their findings when available. We will not ask for labels and labeling in final print until we receive input on the acceptablity of these proposals.

    - We note that no product is currently marketed nor is there a USP monograph with the established name that you have proposed with this application. We recommend that you contact the USP regarding your proposed drug product and keep our office apprised of recommendations from the USP including recommendations regarding the established name of your drug product.

12. Container/Closure:

Strength	***Package size***	***Bottle type***	***Closure***
200 mg	20s	HDPE	CRC
200 mg	1000s	HDPE	Non CRC
200 mg	100s unit dose	Aluminum foil/laminate	
400 mg	20s	HDPE	CRC
400 mg	500s	HDPE	Non CRC
400 mg	100s unit dose	Aluminum foil/laminate	

[Vol. B2.1, p. 26-29]

13. Unit dose blisters container labels and carton labeling are satisfactory in printer's proof, providing the proposed established and proprietary names are found acceptable.

14. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement.
[Vol. B1.2, p. 1037]

15. The firm's physical description of each dispersible tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED].

[Vol. B1.4, p. 2106, 2107]

16. A meeting was held to discuss the conditions of use of this ANDA. The Regulatory Branch informed us that since this drug product was found to be acceptable for filing under a petition, the drug product is not required to meet all the same conditions of use as the reference listed drug. Therefore, the ——— tablet labeling can differ from the reference listed drug and should include statements that indicate that their drug product use is limited due to the ——— tablet dosage form.

We have requested the firm to add the following statement as the first paragraph of the DOSAGE AND ADMINISTRATION section.

> All recommended dosages for amoxicillin are included in this section for informational purposes only. The 200 mg ——— tablet is appropriate only for a 200 mg dose and the 400 mg ——— tablet is appropriate only for a 400 mg dose.

17. - CONTAINER:

- 200 mg – 20s and 100s
- 400 mg - 20s and 500s

  Satisfactory in draft as of the October 15, 2001, submission.
  [NOTE: Pending OPDRA recommendations].
- Unit dose blister

  Satisfactory in draft as of the May 22, 2001, submission.
  [NOTE: Pending OPDRA recommendations].

- CARTON: 100s unit dose

  Satisfactory in draft as of the October 15, 2001, submission.
  [NOTE: Pending OPDRA recommendations].

18. We previously asked the firm the following:

> We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

Firm's response:

If the amoxicillin ——— tablet is inadvertently chewed it will form a soft mass. The drug product if chewed will not behave any differently from the dispersed mixture or if swallowed whole.

19. In the February 13, 2002, submission the firm's indicates, "that per their last telephone communications with the USP [January 2002] the drug product established name as proposed to the USP and the inclusion of the Amoxicillin ——— Tablets as a USP monograph is still in process and has not as yet been published in the Pharmaceutical Forum".

APPEARS THIS WAY
ON ORIGINAL

Date of Review: 3/5/02

Primary Reviewer:
Jacqueline Council, Pharm.D. /S/ Date: 3-11-02

Team Leader: /S/ Date: 3/11/02

cc: ANDA: 65-080
DUP/DIVISION FILE
HFD-613/JCouncil/CHoppes (no cc)
V:\FIRMSNZ\RANBAXY\LTRS&REV\65080na5.I.doc
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **65-080**

Date of Submission: **October 15, 2001**

Applicant's Name: **Ranbaxy Pharmaceuticals Inc.**

Established Name: **Amoxicillin Tablets [redacted] 200 mg and 400 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Your proposed proprietary names [redacted] have been forwarded to the Office of Post-Marketing Drug Risk Assessment for their review and comment. We will inform you of their findings when available. We will not ask for labels and labeling in final print until we receive input on the acceptability of these proposals.

   b. Please comment on the status of your communications with the USP regarding you proposed drug product established name.

   c. Since your drug product is a novel dosage form we request that you provide the following:

      A) Ten [redacted] tablets of each strength, in a container or pouch with your next amendment.

      B) Include a Patient Package Insert to be dispensed to patients along with your drug product. We refer you to 21 CFR 201.57 (f)(2). You may propose text for your Patient Package Insert; however, it should a minimum include at the following:

         - Step-by-step instructions for mixing
         - What liquids to use for mixing and which to avoid
         - When to take the dispersion after mixing
         - If for some reason the patient does not take immediately, how long can the patient keep dispersed mixture
         - What type of container should be used for administration
         - What volume should be used for dispersion of the tablets
         - Instructions regarding "DO NOT SWALLOW or CHEW ...
         - Storage recommendations
         - WARNINGS for Phenylketonurics

         In addition, please inform our Office of the following:

         - How many Patient Package Inserts you plan to provide with each package size and dosage form?
         - How you plan to provide the Patient Package Insert with your product?
         - Your plans for notifying pharmacists of your Patient Package Insert, to aid in assuring that a Patient Package Insert is dispensed to each patient.

   d. The Office of Post-Marketing Drug Risk Assessment (OPDRA) does not recommend the use of your proposed proprietary name [redacted] for reasons listed below.

      See also comments about your proposed dosage form trademark [redacted]

In reviewing the proprietary name "[redacted]", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names include *Maxidex, Maxipime, Maxiflor, Maxifed, Maxifed DM, Amoxapine, Maxaquin,* and *Macrobid.*

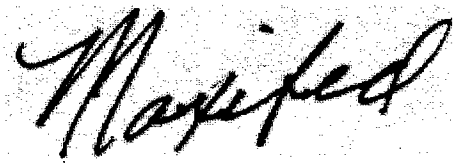
Maxidex is a dexamethasone suspension indicated for the treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. It is also used for treatment of corneal injury from chemical, radiation, or thermal burns or penetration of foreign bodies. It is available as a 0.1% suspension, 5 and 15 ml. *Maxidex* can sound similar to '[redacted]' depending on how one pronounces '[redacted]' (Mahk-si). The OPDRA study showed that the patients did interpret "[redacted]" as *Maxibid.* However, the "dex" of *Maxidex* may differentiate the two proprietary drug names. The '[redacted]' of "[redacted]" can be mistaken as "OD", the medical abbreviation for "both eyes", which would add to the confusion between the names since *Maxidex* is indicated for ophthalmic use. As for the directions of use, both prescriptions could be written as "Use as directed". Even though these two proprietary drug names share similar characteristics, they do differ in dosage forms (suspension vs. tablet), strengths (0.1% vs. 200 mg and 400 mg), and route of administration (topical vs. oral). Due to these differences, the potential risk of a medication error occurring between these two drug products is low.

Maxipime is the proprietary drug name for cefepime hydrochloride and is indicated for uncomplicated and complicated urinary tract infections, uncomplicated skin and skin structure infections, pneumonia, empiric therapy for febrile neutropenic patients, and complicated intra-abdominal infections. It is available in a powder for injection: 500 mg, 1 g, and 2g. *Maxipime* can sound like "[redacted]" depending on one's pronounciation of *Maxipime* (Mahk-si-pim). If a nurse transcribes a prescriber's verbal order for *Maxipime* 2000 mg, it may be mistakenly written down as "[redacted] 200 mg". However, the route of administration (IV vs. oral) and the dosage form (powder for injection vs. tablet) are different. *Maxipime* is also available in 500 mg and 1g while "[redacted]" is available in 400 mg in addition to the 200 mg. Due to these differences, the potential risk of a medication error occurring between these two drug products is low.

Maxiflor is the proprietary drug name for diflorasone diacetate, a corticosteroid, anti-inflammatory agent. It is available as an 0.05% ointment and cream. *Maxiflor* looks similar to "[redacted]" when scripted; however, both drug products differ in route of administration (topical vs. oral), strength (0.05% vs. 200 mg and 400 mg), dosage form (ointment and cream vs. tablet), and directions of use. Due to these differences, the potential risk of a medication error occurring between these two drug products is low.

Maxifed and *Maxifed DM* are proprietary drug names for pseudoephedrine/guaifenesin and pseudoephedrine/dextromethorphan/guaifenesin, repspectively, and are used as cold preparations. *Maxifed* and *Maxifed DM* look similar to "[redacted]" or "[redacted]" (see below) as well as sound similar. Since *Maxifed* and *Maxifed DM* are combination drug products, a prescriber may not indicate the strengths on a prescription. Even though '[redacted]' is available in two strengths (200 mg and 400 mg), a medication error can occur between '[redacted]' and *Maxifed/Maxifed DM* if the prescriber mistakenly leaves the strength off of the "[redacted]" prescription. Like *Maxifed/Maxifed DM*, [redacted] can also be given twice a day. Both drug products also have the same dosage form (tablet) and the same route of administration (oral). If a patient was given "[redacted]" instead of *Maxifed/Maxifed DM*, the patient's cold symptoms would not be treated. The patient would also be exposed to unnecessary side effects such as nausea, vomiting, and diarrhea. An allergic reaction (mild to anaphylactic) may occur if the patient was allergic to drugs in the penicillin drug category. If a patient received *Maxifed/Maxifed DM* instead of '[redacted]', then the patient's infection would not be treated. If the patient had high blood pressure or vascular disease, the *Maxifed/Maxifed DM* would exacerbate the condition due to the pseudoephedrine. Also, the patient would be exposed to unnecessary side effects such as nausea and dizziness.

Writing Sample:



Maxifed

Amoxapine is a tricyclic compound indicated for the relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions. It is indicated for depression accompanied by anxiety or agitation. *Amoxapine* is available as 25 mg, 50 mg, 100 mg, and 150 mg tablets. *Amoxapine* can sound like ' when it is interpreted as " For example, a prescriber may order a prescription by saying, "Calling in *Amoxapine* prescription," but the pharmacist may hear, "Calling in a prescription." Both the and *Amoxapine* can be given three times a day. Both have the same dosage form (tablet) and the same route of administration (oral). However, there are no overlapping strengths. *Amoxapine* is available in 100 mg. If a prescriber orders " 200 mg, 1 tablet 3 times a day, #14", a pharmacist may dispense "*Amoxapine* 100 mg, 2 tablets 3 times a day, #28." This would give the patient an overdose of a tricyclic antidepressant. By mistakenly taking *Amoxapine* instead of ' , the patient would be at risk for developing tardive dyskinesia as well as be exposed to unnecessary side effects such as drowsiness, dry mouth, constipation, and blurred vision. Also, *Amoxapine* should not be given to patients taking monoamine oxidase inhibitors. In addition, the patient would not be adequately treated for his/her infection. If " was dispensed instead of *Amoxapine*, the patient's depression would not be treated. The patient would also be exposed to unnecessary side effects such as nausea, vomiting, and diarrhea. An allergic reaction (mild to anaphylactic) may occur if the patient was allergic to drugs in the penicillin drug category.

Maxaquin is the proprietary name for lomefloxacin hydrochloride, a fluoroquinolone, which is indicated for susceptible strains in lower respiratory tract infections, urinary tract infections, and preoperative prevention of infection. It is available as a 400 mg capsule. *Maxaquin* sounds like due to the "Maxa" and ' respectively. The "quin" and may distinguish the two drug names. However, in the case of *Celebrex* and *Celexa*, both tradenames were confused with each other even though the endings of their names are different. In the case of *Maxaquin* and " , both have the same dosage form (tablet), both have the same route of administration (oral), and both share the same strength (400 mg). There would be a potential risk of a medication error occurring between these two drug products. If a patient received " instead of *Maxaquin*, the patient may not be adequately treated for his/her infection. The patient would also be exposed to unnecessary side effects such as nausea, vomiting, and diarrhea. An allergic reaction (mild to anaphylactic) may occur if the patient was allergic to drugs in the penicillin drug category. If a patient received *Maxaquin* instead of " , the patient may not be adequately treated for his/her infection. The patient would be exposed to unnecessary side effects such as phototoxic reactions, constipation, and vomiting.

Macrobid is the proprietary drug name for nitrofurantoin monohydrate/macrocrystals and is indicated for the treatment of acute uncomplicated urinary tract infections caused by susceptible strains of *Escherichia coli* or *Staphylococcus saprophyticus*. *Macrobid* is available as a 100 mg capsule. sounds and looks similar to *Macrobid*. There are no overlapping strengths between them. However, as in the above *Amoxapine* scenario, a pharmacist may mistakenly dispense "Macrobid 100 mg, take 2 capsules twice a day" instead of ' 200 mg, take 1 tablet twice a day." Both drug products

have the same route of administration (oral) and both can be given twice a day. If a patient receives [redacted] instead of *Macrobid*, the patient may not be adequately treated for his/her infection. The patient would also be exposed to unnecessary side effects such as nausea, vomiting, and diarrhea. An allergic reaction (mild to anaphylactic) may occur if the patient was allergic to drugs in the penicillin drug category. If a patient receives *Macrobid* instead of [redacted], the patient would not be adequately treated. The patient would be exposed to unnecessary side effects such as dizziness, diarrhea, and drowsiness.

Writing Sample:

Macrobid

OPDRA does not recommend using the modifier [redacted] since it can be misinterpreted as a medical abbreviation "OD" (right eye) and "QD" (once a day). It is not recommended to use medical abbreviations within or along with the proprietary name. If the pharmacist interprets the dosing directions as "once a day", the patient may be underdosed if the patient was suppose to take it 2 or 3 times a day. One respondent from the verbal portion of the OPDRA study interpreted the [redacted] as BD, which may stand for "twice daily". [redacted] could also be interpreted as "double dose", which could lead to an overdose of the medication. Also, using [redacted] and [redacted] together seems redundant. In the study conducted by OPDRA, 11 (13%) out of 86 respondents did not include the modifier in their interpretation of [redacted]. Since some prescribers may write a prescription for [redacted] instead of [redacted] the confusion between [redacted] and the above proprietary names would increase.

Also, [redacted] contains the medical abbreviation "[redacted], which indicates that the drug product is dosed twice a day. This would be misleading since amoxicillin can be dosed three times a day depending on the disease state and the patient's tolerability.

The Expert Panel expressed concerns that [redacted] could be confused with the currently available *PCE Dispertab*. *PCE Dispertab* (erythromycin particles in tablets) is supplied as 250 mg and 500 mg tablets. The similarity in [redacted] and *Dispertab* should not lead to name confusion since the prescribers will most likely order these products using the proprietary names (*PCE* and [redacted]), not the names of the dosage formulation. However, due to the naming of the dosage form, a practitioner may be confused on how the dosage form is administered. For example, a practitioner may tell the patient to try to dissolve the *PCE* in water or swallow the [redacted] tablet as a whole without dissolving it in water. To address this problem, please see below for OPDRA *General Comments* #2 under the LABELING, PACKAGING, AND SAFETY RELATED ISSUES.

Due to the above concerns, OPDRA does not recommend the use of the proprietary drug name [redacted]

e. In addition, OPDRA recommends the following labeling revisions to encourage the safest possible use of the drug product.
[NOTE: Some of ODPRA's comments and concerns have been addressed in your latest labeling submission].

General Comments

1. The labels and labeling for [redacted] look very similar to the labels and labeling for [redacted] (cephalexin dispersible tablet), ANDA 65-100. They should be distinguished from each other by using, for example, different colors on the label, highlighting the proprietary drug name and established name, using a different font, and/or using a different configuration of the design.

2. OPDRA has concerns that this product will be placed on the shelf along side of *Amoxil* chewable tablets and capsules. Pharmacists may not realize that the [redacted] tablets must first be dissolved in water before it is administered and may not communicate the correct administration directions to the patients. We recommend that the sponsor provide a patient information sheet containing the direction of use. We also recommend the following statement on the main panel of the container labels and carton labeling:

"DISSOLVE TABLETS IN WATER BEFORE INGESTION"

A. CONTAINER LABEL (200 mg: 5000 tablets, 1000 tablets, unit dose package; 400 mg: 500 tablets, unit dose package)

200 mg: 5000 tablets

OPDRA has no comments on the bulk label.

200 mg: 1000 tablets and 400 mg: 500 tablets

The Usual Dosage statement should be revised to state "Usual Dosage: See Package insert."

200 mg and 400 mg: Unit Dose Packaging

Both the 200 mg and 400 mg labels look similar (black and white). The "200 mg" and "400 mg" should be highlighted with their corresponding color on the labels for the 1000 tablets.

B. CARTON LABELING (200 mg and 400 mg: 100 unit dose tablets)

See above comment under *200 mg: 1000 tablets and 400 mg: 500 tablets*.

C. PACKAGE INSERT

1. The package insert does not contain dosing directions for the indications other than *H. pylori*.

2. Under the DOSAGE AND ADMINISTRATION section, the directions which state that the "[redacted] does not indicate that the tablets must be dissolved in the water. It implies that the tablets can be swallowed whole. Please clarify the directions.

3. The following statement, which refers to capsules and chewable tablets under the DOSAGE AND ADMINISTRATION section, is not appropriate since this drug product must first be dissolved in water before it is administered.

[redacted]

2. CONTAINER:

a. See comments from OPDRA above and revise accordingly.

b. If space permits include the statement "Phenylketonurics: Contains ..." on your unit dose blister label.

3. INSERT

a. General Comment

We acknowledge that you revised your insert labeling by deleting text referring to other amoxicillin dosage forms and strengths in an attempt to have a stand-alone insert for this ANDA. However, we prefer your approach of proposing a combined insert, which references your other approved dosage forms. The added information referencing the other dosage forms allows other Health Care Providers a choice of products best suited for a particular patient.

b. PRECAUTIONS

See General Comment about Patient Package Insert. We refer you to 21 CFR 201.57(f)(2), which states that any printed patient information... be distributed to the patient shall be referred to under the PRECAUTIONS section and that the full text be reprinted at the end of the insert labeling.

c. CLINICAL PHARMACOLOGY

i. General Comments

Throughout the text clarify when you are referring to your drug product. For example, print "amoxicillin tablets [redacted] when referring to your drug product and "conventional amoxicillin tablets" when referring to the innovator's drug product. If you prefer, you may use a proprietary name or propose another statement.

ii. First paragraph, second sentence

We acknowledge that you did not revise the text of the first paragraph and your statement that the sentence is in reference to the effect of food on the absorption of amoxicillin from to the innovator's drug products, "amoxicillin tablets and amoxicillin suspension". Therefore, in your next amendment propose a revised labeling statement indicating that the text does not refer to your drug product. For example:

> The effect of food on absorption of amoxicillin from conventional amoxicillin tablets and from conventional amoxicillin suspension...

iii. Fourth paragraph

To clarify this paragraph please provide the following:

A) First sentence -

[redacted]".

B) Second sentence –

You listed only one administration dose for amoxicillin suspension. However, you listed two average peak blood levels. Please comment.

C) Third sentence –

You listed only one administration dose for the amoxicillin [redacted] tablet. However, you listed two average peak blood levels. Please comment.

D) The pharmacokinetic data for amoxicillin suspension in the fourth paragraph is not listed in the reference listed drug insert labeling. Therefore include a statement to clarify that the pharmacokinetic data is not from the reference listed drug and are the results of your firm's pharmacokinetic study.

d. DOSAGE AND ADMINISTRATION

i. First sentence

Amoxicillin [redacted] may be given...

ii. Direction for [redacted] Tablets

[redacted]

iii. Revise the third paragraph to read as follows:

[redacted]

iv. Print the fourth paragraph, **ALL RECOMMENDED DOSAGE ... 400 MG DOSE"** in bold uppercase print.

e. HOW SUPPLIED

See comment 4(b) above and provide full patient information after this section.

Please insert labeling, as instructed above, and submit in draft. We will not request final printed labeling until resolution of your proposed proprietary and established name issues have been resolved.

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

APPEARS THIS WAY
ON ORIGINAL

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

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 500s (400 mg) and 1000s (200 mg)

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Amoxil® for Oral Suspension
ANDA Number: 62-226
ANDA Drug Name: Amoxil® (amoxicillin trihydrate) for Oral Suspension
ANDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 5/16/00 (S-002)[NDA 50-754]
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:
Basis of Approval for the Carton Labeling:
Other Comments: The RLD is an ANDA but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

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? 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 OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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)		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?		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	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.			

APPEARS THIS WAY
ON ORIGINAL

NOTE TO THE CHEMIST:

DOSAGE AND ADMINISTRATION section

The firm revised their Directions which previously read, "
to read "

Did Ranbaxy provide additional data to support their revised directions?

NOTE TO BIO.

The firm revised the CLINICAL PHARMACOLOGY section of their insert labeling. Is the revised text in the second and fourth paragraphs accurate?

Is data in Table 2 accurate as well as, the text immediately prior to Table 2 and immediately following Table 2?

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. The RLD is an ANDA (Amoxil® for Oral Suspension) but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer: Ranbaxy, India.

4. Package Size:

   Both strengths will be available in UD 100s. The 200 mg tablets will be available in 1000s and the 400 mg tablets will be available in 500s.

   In the submission dated May 22, 2001, the firm added a package size of 20s for the 200 mg and 400 mg drug product.

5. Storage/dispensing recommendations

   Store at controlled room temperature 15o to 30oC (59o to 86oF)(see USP). Dispense in a tight container.

6. I was not able to verify the tablet descriptions as seen in the HOW SUPPLIED section.

7. The firm was asked that all information in the CLINICAL PHARMACOLOGY section not relating to this drug product be replaced by product specific information.

8. After discussion with J. Lee and C. Kim of BIO, it was determined that despite the fact that there are food references in the Amoxicillin RLD insert BIO has a policy stating that no food studies will be requested of any generic Amoxicillin applicant no matter what the dosage form. [Noted from previous review].

10. In the submission dated May 22, 2001, the firm has revised a combined insert to include the conventional tablet and the chewable tablet dosage forms.

11. Ranbaxy acknowledged the following comments in their submission dated May 22, 2001.

    - Your proposed proprietary name ( ) and your dose form trademark ( ) have been forwarded to the Office of Post-Marketing Drug Risk Assessment for their review and comment. We will inform you of their findings when available. We will not ask for labels and labeling in final print until we receive input on the acceptablity of these proposals.

    - We note that no product is currently marketed nor is there a USP monograph with the established name that you have proposed with this application. We recommend that you contact the USP regarding your proposed drug product and keep our office apprised of recommendations from the USP including recommendations regarding the established name of your drug product.

12. Container/Closure:

Strength	***Package size***	***Bottle type***	***Closure***
200 mg	20s	HDPE	CRC
200 mg	1000s	HDPE	Non CRC
200 mg	100s unit dose	Aluminum foil/laminate	
400 mg	20s	HDPE	CRC
400 mg	500s	HDPE	Non CRC
400 mg	100s unit dose	Aluminum foil/laminate	

[Vol. B2.1, p. 26-29]

13. Unit dose blisters container labels and carton labeling are satisfactory in printer's proof, providing the proposed established and proprietary names are found acceptable.

14. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement.
[Vol. B1.2, p. 1037]

15. The firm's physical description of each ——— tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED].

[Vol. B1.4, p. 2106, 2107]

16. A meeting was held to discuss the conditions of use of this ANDA. The Regulatory Branch informed us that since this drug product was found to be acceptable for filing under a petition, the drug product is not required to meet all the same conditions of use as the reference listed drug. Therefore, the ——— tablet labeling can differ from the reference listed drug and should include statements that indicate that their drug product use is limited due to the ——— tablet dosage form.

We have requested the firm to add the following statement as the first paragraph of the DOSAGE AND ADMINISTRATION section.

> All recommended dosages for amoxicillin are included in this section for informational purposes only. The 200 mg ——— tablet is appropriate only for a 200 mg dose and the 400 mg ——— tablet is appropriate only for a 400 mg dose.

17. - CONTAINER:

- 200 mg – 20s and 100s
- 400 mg - 20s and 500s

  Satisfactory in draft as of the October 15, 2001, submission.
  [NOTE: Pending OPDRA recommendations].
- Unit dose blister

  Satisfactory in draft as of the May 22, 2001, submission.
  [NOTE: Pending OPDRA recommendations].

- CARTON: 100s unit dose

  Satisfactory in draft as of the October 15, 2001, submission.
  [NOTE: Pending OPDRA recommendations].

18. We previously asked the firm the following:

> We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

Firm's response:

If the amoxicillin ——— tablet is inadvertently chewed it will form a soft mass. The drug product if chewed will not behave any differently from the dispersed mixture or if swallowed whole.

Date of Review: 11/20/01 & 11/26/01

Date of Submission: 10/15/01

Primary Reviewer: /S/ 12/6/01
Jacqueline Council, Pharm.D. Date:

Team Leader: /S/ Date: 12/6/01

cc: ANDA: 65-080
DUP/DIVISION FILE
HFD-613/JCouncil/CHoppes (no cc)
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Review

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

ANDA Number: **65-080**

Date of Submission: **May 22, 2001**

Applicant's Name: **Ranbaxy Pharmaceuticals Inc.**

Established Name: **Amoxicillin Tablets, [redacted], 200 mg and 400 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

   We acknowledge that you have communicated with the USP regarding your proposed drug product established name and are waiting for their response.

2. CONTAINER:

   a. 200 mg – 20s and 100s
   400 mg - 20s and 500s

      i. Relocate the text "Phenylketonurics..." to appear immediately following the, "Each [redacted] tablet contains..." statement. [If sufficient space is not available, relocate your "Manufactured for..." and "Manufactured by..." statements to other side panel].

      ii. Include directions for administration of your [redacted] tablets.

   b. Unit dose blister

      No further comments at this time.

3. CARTON: 100s unit dose

   See comment 2(a)(ii) under CONTAINER.

4. INSERT

   a. DESCRIPTION

      First sentence –

      [redacted] tablets contains...

   b. CLINICAL PHARMACOLOGY

      We acknowledge that you revised portions of the CLINICAL PHARMACOLOGY section to include your drug product specific pharmacokinetic data. However, please provide the following additional information regarding your drug product labeling in your next amendment.

      i. First paragraph, second sentence

      . [redacted] tablets have been partially investigated. The...

      ii Fourth paragraph

We acknowledge that you added this paragraph to include pharmacokinetic data specific to your drug product, as requested. However, please clarify and/or provide the following additional information:

A) In the second sentence you reported two ranges of average peak blood levels. However, you have only listed one administration dose instead of two to coincide with the two listed ranges, as seen in the reference listed drug insert labeling. Please comment.

B) We note that you list 400 mg/5 mL as an administration dosage when referring to your [redacted] tablet. However, this is not the resulting concentration when your [redacted] tablet is dispersed in [redacted] of water as instructed in your DOSAGE AND ADMINISTRATION section. Please comment.

C) Once your [redacted] tablet is dispersed in water, how do you refer to the mixture, [i.e. dispersed mixture or suspension]?

iii. We note that you have comparative pharmacokinetic data referring to the suspension even though your insert labeling does not include this dosage form. However, you have omitted portions of the text referring to the chewable tablets dosage form. We request that you include data for both dosage forms.

iv. Last Table

A) In the sentence immediately prior to the table you indicate that the pharmacokinetic study compares a "chewable tablet" to an "oral suspension" dosage form. However, in the table the suspension and dispersible tablet dosage forms are listed, and there is no mention of the chewable dosage form. Please comment.

B) In the reference listed drug comparative pharmacokinetic study the volunteers were administered the dose at the start of a light meal. In your study the dose was administrated following an overnight fast. Please comment.

d. PRECAUTIONS [Phenylketonurics]

... 4.5 mg phenylalanine ... [add "mg"]

e. DOSAGE AND ADMINISTRATION

i. General Comment

Since your drug product can not provide all doses possible for the reference listed drug, add an explanatory statement. We offer the following as an example:

> All recommended dosages for amoxicillin are included in this section for informational purposes only. The 200 mg [redacted] is appropriate only for a 200 mg dose and the 400 mg [redacted] is appropriate only for a 400 mg dose.

If you prefer, you may propose another statement.

ii. First sentence –

A) Amoxicillin [redacted]

B) [redacted]

iii. Revise the subtitle "[redacted] to read "[redacted]

iv. We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

v. Table

A) Add a bold black horizontal line immediately following the column headings.

B) We note that you omitted portions of your previously submitted administration text. Revise the administration text to be consistent with the reference listed drug including all dosage strengths and frequencies.

vi. You have omitted the paragraph referring to alternate means of administration for pediatric patients, i.e. ... [redacted] . Can your tablet be dispersed in the above [redacted]

vii. Add a line space immediately prior to the paragraph, "All patients with gonorrhea... Laboratory Tests.)".

f. HOW SUPPLIED

i. Indicate that your tablets have a strawberry flavor.

ii. Indicate that your tablets are "unscored".

Please revise your container labels, carton labeling and insert labeling, as instructed above, and submit 4 draft copies of each. We will not request final printed labeling until resolution of your proposed proprietary and established name issues have been resolved.

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

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

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 500s (400 mg) and 1000s (200 mg)

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Amoxil® for Oral Suspension
ANDA Number: 62-226
ANDA Drug Name: Amoxil® (amoxicillin trihydrate) for Oral Suspension
ANDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 5/16/00 (S-002)[NDA 50-754]
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:
Basis of Approval for the Carton Labeling:
Other Comments: The RLD is an ANDA but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

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? 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 OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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)		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?		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	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.			

APPEARS THIS WAY
ON ORIGINAL

NOTE TO BIOEQUIVALENCE REVIEWER

In the CLINICAL PHARMACOLOGY section of the package insert labeling The firm included product specific pharmacokinetic data for their proposed [redacted] tablet dosage form.

Is the text provided in the second and fourth paragraphs ["Orally administered doses of 400 mg amoxicillin [redacted] tablets ... respectively" and "Amoxicillin [redacted] tablets 400 mg ...respectively"] accurate?

Response: These paragraphs are correct. C.K.

Did Ranbaxy perform a comparative bioequivalence study comparing their [redacted] tablet with the reference listed drug oral suspension?

In the last table of the CLINICAL PHARMACOLOGY section, Ranbaxy indicates that they performed a comparative pharmacokinetic study comparing the "chewable tablet" with an oral suspension"? [See sentence immediately prior to the table]. However, in the table they compare the suspension dosage form with the [redacted] tablet dosage form. Which dosage forms did the firm use in their bioequivalence study?

NOTE TO THE CHEMIST

1. Ranbaxy indicates that their 200 mg and 400 mg amoxicillin [redacted] tablets contains 5.6 mg of phenylalanine. Is this accurate?

2. Did Ranbaxy provide data to support their statement, ".. [redacted]

NOTE TO THE CHEMIST

1. Ranbaxy indicates that their 200 mg and 400 mg amoxicillin [redacted] tablets contains 5.6 mg of phenylalanine. Is this accurate?

[Ganunis, Ruth M] Yes, each tablet has [redacted] of aspartame, which gives 5.6 mg of phenylalanine.

2. Did Ranbaxy provide data to support their statement, ".. [redacted]

[Ganunis, Ruth M]
Yes

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. The RLD is an ANDA (Amoxil® for Oral Suspension) but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer:

   Ranbaxy, India.

4. Package Size:

   Both strengths will be available in UD 100s. The 200 mg tablets will be available in 1000s and the 400 mg tablets will be available in 500s.

   In the submission dated May 22, 2001, the firm added a package size of 20s for the 200 mg and 400 mg drug product.

5. Storage/dispensing recommendations

   Store at controlled room temperature 15o to 30oC (59o to 86oF)(see USP). Dispense in a tight container.

6. I was not able to verify the tablet descriptions as seen in the HOW SUPPLIED section.

7. The firm was asked that all information in the CLINICAL PHARMACOLOGY section not relating to this drug product be replaced by product specific information.

8. After discussion with J. Lee and C. Kim of BIO, it was determined that despite the fact that there are food references in the Amoxicillin RLD insert BIO has a policy stating that no food studies will be requested of any generic Amoxicillin applicant no matter what the dosage form. [Noted from previous review].

10. In the submission dated May 22, 2001, the firm has revised a combined insert to include the conventional tablet and the chewable tablet dosage forms.

11. Ranbaxy acknowledged the following comments in their submission dated May 22, 2001.

    - Your proposed proprietary name (_____) and your dose form trademark (_____) have been forwarded to the Office of Post-Marketing Drug Risk Assessment for their review and comment. We will inform you of their findings when available. We will not ask for labels and labeling in final print until we receive input on the acceptablity of these proposals.

    - We note that no product is currently marketed nor is there a USP monograph with the established name that you have proposed with this application. We recommend that you contact the USP regarding your proposed drug product and keep our office apprised of recommendations from the USP including recommendations regarding the established name of your drug product.

12. Container/Closure:

Strength	*Package size*	*Bottle type*	*Closure*
200 mg	20s	HDPE	CRC
200 mg	1000s	HDPE	Non CRC
200 mg	100s unit dose	Aluminum foil/laminate	
400 mg	20s	HDPE	CRC
400 mg	500s	HDPE	Non CRC
400 mg	100s unit dose	Aluminum foil/laminate	

[Vol. B2.1, p. 26-29]

13. Unit dose blisters container labels and carton labeling are satisfactory in printer's proof, providing the proposed established and proprietary names are found acceptable.

14. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement.
[Vol. B1.2, p. 1037]

15. The firm's physical description of each ——— tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED].

[Vol. B1.4, p. 2106, 2107]

16. A meeting was held to discuss the conditions of use of this ANDA. The Regulatory Branch informed us that since this drug product was found to be acceptable for filing under a petition, the drug product is not required to meet all the same conditions of use as the reference listed drug. Therefore, the dispersible tablet labeling can differ from the reference listed drug and should include statements that indicate that their drug product use is limited due to the dispersible tablet dosage form.

We have requested the firm to add the following statement as the first paragraph of the DOSAGE AND ADMINISTRATION section.

> All recommended dosages for amoxicillin are included in this section for informational purposes only. The 200 mg ——— is appropriate only for a 200 mg dose and the 400 mg ——— is appropriate only for a 400 mg dose.

Date of Review: 6/26/01 and 9/5/01

Date of Submission: 5/22/01

Primary Reviewer:
Jacqueline Council, Pharm.D. /S/ Date: 10-3-01

Team Leader: /S/ Date: 10/3/01

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cc: ANDA: 65-080
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Review

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

ANDA Number: **65-080** Date of Submission: **November 29, 2000**

Applicant's Name: **Ranbaxy Pharmaceuticals Inc.**

Established Name: **Amoxicillin ——— Tablets, 200 mg and 400 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Your proposed proprietary name (———) and your dose form trademark (——— ™) have been forwarded to the Office of Post-Marketing Drug Risk Assessment for their review and comment. We will inform you of their findings when available. We will not ask for labels and labeling in final print until we receive input on the acceptablity of these proposals.

   b. We note that no product is currently marketed nor is there a USP monograph with the established name that you have proposed with this application. We recommend that you contact the USP regarding your proposed drug product and keep our office apprised of recommendations from the USP including recommendations regarding the established name of your drug product.

2. CONTAINER 500s (400 mg) and 1000s (200 mg)

   See GENERAL COMMENTS above.

3. UNIT DOSE BLISTER

   a. See GENERAL COMMENTS above.

   b. "tablet" rather than ' ———

4. UNIT DOSE CARTON (100s)

   a. See GENERAL COMMENTS above.

   b. Under "**Phenylketonurics**:" add the statement "See accompanying prescribing information."

5. INSERT

   a. DESCRIPTION

      Insure that the reference symbol superscripted above the word "aspartame" is the same as that used in the footnote "See **PRECAUTIONS**".

   b. CLINICAL PHARMACOLOGY

      Delete all the information in this section that does not relate to your drug product and replace it with information specific to your drug product.

   c. ADVERSE REACTIONS

      Improve the print quality of the first paragraph.

d. DOSAGE AND ADMINISTRATION

i. We note that there is an inconsistency in the dosing information you provide as a side-by-side comparison and that which you propose in your draft insert labeling.

ii. Delete the first paragraph.

iii. The labeling of the product you reference (the RLD) gives dosing recommendations based on body weight of infants (mg/kg basis). That RLD product can be given with instructions, e.g., "2.5 mL from an oral syringe" that provide for dosages that are not provided with your product. Please explain how your drug product meets all the conditions of use supported by the drug product that you reference.

iv. We note that insert labeling for the RLD has information regarding whether or not that product may be taken with food. We believe that your product should also have this information.

v. In the review of your proposed draft insert labeling, we note that you have omitted dosing recommendations for conditions of use approved for the RLD. Please note that the ANDA regulations require your product to have all the conditions of use of the product you reference.

On the other hand, labeling proposed in your side-by-side comparison has dosing recommendations, e.g., 875 mg every 12 hours or 500 mg every 8 hours. Please explain how your proposed product can meet these dosing recommendations.

Please revise your unit dose blister labels and unit dose carton and insert labeling, as instructed above, and submit 4 draft copies of each.

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.

/s/

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

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

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 500s (400 mg) and 1000s (200 mg)

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Amoxil® for Oral Suspension
ANDA Number: 62-226
ANDA Drug Name: Amoxil® (amoxicillin trihydrate) for Oral Suspension
ANDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: 5/16/00 (S-002)[NDA 50-754]
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:
Basis of Approval for the Carton Labeling:
Other Comments: The RLD is an ANDA but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

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? 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 OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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)		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?		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	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.			

NOTES/QUESTIONS TO THE CHEMIST:

1. **We are requesting that the firm submit their proposed established name to the USP for evaluation.**

2. **I was unable to verify the tablet descriptions as seen in the HOW SUPPLIED section.**

FOR THE RECORD:

1. The RLD is an ANDA (Amoxil® for Oral Suspension) but it shares an insert with an NDA (50-754 - 500 mg and 875 mg tablets) - the capsules, tablets, chewable tablets, and powder for oral suspension all share an insert and all are ANDAs except for the tablets and the chewable tablets. The most recently approved supplement for these products is NDA 50-754/S-002 (approved 5/16/00). This is the labeling that I used to do my review.

2. There are no patents or exclusivities for this drug product.

3. Ranbaxy is the manufacturer.

4. Both strengths will be available in UD 100s. The 200 mg tablets will be available in 1000s and the 400 mg tablets will be available in 500s. Both containers are made of HDPE. The backing on the UD blisters is made of an aluminum foil laminate.

5. Storage/dispensing recommendations

   Store at controlled room temperature 15o to 30oC (59o to 86oF)(see USP). Dispense in a tight container.

6. I was not able to verify the tablet descriptions as seen in the HOW SUPPLIED section.

7. The proposed proprietary name [redacted] and dose form trademark [redacted] have been sent to OPDRA for evaluation.

8. There is some discussion as to what the established name of this drug product should be. Names that have been suggested are " [redacted] "Amoxicillin Tablets (for oral suspension)", " [redacted] We have requested that the firm submit their proposal to the USP in hopes of the creation of a new monograph.

9. After discussion with J. Council, it was decided that we ask that all information in the CLINICAL PHARMACOLOGY section not relating to this drug product be replaced by product specific information.

10. After discussion with J. Lee and C. Kim of BIO, it was determined that despite the fact that there are food references in the Amoxicillin RLD insert BIO has a policy stating that no food studies will be requested of any generic Amoxicillin applicant no matter what the dosage form.

Date of Review: **2-21-01** **Date of Submission:** **11-29-00**

Primary Reviewer: **Adolph Vezza** /S/ **Date:** 3/5/01

Team Leader: **Charlie Hoppes** /S/ **Date:** 3/6/01

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cc: ANDA: 65-080
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/2/21/01|V:\FIRMSNZ\RANBAXY\LTRS&REV\65080na1.I
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-080

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 1

2. ANDA # 65-080

3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon - 122 011, India

U.S. Agent:
Shirley Ternyik
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

Phone: (609) 720-5612
Fax: (609) 720-1155

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Amoxil® (Amoxicillin powder for oral suspension), of SmithKline Beecham Pharmaceuticals, NDA 62-226. The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Amoxicillin Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 11/29/00

FDA:
Acceptance for filing: 12/29/00
Division of Bioequivalence: 2/16/01

10. PHARMACOLOGICAL CATEGORY
Antibacterial

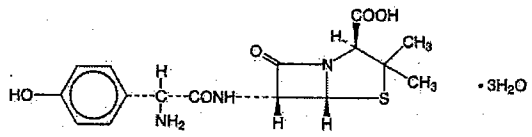
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Ranbaxy, API

13. DOSAGE FORM
Tablets

14. POTENCIES
200 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE
(2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
$C_{16}H_{19}N_3O_5S \cdot 3H_2O$. 419.45



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application is the for a new dosage form, Amoxicillin tablets. The ANDA is based on the approved suitability petition (Docket # 99P-5450/CP-1) dated June 13, 2000. The subject of the suitability petition was a change in the dosage form from

[redacted] The Division of Labeling requested that the firm contact the USP regarding their proposed drug product, and keep ODG aware of USP recommendations.

Bioequivalence, not acceptable 2/16/01
Labeling, not acceptable 2/21/01
DMF for active, acceptable 9/15/00
EER, acceptable 1/11/01

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (Minor)

19. REVIEWER: Ruth Ganunis
DATE COMPLETED: 3/21/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 20

Page(s) of trade secret and /or confidential commercial information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 2

2. ANDA # 65-080

3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon - 122 011, India

U.S. Agent:
Shirley Ternyik
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

Phone: (609) 720-5612
Fax: (609) 720-1155

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Amoxil® (Amoxicillin powder for oral suspension), of SmithKline Beecham Pharmaceuticals, NDA 62-226. The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Amoxicillin [redacted] Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 11/29/00
Bioequivalence, amendment: 3/19/01
Bioequivalence, new correspondence: 3/27/01
Chemistry and labeling, amendment: 5/22/01

FDA:
Acceptance for filing: 12/29/00
Bioequivalence review, not acceptable: 2/16/01
Labeling review, not acceptable: 3/6/01
Chemistry review, not acceptable: 4/4/01
Bioequivalence review, acceptable: 3/28/01

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

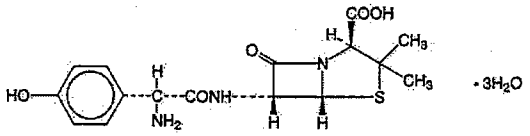
12. RELATED IND/NDA/DMF(s)
Ranbaxy, API

13. DOSAGE FORM
Tablets

14. POTENCIES
200 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE
(2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
$C_{16}H_{19}N_3O_5S \cdot 3H_2O$. 419.45

APPEARS THIS WAY
ON ORIGINAL



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application is for a new dosage form, Amoxicillin [redacted] Tablets. The ANDA is based on the approved suitability petition (Docket # 99P-5450/CP-1) dated June 13, 2000. The subject of the suitability petition was a change in the dosage form from [redacted] The firm has submitted suggestions for a compendial monograph to the USP (5/22/01 amendment, attachment 8).

Bioequivalence, acceptable 3/28/01
Labeling, not acceptable 2/21/01
DMF for active, acceptable 9/15/00
EER, acceptable 1/11/01

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (FAX)

19. REVIEWER: Ruth Ganunis
DATE COMPLETED: June 8, 2001

APPEARS THIS WAY
ON ORIGINAL

Redacted 23

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 3

2. ANDA # 65-080

3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon - 122 011, India

U.S. Agent:
Shirley Ternyik
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

Phone: (609) 720-5612
Fax: (609) 720-1155

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Amoxil® (Amoxicillin powder for oral suspension), of SmithKline Beecham Pharmaceuticals, NDA 62-226. This application was the subject of an approved suitability petition (6/13/00). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Amoxicillin Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 11/29/00
Bioequivalence, amendment: 3/19/01
Bioequivalence, new correspondence: 3/27/01
Chemistry and labeling, amendment: 5/22/01
Chemistry Amendment: 8/15/01

Labeling Amendment: 10/15/01
Labeling Amendment: 2/13/02

FDA:
Acceptance for filing: 12/29/00
Bioequivalence review, not acceptable: 2/16/01
Labeling review, not acceptable: 3/6/01
Chemistry review, not acceptable: 4/4/01
Bioequivalence review, acceptable: 3/28/01
Chemistry review, not acceptable: 7/25/01
Proprietary name review: 11/16/01
Labeling review, not acceptable: 12/6/01
Proprietary name review: 12/31/01
Labeling review, not acceptable: 3/11/02

10. PHARMACOLOGICAL CATEGORY
Antibacterial

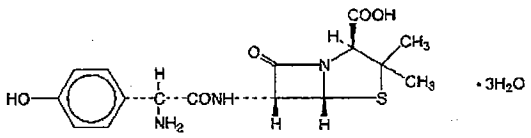
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Ranbaxy, API

13. DOSAGE FORM
Tablets

14. POTENCIES
200 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE
(2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
$C_{16}H_{19}N_3O_5S \cdot 3H_2O$. 419.45



16. RECORDS AND REPORTS
N/A

17. COMMENTS
The ANDA is based on the approved suitability petition (Docket # 99P-5450/CP-1) dated June 13, 2000. The subject of the suitability petition was a change in the dosage form from [redacted] The firm has submitted suggestions for a compendial monograph to the USP (5/22/01 amendment, attachment 8).

Comment: There are no further chemistry questions at this time. The labeling deficiencies will be sent to the firm.

Bioequivalence, acceptable 3/28/01
Labeling, not acceptable
DMF for active, acceptable 9/15/00
EER, acceptable 1/11/01

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (minor)

19. REVIEWER: Ruth Ganunis
DATE COMPLETED: 8/28/01; 3/11/02 (as revised)

APPEARS THIS WAY
ON ORIGINAL

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Chemistry Comments to be Provided to the Applicant

ANDA: 65-080 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Amoxicillin Tablets [redacted], 200 mg and 400 mg.

The deficiencies presented below represent minor deficiencies.

Please refer to the attached labeling deficiencies.

Sincerely yours,

/S/ 3/13/02

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 4

2. ANDA # 65-080

3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon - 122 011, India

U.S. Agent:
Abha Pant
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

Phone: (609) 720-5666
Fax: (609) 720-1155

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Amoxil® (Amoxicillin powder for oral suspension), of SmithKline Beecham Pharmaceuticals, NDA 62-226. This application was the subject of an approved suitability petition (6/13/00). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Amoxicillin Tablets for Oral Suspension

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 11/29/00
Bioequivalence, Amendment: 3/19/01
Bioequivalence, New Correspondence: 3/27/01
Chemistry and Labeling, Amendment: 5/22/01
Chemistry Amendment: 8/15/01

Labeling Amendment: 10/15/01
Labeling Amendment: 2/13/02
Chemistry Amendment: 8/6/02

FDA:
Acceptance for filing: 12/29/00
Bioequivalence review, not acceptable: 2/16/01
Labeling review, not acceptable: 3/6/01
Chemistry review #1, not acceptable: 4/4/01
Bioequivalence review, acceptable: 5/7/01
Chemistry review #2, not acceptable: 7/25/01
Proprietary name review: 11/16/01
Labeling review, not acceptable: 12/6/01
Proprietary name review: 12/31/01
Labeling review, not acceptable: 3/11/02
Chemistry review #3, not acceptable: 3/11/02
Chemistry telephone conference: 7/31/02

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Ranbaxy, API

[redacted]

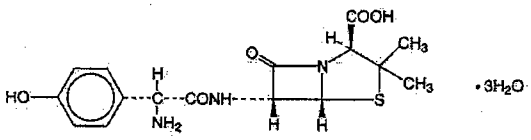
13. DOSAGE FORM
Tablets for Oral Suspension

14. POTENCIES
200 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE

(2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

$C_{16}H_{19}N_3O_5S \cdot 3H_2O$. 419.45



16. RECORDS AND REPORTS

N/A

17. COMMENTS

The ANDA is based on the approved suitability petition (Docket # 99P-5450/CP-1), dated June 13, 2000. The subject of the suitability petition was a change in the dosage form from [redacted] The firm submitted suggestions for a compendial monograph to the USP (5/22/01 amendment, attachment 8).

The deficiency sent to the firm with chemistry review #3 referred the applicant to labeling deficiencies. The firm has since revised the dispersion conditions in the product labeling. Chemistry deficiencies regarding the change in dispersion conditions were communicated to the firm in the 7/31/02 telephone conference. The subject of this review is the firm's 8/6/02 amendment response. In addition, since the last review, a monograph for Amoxicillin Tablets for Oral Suspension was published as an in-process revision in the July-August 2002 PF vol. 28 (4).

Bioequivalence, acceptable 3/28/01
Labeling, not acceptable
DMF for active, acceptable 12/19/01
EER, acceptable 1/11/01

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable (pending labeling)

19. REVIEWER: Ruth Ganunis

DATE COMPLETED: 8/12/02

APPEARS THIS WAY
ON ORIGINAL

Redacted 21

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 5

2. ANDA # 65-080

3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon - 122 011, India

U.S. Agent:
Abha Pant
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

Phone: (609) 720-5666
Fax: (609) 720-1155

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Amoxil® (Amoxicillin powder for oral suspension), of SmithKline Beecham Pharmaceuticals, NDA 62-226. This application was the subject of an approved suitability petition (6/13/00). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Amoxicillin Tablets for Oral Suspension

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 11/29/00
Bioequivalence, Amendment: 3/19/01
Bioequivalence, New Correspondence: 3/27/01
Chemistry and Labeling, Amendment: 5/22/01
Chemistry Amendment: 8/15/01
Labeling Amendment: 10/15/01

Labeling Amendment: 2/13/02
Chemistry Amendment: 8/6/02
Labeling Amendment: 11/21/02
Telephone Amendments 12/9/02 & 12/10/02 (Information for 60's size)

FDA:
Acceptance for filing: 12/29/00
Bioequivalence review, not acceptable: 2/16/01
Labeling review, not acceptable: 3/6/01
Chemistry review #1, not acceptable: 4/4/01
Bioequivalence review, acceptable: 5/7/01
Chemistry review #2, not acceptable: 7/25/01
Proprietary name review: 11/16/01
Labeling review, not acceptable: 12/6/01
Proprietary name review: 12/31/01
Labeling review, not acceptable: 3/11/02
Chemistry review #3, not acceptable: 3/11/02
Chemistry telephone conference: 7/31/02
Labeling review, acceptable: 12/4/02

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Ranbaxy, API

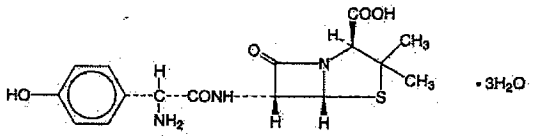
[redacted]

13. DOSAGE FORM
Tablets for Oral Suspension

14. POTENCIES
200 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE

(2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
$C_{16}H_{19}N_3O_5S \cdot 3H_2O$. 419.45



16. RECORDS AND REPORTS N/A

17. COMMENTS

This is a reassignment from R. Ganunis. Her review #4 (8/14/02) recommends approval pending labeling. Since then there are issues regarding API DMF # [redacted] (Annual Update 9/13/02), and the additional 60's packaging size - subject of this review.

The ANDA is based on the approved suitability petition (Docket # 99P-5450/CP-1), dated June 13, 2000. The subject of the suitability petition was a change in the dosage form from [redacted] The firm submitted suggestions for a compendial monograph to the USP (5/22/01 amendment, attachment 8).

The deficiency sent to the firm with chemistry review #3 referred the applicant to labeling deficiencies. The firm has since revised the dispersion conditions in the product labeling. Chemistry deficiencies regarding the change in dispersion conditions were communicated to the firm in the 7/31/02 telephone conference. The subject of chemistry review #4 is the firm's 8/6/02 amendment response. In addition, since review #3, a monograph for Amoxicillin Tablets for Oral Suspension was published as an in-process revision in the July-August 2002 PF vol. 28 (4).

Status Summary for #65-080:

Bioequivalence, acceptable 5/7/01
Labeling, acceptable 12/4/02
DMF # [redacted] for API, acceptable 12/10/02
EER, acceptable 1/11/01

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: Maria C. Shih
DATE COMPLETED: 12/13/02

Redacted 20

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 6

2. ANDA # 65-080

3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon - 122 011, India

U.S. Agent:
Abha Pant
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

Phone: (609) 720-5666
Fax: (609) 720-1155

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Amoxil® (Amoxicillin powder for oral suspension), of SmithKline Beecham Pharmaceuticals, NDA 62-226. This application was the subject of an approved suitability petition (6/13/00). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Amoxicillin Tablets for Oral Suspension

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 11/29/00
Bioequivalence, Amendment: 3/19/01
Bioequivalence, New Correspondence: 3/27/01
Chemistry and Labeling, Amendment: 5/22/01
Chemistry Amendment: 8/15/01
Labeling Amendment: 10/15/01

Labeling Amendment: 2/13/02
Chemistry Amendment: 8/6/02
Labeling Amendment: 11/21/02
Telephone Amendments 12/9/02 & 12/10/02 (Information for 60's size)
Chemistry Amendment: 6/5/03
Chemistry Amendment: 6/18/03

FDA:
Acceptance for filing: 12/29/00
Bioequivalence review, not acceptable: 2/16/01
Labeling review, not acceptable: 3/6/01
Chemistry review #1, not acceptable: 4/4/01
Bioequivalence review, acceptable: 5/7/01
Chemistry review #2, not acceptable: 7/25/01
Proprietary name review: 11/16/01
Labeling review, not acceptable: 12/6/01
Proprietary name review: 12/31/01
Labeling review, not acceptable: 3/11/02
Chemistry review #3, not acceptable: 3/11/02
Chemistry telephone conference: 7/31/02
Labeling review, acceptable: 12/4/02
Chemistry review #4, acceptable pending labeling: 8/14/02
Chemistry review #5, acceptable pending labeling: 12/13/02

10. PHARMACOLOGICAL CATEGORY
Antibacterial

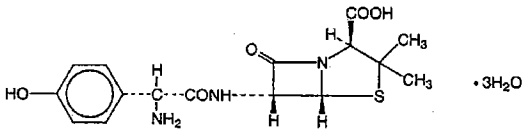
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
[redacted] Ranbaxy, API
[redacted]

13. DOSAGE FORM
Tablets for Oral Suspension

14. POTENCIES
200 mg and 400 mg

15. CHEMICAL NAME AND STRUCTURE
(2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
$C_{16}H_{19}N_3O_5S \cdot 3H_2O$. 419.45



16. RECORDS AND REPORTS N/A

17. COMMENTS
The ANDA is based on the approved suitability petition (Docket # 99P-5450/CP-1), dated June 13, 2000. The subject of the suitability petition was a change in the dosage form from [redacted] The firm submitted suggestions for a compendial monograph to the USP (5/22/01 amendment, attachment 8). There is now an official USP monograph for Amoxicillin Tablets for Oral Suspension.

Review #4 (R. Ganunis, 8/14/02) recommends approval pending labeling. Review #5 (M. Shih, 6/18/03) covered subsequent issues regarding API DMF # [redacted] (Annual Update 9/13/02), and the additional 60's packaging size. Approval was again recommended for the application, pending labeling.

The subjects of this review (#6) are the June 5 and June 18, 2003 submissions. The June 5, 2003 submission updates the application with regard to publication of the USP monograph for Amoxicillin Tablets for Oral Suspension USP. The June 18, 2003 submission contains data to resolve labeling issues. The submission addresses concerns about the volume of water needed for complete dispersion of the tablet and complete delivery of the dose.

Status Summary for #65-080:
Bioequivalence, acceptable 5/7/01
Labeling, acceptable
DMF [redacted] for API, acceptable 12/10/02
EER, acceptable 1/11/01

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: R. Ganunis
DATE COMPLETED: 7/10/03

Redacted 21

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-080

BIOEQUIVALENCE REVIEW(S)

Amoxicillin [redacted] Tablets
200 mg and 400 mg
ANDA 65-080
Reviewer: Carol Y. Kim
V:\firmsnz\ranbaxy\ltrs&rev\65080stf.N00

Ranbaxy Laboratories Limited
Gurgaon, India
Submission Date: 11/29/00

Review of a Bioavailability Study and Dissolution Data

I. Introduction

First Generic: Yes

Indication: For treatment of infections due to ß-lactamase-negative susceptible strains

Contents of Submission:

- Fasting BE: 400 mg
- Waiver request: 200 mg
- *In vitro* dissolution data: 400 mg and 200 mg

RLD: Amoxil^{R} (Amoxicillin) Powder for Oral Suspension, 400 mg/5 ml, manufactured by SmithKline Beecham Pharmaceuticals (NDA# 050760, April 15, 1999)

Recommended Dose: 500-875 mg Q12 hours or 250-500 mg Q 8 hours

II. Background

1. 6/13/00: Suitability Petition, #99P-5450/CP1, was approved for the change in dosage form from Amoxil^{R} (Amoxicillin) Powder for Oral Suspension, 400 mg/5 ml and 200 mg/5 ml, to [redacted] tablets. See attachment # 1 for details.

2. 11/13/00: #00-257: Control Correspondence submitted by Ranbaxy, Amoxicillin [redacted] Tablets

The DBE recommended the firm conduct the following *in vivo* bioavailability studies due to proportionality differences in the formulations of the RLDs:

a. Fasting BE study on 875 mg, a waiver may be requested for the 500 mg strength;
b. Fasting BE study on 400 mg, a waiver may be requested for the 200 mg strength;
c. Fasting BE study on 250 mg, a waiver may be requested for the 125 mg strength.

The DBE concluded that a bioavailability study under fed conditions will not be requested for Amoxicillin [redacted] Tablets.

III. Pharmacokinetics

Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The half-life of amoxicillin is 61.3 minutes. Orally administered doses of 250 mg and 500 mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 microgram/mL to 5 microgram/mL and 5.5 microgram/mL to 7.5 microgram/mL respectively.

IV. Study No. 001863: Randomized, 2-Way Crossover, Comparative Bioavailability Study comparing Ranbaxy's Amoxicillin [redacted] Tablets, 400 mg, and SimthKline Beecham's Amoxil^{R} Powder for Oral Suspension, 400 mg/5ml, in Healthy Male Volunteers Under Fasting Conditions

Study Information

Clinical Facility*:	[redacted]
Principal Investigator:	[redacted]
Clinical Study Dates:	Period 1: 9/8/00-9/9/00 Period 2: 9/15/00-9/16/00
Analytical Facility*:	[redacted]
Analytical Director:	[redacted]
Analytical Study Dates:	9/20/00-10/2/00
Storage Period:	No > 24 days at -80°C

[redacted]

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Amoxicillin [redacted] Tablet	Amoxil^{R} Power for Oral Suspension
Manufacturer:	Ranbaxy	SKB
Manufacture Date:	7/00	N/A
Expiration Date:	-	6/01
ANDA Batch Size:	[redacted]	-
Full Batch Size:	[redacted]	-
Batch/Lot Number:	1080821	NA 2979
Strength:	400 mg	400 mg/5ml
Dosage Form:	1 Tablet [redacted]	Powder
Dose Administered*:	1 tablet	5 ml
Study Condition:	fasting	fasting
Length of Fasting:	Overnight fasting pre-dosing 4 hours post-dosing	Overnight fasting pre-dosing 4 hours post-dosing

*Suspension doses: Within 24 hours prior to dosing, each bottle was reconstituted using distilled water. In the hour before dosing, each bottle of amoxicillin suspension was thoroughly mixed for 5 minutes on a mechanical shaker. All doses were measured and dispensed with an oral syringe delivery system. After subjects received their doses, the individual syringes were well rinsed at least twice with some of the 240 ml of water that was to accompany the dose.

[redacted] tablet doses: The test product was added to a dosing vessel containing 10 ml of the dosing water. The dosing vessel was swirled until the test product was dispersed. The suspension was then administered to the subject. The dosing vessel was rinsed twice with part of the remaining 230 ml of water. The subjects drank the rinsed water and the remainder of the 230 ml to ensure that they received the complete dose.

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Washout Period:**	7 days
No. of Treatments:	2	**Center**	single

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	24 + 2 alternates
Route of Administration:	oral	**No. of Subjects Completing:**	26
		No. of Subjects Plasma Analyzed:	24 (subjects #1-#24)
		No. of Dropouts:	0
		Sex(es) Included:	Males
		Age:	18-45 years
		Healthy Volunteers Only:	Y
		No. of Adverse Events:	1

Inclusion/Exclusion Criteria:	Vol. 1.2 (p. 190-191)
Housing:	The night before dosing until after the 8 hour blood draw
Blood Sampling:	0, 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 3, 3.5, 4, 5, 6 and 8 hours post dose
Volume:	5 ml

Study Results

1) Clinical

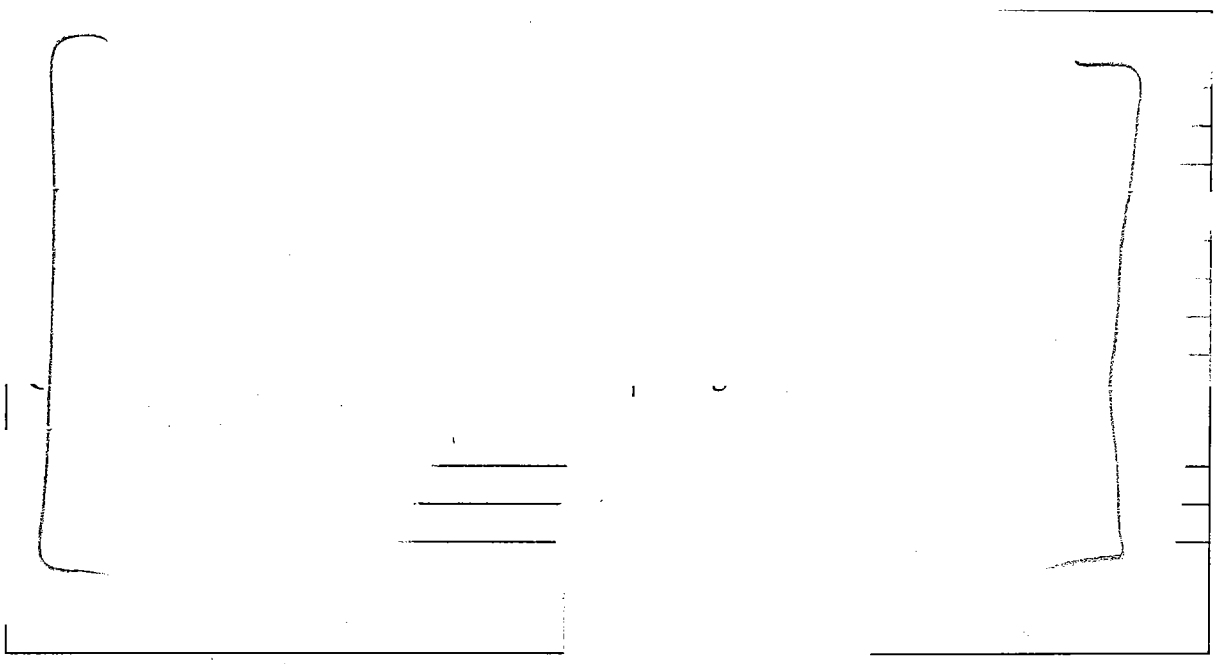
Adverse Events: -Total- 1 adverse event in association to the study drug
-1 event (1 subject)-treatment A, drug related
-The adverse event was a mild headache. (vol. 1.2, p. 337)

Bcorg
11/29/50

Redacted 1

Page(s) of trade secret and /or confidential commercial information

During Assay Validation



Conclusion: The analytical method is acceptable.

3) Pharmacokinetic/Statistical Analysis

Mean Amoxicillin plasma levels of 24 subjects are summarized in Table 1.

Table 1

Mean(CV) Plasma Concentrations of Amoxicillin (ug/ml)

Test=Ranbaxy's Amoxicillin ——— Tablets, 400 mg, Dose Administered=1 tablet, fasting
Reference=Amoxil^{R} Powder for Oral Suspension, 400 mg/5 ml, Dose Administered=5 ml, fasting

Time (hours)	Test	%CV	Reference	%CV	Ratio (T/R)*
0	0	0	0	0	-
0.25	0.75	68.5	0.89	53.3	0.84
0.5	3.46	42.9	4.38	39.1	0.79
0.75	5.93	35.3	7.38	26.4	0.80
1	7.10	30.2	8.34	23.5	0.85
1.25	7.21	27.9	7.68	23.2	0.94
1.5	6.62	27.0	6.82	20.2	0.97
1.75	5.82	22.1	5.78	20.6	1.01
2	5.01	21.0	4.97	19.6	1.01
2.5	3.74	23.1	3.60	19.0	1.04

3	2.67	23.6	2.52	21.7	1.06
3.5	1.95	27.4	1.85	22.5	1.05
4	1.39	29.5	1.31	22.8	1.06
5	0.74	34.4	0.66	29.8	1.12
6	0.43	34.9	0.38	27.2	1.13
8	0.15	49.2	0.14	39.3	1.07

*calculated by the reviewer

Analysis of variance was performed on each pharmacokinetic parameter using SAS PROC GLM. Mean reported pharmacokinetic parameters for hydrocodone and ibuprofen are shown in Table 2. The Geometric means of the ln-transformed pharmacokinetic parameters, means, and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2
Mean Amoxicillin Plasma Pharmacokinetic Parameters

Parameter*	Test Mean	Test %CV	Ref Mean	Ref %CV	T/R Ratio
AUCT	17.83	17.56	18.49	17.03	0.96
AUCI	18.15	17.69	18.82	16.97	0.96
CMAX	7.76	24.36	8.60	20.71	0.90
TMAX	1.16	26.14	1.02	22.74	1.14
KEL	0.54	17.36	0.52	18.93	1.04
THALF	1.32	16.85	1.38	18.50	0.96

*AUCT=ug*hr/ml, AUCI=ug*hr/ml, TMAX=hr, CMAX=ug/ml

Table 3
Geometric Mean ratios and 90% confidence intervals for Amoxicillin

	Geometric Means		Geometric Mean	90%CI	
Parameter*	Test	Reference	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LAUC0-inf	17.87	18.56	0.96	93.76	98.89
LAUC0-t	17.56	18.23	0.96	93.76	98.87
LCmax	7.54	8.42	0.89	85.31	94.10

*LAUC0-inf =ng*hr/ml, LAUC0-t=ng*hr/ml, LCMAX=ng/ml

Comments:

1. No significant period or sequence effect for amoxicillin was noted on LAUCT, LAUCI and LCMAX ($p>0.05$). However, a significant treatment effect was seen on LAUCT, LAUCI, and LCMAX ($p<0.05$). This observation does not effect the integrity of the study.

2. The pharmacokinetic parameters and 90% confidence intervals re-calculated by the reviewer were in good agreement with the values determined by the firm.

3. The mean (%CV) AUC_T/AUC_I ratios of amoxicillin were 98.19 (0.5), range 96.8 to 98.9, and 98.33 (0.5), range 97.5 to 99.1, for test and reference, respectively.

4. The 90% confidence intervals of ln-transformed AUCT, AUCI, and CMAX for amoxicillin are all within 80-125% range.

Conclusion: The study is acceptable.

Table 4: Root Mean Square Error (MSE) for ln-transformed AUCT and Cmax

Amoxicillin	fasting	
	ln AUCT	ln CMAX
MSE, Test & Reference	0.05350219	0.09934519

V. Dissolution (Not to be released under FOI)

The firm submitted dissolution data for Amoxicillin Tablets [redacted], 400 mg and 200 mg, obtained using USP 24 Apparatus II at 75 rpm in 900 ml of water.

Firm's Proposed method

Method of dissolution	USP <711>, Apparatus II (paddles)
Speed	75 rpm
No. of Units Tested	12
Media Tested	Water
Temperature	37°C
Volume	900 ml
Assay Methodology	[redacted]
Specification	NLT [redacted] (Q) of labeled amount of Amoxicillin in 90 minutes
Reference Products	Amoxil[R] Powder for Oral Suspension, 400 mg/5 ml and 200 mg/5 ml

Results of In Vitro Dissolution Profile Summary for Amoxicillin [redacted] Tablets, 400 and 200 mg vs. Amoxil[R] Powder for Oral Suspension, 400 mg/5 ml and 200 mg/5 ml.

Amoxicillin Tablets [redacted], 400 mg Test Lot # 1080821 Exp: 6/02				Amoxil[R] Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA 2979 Exp: 6/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
15	101.2	[redacted]	3.03	62	[redacted]	10.5
30	101.5	[redacted]	3.33	98	[redacted]	4.7
45	101.4	[redacted]	3.30	110	[redacted]	0.82
60	101.5	[redacted]	3.70	111	[redacted]	0.99
90	103.8	[redacted]	3.22	111	[redacted]	0.63

Amoxicillin Tablets [redacted], 200 mg Test Lot # 1080815 Exp: 6/02				Amoxil[R] Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
15	99.7	[redacted]	.74	106	[redacted]	2.83

30	100.8		3.67	109		0.92
45	100.1		3.07	110		1.36
60	100.7		2.81	110		1
90	100.7		2.83	110		1.18

Dissolution testing site: not reported

Comments

The firm names their product Amoxicillin Tablets USP (———— . It is inappropriate to cite the USP name when there is no corresponding official compendial monograph for Amoxicillin ———— Tablet in the USP. Since there is no compendial or FDA-recommended dissolution method available for Amoxicillin ———— Tablet, the DBE asked the firm on 2/6/01 to submit additional dissolution data applying the following testing conditions:

1. Paddle Speed: 25, 50, and 75 rpm
2. Media: water, 0.1 N HCl, and pH 6.8 buffer

The DBE requested this data to optimize the dissolution testing for this product.

On 2/9/01, the firm notified the DBE that they are unable to supply the requested information in a timely manner.

VI. Composition of Formulation (not to be released under FOI)

Ingredients	mg/tablet	mg/tablet
Amoxicillin as Amoxillin USP* (as trihydrate)	200 mg	400 mg
Croscarmellose Sodium NF		
FD&C Red No. 40 Aluminum Lake (		
Croscarmellose Sodium NF		
Strawberry Guarana		
FD&C Red No. 40 Aluminum Lake		
Colloidal Silicon Dioxide NF		
Aspartame NF		
Microcrystalline Cellulose NF		
Magnesium Stearate NF		
Total	**500.0**	**1000.0**

*This quantity is based on theoretical values of 100% w/w assay on ———— and ———— content. Actual quantity per tablet will be based on actual assay and

water content.
^The same flavor has been used in an approved ANDA # 65-021 by Ranbaxy (Amoxillin Chewable Tablets, 250 mg and 125 mg, 12/23/99)

As per Rona Sun, colloidal silicon dioxide is listed under silicon dioxide. Based on her database, all inactive ingredients are within the limits specified by the FDA Inactive Ingredient Guide (1996). See attached e-mail.

Assay and Content Uniformity

Product	Assay %	Content Uniformity %
Test, Amoxillin Tablets [redacted] 400 mg Lot # 1080821	[redacted]	99.7 (0.93)
Reference, Amoxil[R] Powder for Oral Suspension, 400 mg/ 5ml Lot # NA 2979	[redacted]	-
Test, Amoxillin Tablets [redacted] 200 mg Lot # 1080815	[redacted]	101.5 (2.2)
Reference, Amoxil[R] Powder for Oral Suspension, 200 mg/ 5ml Lot # NB0098	[redacted]	-

VII. Waiver Request

1. The firm requested a waiver of *in vivo* bioavailability testing for the 200 mg tablets.

2. The lists of active and inactive ingredients in the proposed test formulation, Amoxicillin Tablets [redacted], are proportionally similar in 400 mg and 200 mg tablets. The total weight in 400 mg tablet is double the amount present in 200 mg tablet.

VIII. Deficiency comments

1. The firm should provide additional dissolution data for both 200 mg and 400 mg strength of test and reference products applying the following testing conditions:

   Apparatus: USP 24 Apparatus II (paddles)
   Paddle Speed: 25, 50, and 75 rpm
   Media: water, 0.1 N HCl, and pH 6.8 buffer

   The firm does not need to repeat the dissolution testing in water at 75 rpm.

2. The firm should note that it is inappropriate to cite [redacted] next to their product name when there is no corresponding [redacted] for Amoxicillin [redacted] Tablet in the [redacted]

APPEARS THIS WAY
ON ORIGINAL

IX. Recommendation

1. The single-dose bioavailability study, 001863, under fasting conditions, conducted by Ranbaxy Laboratories Limited, on its Amoxicillin ———— Tablets, 400 mg, lot #1080821, comparing it to Amoxil^{R} Powder for Oral Suspension, 400 mg/5ml, lot #NA 2979, manufactured by SmithKline Beecham, is found acceptable by the Division of Bioequivalence.

2. The dissolution testing is found incomplete by the Division of Bioequivalence for the reasons given in the deficiency comments.

3. The request for waiver of *in vivo* bioavailability testing of Ranbaxy's Amoxicillin ———— Tablets, 200 mg, is denied at this time for the reasons given in the deficiency comments.

The firm should be informed of the deficiency comments and recommendation.

/S/

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVIT 2/15/01
FT INITIALLED BY BDAVIT 2/16/01

/S/ Date: 2/16/01

Concur: /S/ Date: 2/26/2001

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #65080
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim 2/16/01
HFD-658/ Bio team Leader B. Davit 2/16/01
HFD-617/ Project Manager
HFD-650/ D. Conner 2/26/2001

BIOEQUIVALENCY - Incomplete Submission date: 11/29/00

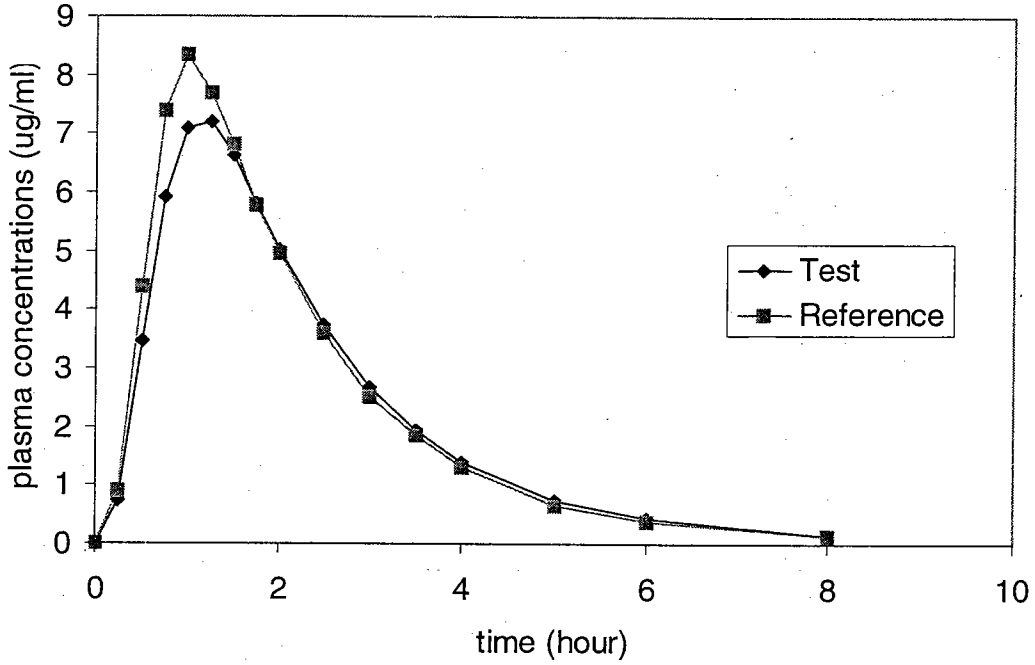
OIC **1. Fasting Study (STF)** **Strength: 400 mg**
Clinical: [redacted] **Outcome: IC**
Analytical: [redacted]

OIC **2. Dissolution Waiver (DIW)** **Strength: 200 mg**
Outcome: IC

Outcome Decisions: IC - incomplete

APPEARS THIS WAY
ON ORIGINAL

Fig. 1: Mean plasma concentrations of Amoxicillin, ANDA #65-080, under fasting conditions



APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES

ANDA # 65-080 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Amoxicillin [redacted] Tablets, 200 mg and 400 mg

The division of Bioequivalence has completed its review. The following deficiencies have been identified:

1. **Please provide additional dissolution data for both 200 mg and 400 mg strengths of test and reference products applying the following testing conditions:**

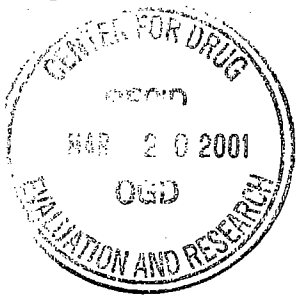
   Apparatus : USP 24 Apparatus II (paddles)
   Paddle Speed : 25, 50 and 75 rpm
   Media: water, 0.1N HCl, and pH 6.8

   You do not need to repeat dissolution testing in water using Apparatus II at 75 rpm.

   The additional dissolution data has been generated on both 200 mg and 400 mg strengths of Amoxicillin [redacted] Tablets and the reference product Amoxil ® Suspension using the parameters as recommended by the Agency. The dissolution data profiles are attached.

2. **Please note that it is inappropriate to site " [redacted] " next to your product name when there is no corresponding [redacted] for Amoxicillin [redacted] Tablets in the [redacted].**

   We note and acknowledge Agency's comment. As per Agency's recommendation, we will not use " [redacted] " in the product name unless the dosage form is included in the [redacted].



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #65-080 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Amoxicillin [redacted] Tablets, 200 mg and 400 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 900 ml of water at 37°C using USP 24 Apparatus II (paddle) at 75 rpm. The test should meet the following specifications:

> Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/s/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Amoxicillin ~~[redacted]~~ Tablets
200 mg and 400 mg
ANDA 65-080
Reviewer: Carol Y. Kim
V:\firmsnz\ranbaxy\ltrs&rev\65080sta.301

Ranbaxy Laboratories Limited
Gurgaon, India
Submission Date: 3/19/01
3/27/01

Review of an Amendment

I. Objective

In this Amendment, the firm submitted their responses to the DBE telephone request and Bioequivalence Deficiency dated February 6, 2001 and March 6, 2001, respectively. Since there is no compendial or FDA-recommended dissolution method available for Amoxicillin ~~[redacted]~~ Tablet, the DBE asked the firm to submit additional dissolution data to optimize the dissolution testing for this product.

II. Background

1. 2/6/01: The DBE asked the firm to submit additional dissolution data applying the following testing conditions:

   Paddle Speed: 25, 50, and 75 rpm
   Media: water, 0.1 N HCl, and pH 6.8 buffer

2. 2/9/01: The firm notified the DBE that they are unable to supply the requested information in a timely manner.

3. 3/6/01: The DBE issued a deficiency due to incomplete dissolution data.

4. 3/27/01: The firm submitted correct expiration date for Amoxil^{R} Suspension 400 mg/5 ml. (see new correspondence)

III. Firm's responses to Deficiency Comments

DBE's comment #1:

"Please provide additional dissolution data for both 200 mg and 400 mg strength of test and reference products applying the following testing conditions:

Apparatus: USP 24 Apparatus II (paddles)
Paddle Speed: 25, 50, and 75 rpm
Media: water, 0.1 N HCl, and pH 6.8 buffer

Firm's response:

See below for additional dissolution data.

DBE's comment #2:

"Please note that it is inappropriate to cite " — next to your product name when there is no corresponding official compendial monograph for Amoxicillin — Tablets in the —

Firm's response:

"We note and acknowledge Agency's comment. As per Agency's recommendation, we will not use '— in the product name unless the dosage form is included in the monograph".

IV. Dissolution data

Results of In Vitro Dissolution Profile Summary for Amoxicillin — Tablets, 200 and 400 mg vs. Amoxil[R] Powder for Oral Suspension, 200 mg/5 ml and 400 mg/5 ml in different tested media

200 mg

Water, 900 ml, 25 rpm							Water, 900 ml, 50 rpm					
Amoxicillin Tablets — 200 mg Test Lot # 1080815 Exp: 6/02				Amoxil[R] Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01			Amoxicillin Tablets (—), 200 mg Test Lot # 1080815 Exp: 6/02			Amoxil[R] Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	27	—	12.6	10	—	21.0	86	—	2.0	24	—	12.5
10	40	—	11.5	14	—	17.9	88	—	2.0	37	—	8.1
15	47	—	11.1	20	—	13.5	88	—	1.9	51	—	5.5
30	55	—	9.5	41	—	8.3	89	—	1.6	86	—	2.4
45	61	—	8.5	60	—	5.0	88	—	1.9	101	—	1.2
60	64	—	8.3	76	—	5.5	89	—	1.8	92	—	1.8
90	67	—	8.2	94	—	2.7	89	—	2.1	91	—	1.9

Water, 900 ml, 75 rpm							Phosphate buffer pH 6.8, 25 rpm					
Amoxicillin Tablets —, 200 mg Test Lot # 1080815 Exp: 6/02				Amoxil[R] Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01			Amoxicillin Tablets (— 200 mg Test Lot # 1080815 Exp: 6/02			Amoxil[R] Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
	98	—	2.4	91	—	6.2	14	—	24.3	11	—	10.9

10	97	2.0	106	1.3	20	15.0	13	14.6			
5	98	2.7	106	1.5	25	13.6	16	8.1			
30	97	2.2	106	1.5	33	12.1	24	5.4			
45	97	1.8	106	2.1	39	9.2	33	4.2			
60	96	2.5	106	1.5	42	9.0	41	4.1			
90	96	2.8	106	1.5	48	7.1	62	3.1			

Phosphate Buffer pH 6.8, 50 rpm							Phosphate Buffer pH 6.8, 75 rpm					
Amoxicillin Tablets (, 200 mg Test Lot # 1080815 Exp: 6/02				Amoxil® Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01			Amoxicillin Tablets , 200 mg Test Lot # 1080815 Exp: 6/02			Amoxil® Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	74		9.5	13		12.3	93		2.7	81		11.1
10	78		4.9	20		9.0	94		4.1	104		1.5
15	81		3.0	27		6.3	94		1.3	106		1.2
30	83		3.6	56		5.5	92		3.7	105		0.9
45	81		4.1	76		4.6	93		3.2	105		0.9
60	84		3.0	100		1.7	95		1.3	105		1.0
90	84		2.7	103		1.1	92		5.5	106		0.7

.1 N HCl, 900 ml, 25 rpm							0.1 N HCl, 900 ml, 50 rpm					
Amoxicillin Tablets (200 mg Test Lot # 1080815 Exp: 6/02				Amoxil® Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01			Amoxicillin Tablets , 200 mg Test Lot # 1080815 Exp: 6/02			Amoxil® Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	36		18.3	8		13.8	88		1.6	17		8.2
10	46		5.9	15		9.3	88		2.0	27		5.6
15	49		5.1	19		5.8	86		1.9	37		6.5
30	54		7.4	39		5.1	82		2.9	57		16.3
45	57		7.2	45		5.1	81		1.7	79		2.0
60	55		8.4	57		4.2	77		2.1	77		1.9
90	57		9.6	72		2.5	73		2.9	77		2.7

0.1 N HCl, 900 ml, 75 rpm						
Amoxicillin Tablets [redacted], 200 mg Test Lot # 1080815 Exp: 6/02				Amoxil® Powder for Oral Suspension 200 mg/5 ml Reference Lot #: NB0098 Exp: 8/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	96	[redacted]	3.5	80	[redacted]	8.0
10	92	[redacted]	2.7	88	[redacted]	1.6
15	92	[redacted]	3.4	88	[redacted]	2.5
30	86	[redacted]	4.1	85	[redacted]	1.6
45	83	[redacted]	4.0	82	[redacted]	2.8
60	82	[redacted]	3.5	81	[redacted]	3.7
90	79	[redacted]	3.5	77	[redacted]	3.2

400 mg

Water, 900 ml, 25 rpm							Water, 900 ml, 50 rpm					
Amoxicillin Tablets [redacted], 400 mg Test Lot # 1080821 Exp: 6/02				Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA2979 Exp: 6/01			Amoxicillin Tablets [redacted], 400 mg Test Lot # 1080821 Exp: 6/02			Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA2979 Exp: 6/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
[redacted]	23	[redacted]	5.7	6	[redacted]	21.7	82	[redacted]	7.2	13	[redacted]	24.6
10	36	[redacted]	20.6	8	[redacted]	13.8	88	[redacted]	3.5	22	[redacted]	9.1
15	38	[redacted]	16.3	13	[redacted]	8.5	88	[redacted]	4.3	32	[redacted]	6.6
30	46	[redacted]	18.0	27	[redacted]	5.6	89	[redacted]	3.9	58	[redacted]	6.2
45	54	[redacted]	13.5	42	[redacted]	5.7	89	[redacted]	3.6	75	[redacted]	8.3
60	56	[redacted]	10.5	53	[redacted]	2.8	89	[redacted]	3.6	87	[redacted]	5.3
90	57	[redacted]	8.1	76	[redacted]	2.8	90	[redacted]	3.9	95	[redacted]	

Water, 900ml, 75 rpm							Phosphate buffer pH 6.8, 900 ml, 25 rpm					
Amoxicillin Tablets [redacted], 400 mg Test Lot # 1080821 Exp: 6/02				Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA2979 Exp: 6/01			Amoxicillin Tablets [redacted], 400 mg Test Lot # 1080821 Exp: 6/02			Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA2979 Exp: 6/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	101	[redacted]	1.5	24	[redacted]	12.9	12	[redacted]	9.2	4	[redacted]	22.5
10	101	[redacted]	1.2	40	[redacted]	12.5	16	[redacted]	13.8	5	[redacted]	34.0
15	100	[redacted]	1.2	53	[redacted]	5.5	18	[redacted]	15.6	7	[redacted]	15.7
30	101	[redacted]	1.2	101	[redacted]	4.4	21	[redacted]	18.6	11	[redacted]	11.8
45	101	[redacted]	1.3	106	[redacted]	3.2	29	[redacted]	19.3	17	[redacted]	9.4
60	100	[redacted]	2.9	106	[redacted]	3.1	33	[redacted]	11.5	20	[redacted]	11.5
[redacted]	101	[redacted]	1.6	108	[redacted]	0.9	38	[redacted]	11.6	28	[redacted]	11.4

Phosphate buffer pH 6.8, 900 ml, 50 rpm							Phosphate buffer pH 6.8, 900 ml, 75 rpm					
Amoxicillin Tablets ([redacted], 400 mg Test Lot # 1080821 Exp: 6/02				Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA2979 Exp: 6/01			Amoxicillin Tablets ([redacted], 400 mg Test Lot # 1080821 Exp: 6/02			Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA2979 Exp: 6/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	76	[redacted]	7.0	10	[redacted]	11.0	96	[redacted]	3.8	20	[redacted]	30.0
10	77	[redacted]	6.2	14	[redacted]	10.7	95	[redacted]	1.3	35	[redacted]	8.6
15	79	[redacted]	4.7	19	[redacted]	11.6	90	[redacted]	4.9	71	[redacted]	3.1
30	77	[redacted]	6.9	36	[redacted]	11.1	93	[redacted]	2.0	102	[redacted]	1.2
45	80	[redacted]	4.9	47	[redacted]	5.1	96	[redacted]	2.4	102	[redacted]	1.7
60	81	[redacted]	4.0	66	[redacted]	4.5	94	[redacted]	2.6	102	[redacted]	1.1
90	78	[redacted]	1.9	95	[redacted]	4.2	95	[redacted]	3.3	100	[redacted]	2.3

0.1 N HCl, 900 ml, 25 rpm							0.1 N HCl, 900 ml, 50 rpm					
Amoxicillin Tablets ([redacted], 400 mg Test Lot # 1080821 Exp: 6/02				Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA2979 Exp: 6/01			Amoxicillin Tablets ([redacted], 400 mg Test Lot # 1080821 Exp: 6/02			Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot #: NA2979 Exp: 6/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
[redacted]	34	[redacted]	14.7	10	[redacted]	9.0	94	[redacted]	1.5	14	[redacted]	5.0
0	45	[redacted]	14.4	12	[redacted]	6.7	92	[redacted]	1.5	24	[redacted]	5.8
15	49	[redacted]	11.2	15	[redacted]	5.3	88	[redacted]	3.3	29	[redacted]	3.4
30	54	[redacted]	8.1	24	[redacted]	3.8	84	[redacted]	1.7	50	[redacted]	2.0
45	53	[redacted]	9.4	33	[redacted]	3.6	81	[redacted]	1.0	65	[redacted]	1.8
60	54	[redacted]	6.5	41	[redacted]	3.2	79	[redacted]	1.6	76	[redacted]	2.9
90	52	[redacted]	8.3	58	[redacted]	4.5	74	[redacted]	3.2	82	[redacted]	3.9

0.1 N HCl, 900 ml, 75 rpm						
Amoxicillin Tablets ([redacted], 400 mg Test Lot # 1080821 Exp: 6/02				Amoxil® Powder for Oral Suspension 400 mg/5 ml Reference Lot # NA2979 Exp: 6/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	84	[redacted]	1.9	22	[redacted]	5.0
10	82	[redacted]	1.5	38	[redacted]	3.7
15	81	[redacted]	1.2	58	[redacted]	18.3
30	77	[redacted]	2.1	79	[redacted]	3.7
45	73	[redacted]	3.0	82	[redacted]	1.7
60	72	[redacted]	1.4	80	[redacted]	1.5
90	68	[redacted]	1.3	69	[redacted]	5.9

V. Comments

1. The single-dose bioavailability study, 001863, under fasting conditions, conducted by Ranbaxy Laboratories Limited, on its Amoxicillin [redacted] Tablets, 400 mg, lot #1080821, comparing it to Amoxil^R Powder for Oral Suspension, 400 mg/5ml, lot #NA 2979, manufactured by SmithKline Beecham, was found acceptable by the Division of Bioequivalence on 2/26/01.

2. Amoxicillin decomposes in acidic media. (see attachment #1) This is most likely the reason why the amount of amoxicillin assayed in the 0.1 N HCl media decreases with time, particularly at 50 and 75 rpm.

3. The dissolution testing conducted by Ranbaxy Laboratories Limited on its Amoxicillin [redacted] Tablets, 200 mg and 400 mg, in 900 ml water using Apparatus II (paddles) at 75 rpm is acceptable.

4. The Division of Bioequivalence recommends that the specifications for Amoxicillin [redacted] Tablets, 200 mg and 400 mg, should be NLT [redacted] (Q) in 30 minutes. The firm proposed dissolution specifications of NLT [redacted] (Q) in 90 minutes.

5. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. Dissolution testing should be conducted in 900 ml of water, at 37°C using USP 24 Apparatus II (paddles) at 75 rpm. The test should meet the following specification:

   Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

6. The two test formulations, Amoxicillin [redacted] Tablets, 200 mg and 400 mg, are proportionally similar. All formulations met the dissolution specifications of NLT [redacted] (Q) of the labeled strength in 30 minutes.

7. Based on acceptable *in vivo* bioavailability study and *in vitro* dissolution data conducted by the firm on its Amoxicillin [redacted] Tablets, 200 mg and 400 mg, the waiver for the 200 mg strength tablets of the test product is granted.

VI. Recommendations

1. The single-dose bioavailability study, 001863, under fasting conditions, conducted by Ranbaxy Laboratories Limited, on its Amoxicillin [redacted] Tablets, 400 mg, lot #1080821, comparing it to Amoxil^R Powder for Oral Suspension, 400 mg/5ml, lot #NA 2979, manufactured by SmithKline Beecham, is found acceptable and complete by the Division of Bioequivalence.

2. The dissolution testing conducted in 900 ml water using Apparatus II (paddles) at 75 rpm by Ranbaxy Laboratories Limited on its Amoxicillin ——— Tablets, 200 mg and 400 mg, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. Dissolution testing should be conducted in 900 ml of water, at 37°C using USP 24 Apparatus II (paddles) at 75 rpm. The test should meet the following specification:

   Not less than —— Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

4. Based on acceptable *in vivo* bioavailability study and *in vitro* dissolution data conducted by the firm on its Amoxicillin ——— Tablets, 200 mg and 400 mg, the waiver for the 200 mg strength tablets of the test product is granted.

The firm should be informed of the above comments and recommendation.

/S/

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

BMD 3/28/01

/S/

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT

Date: 3/30/01

/S/

Concur:

Date: 5/7/2001

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #65080
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

V:\FIRMSnz\ranbaxy\ltrs&rev\65080sta.301

Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim 3/29/01
HFD-658/ Bio team Leader B. Davit 3/30/01
HFD-658/ Reviewer N.Tran 4-5-01
HFD-650/ S. Mazzella
HFD-650/ D. Conner for 5/7/2001

BIOEQUIVALENCY - Acceptable Submission date: 3/19/01

OK **1. Study Amendment (STA)** (3/19/01) **Strength: 200 mg and 400 mg** **Outcome: AC**

OK **2. New Correspondence** (3/27/01) **Strength: 200 mg and 400 mg** **Outcome: AC**

Outcome Decisions: AC - acceptable

APPEARS THIS WAY
ON ORIGINAL

Fig. 1: Dissolution profile comparision in water (ANDA #65-080, 200 mg strength)

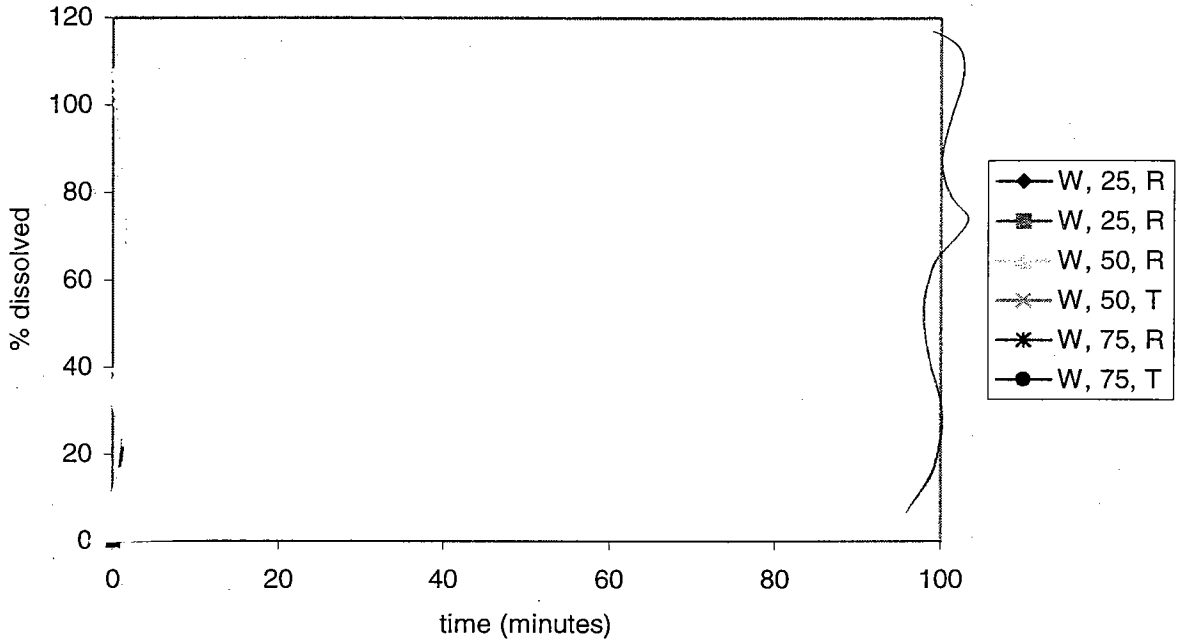


Fig. 2: Dissolution profile comparision in pH 6.8 (ANDA #65-080, 200 mg strength)

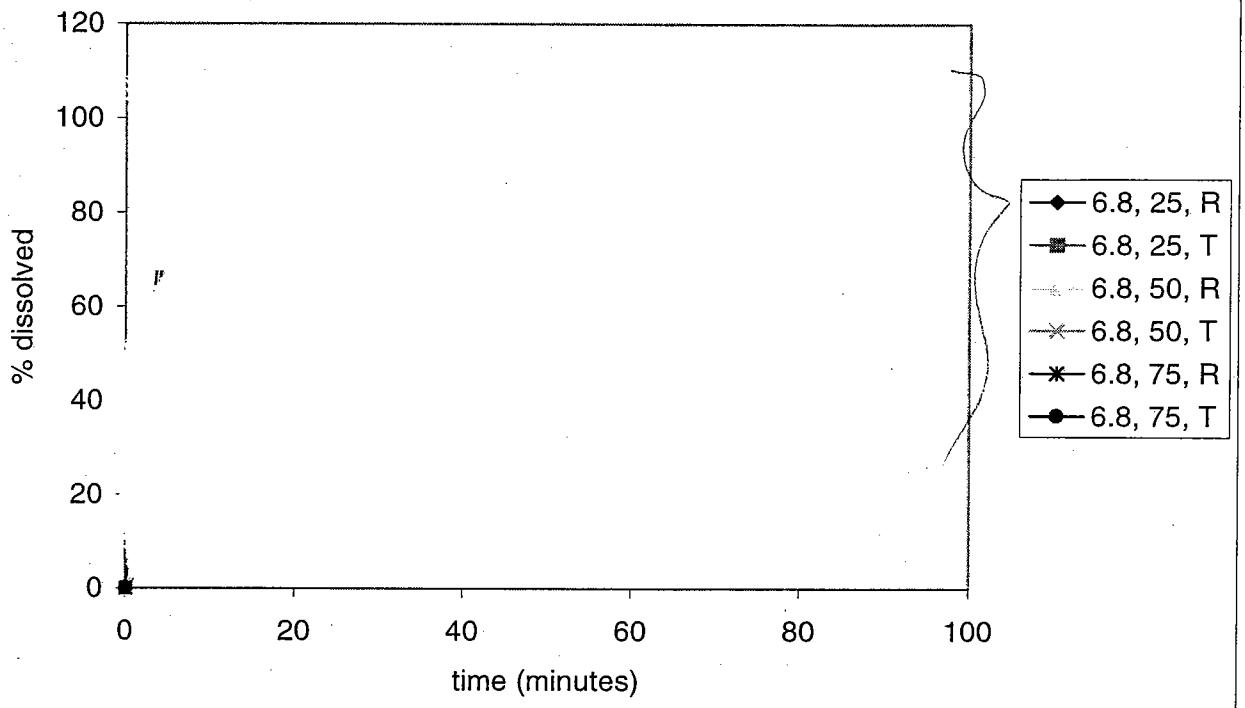


Fig. 3: Dissolution profile comparision in 0.1 N HCl (ANDA #65-080, 200 mg strength)

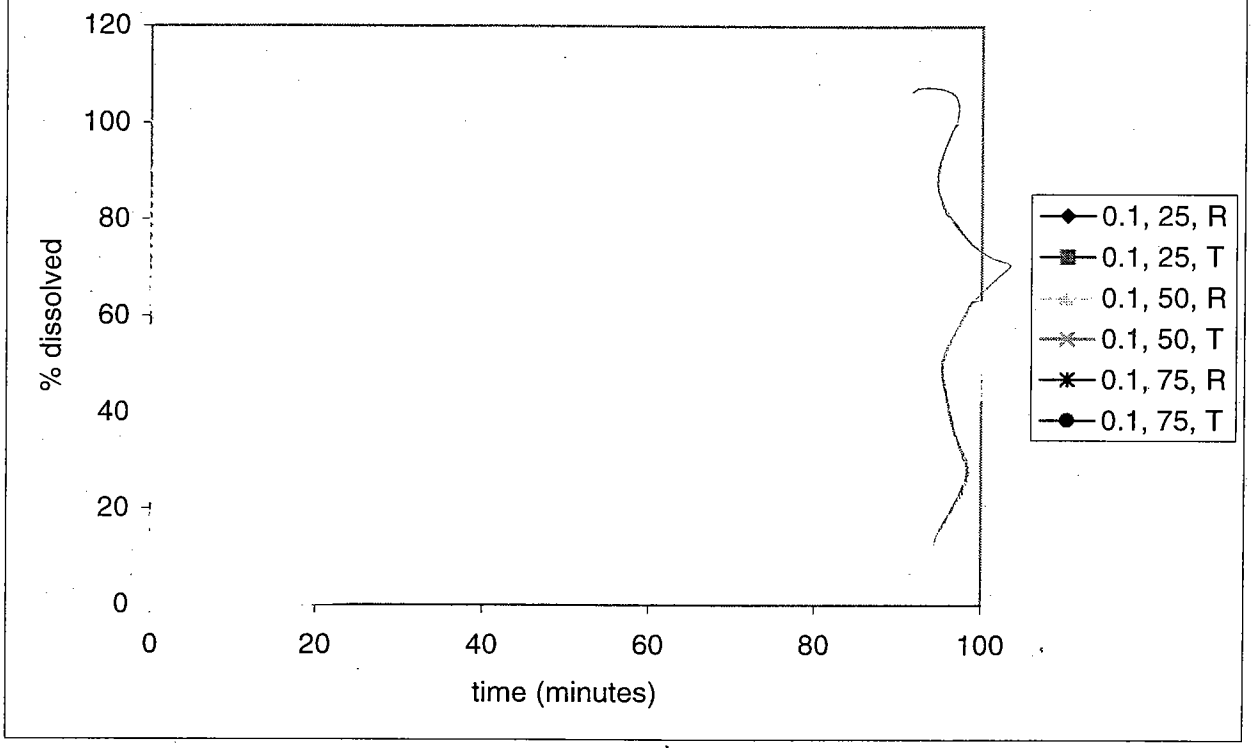


Fig. 4: Dissolution profile comparision in water (ANDA #65-080, 400 mg strength)

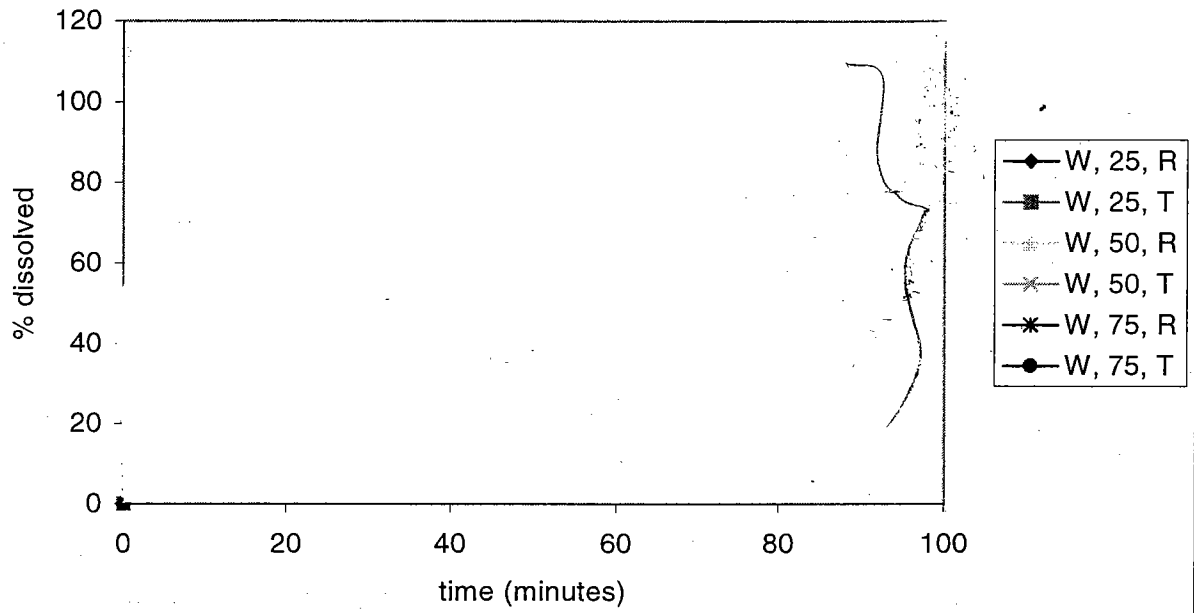


Fig. 5: Dissolution profile comparison in pH 6.8 (ANDA #65-080, 400 mg strength)

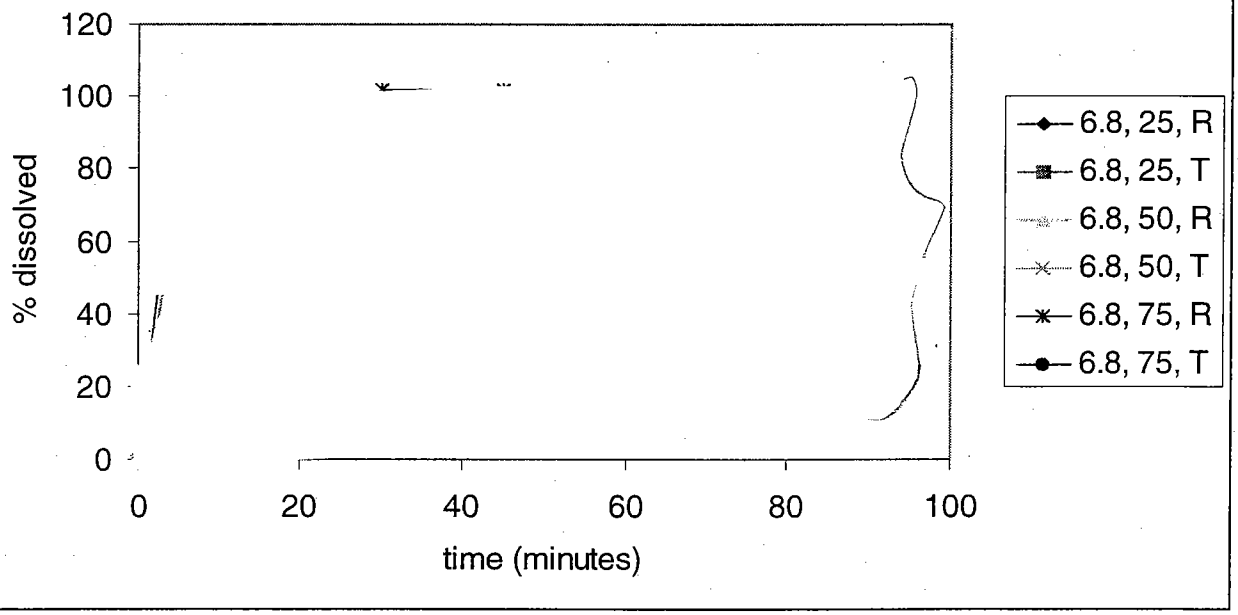
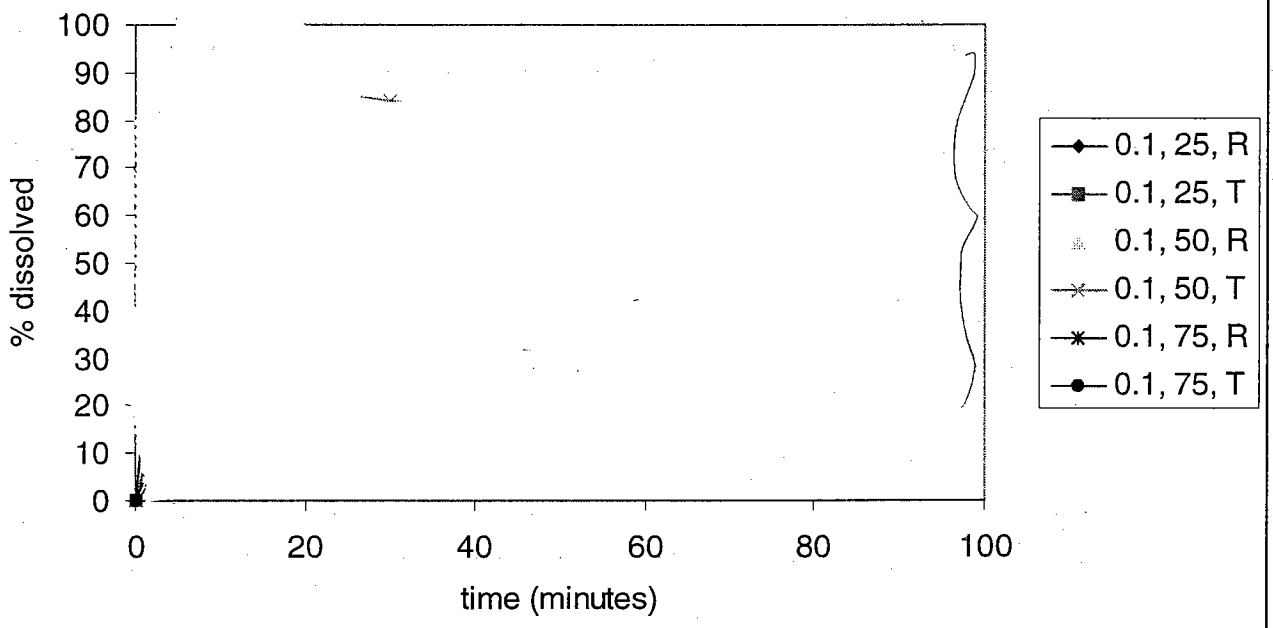


Fig. 6: Dissolution profile comparison in 0.1 N HCl (ANDA #65-080, 400 mg strength)



APPEARS THIS WAY
ON ORIGINAL

Attachment #1

9044021

1: *J Antimicrob Chemother* 1997 Jan;39(1):5-12

The stability of amoxycillin, clarithromycin and metronidazole in gastric juice: relevance to the treatment of Helicobacter pylori infection.

Erah PO, Goddard AF, Barrett DA, Shaw PN, Spiller RC

Department of Pharmaceutical Sciences, University of Nottingham, University Park, UK.

Although omeprazole is an important component in anti-Helicobacter pylori therapeutic regimes using clarithromycin, amoxycillin and metronidazole, the mechanism by which it enhances antimicrobial action is unknown. One potential explanation for this effect is increased antibiotic chemical stability resulting from gastric pH changes induced by co-administration of omeprazole. The chemical stability of clarithromycin, amoxycillin and metronidazole was investigated in aqueous solutions and in human gastric juice collected before and after a 7-day course of omeprazole. Amoxycillin, clarithromycin and metronidazole were prepared in buffered aqueous solutions of pH 1.0 to 8.0 and in gastric juice of pH 2.0 and 7.0. The gastric juice samples were obtained from fasted H. pylori-negative volunteers before and after they had received a 7-day course of omeprazole. All the samples were incubated at 37 degrees C and analysed at intervals by HPLC. Amoxycillin, clarithromycin and metronidazole were stable in aqueous solutions of pH 4.0-7.0, pH 5.0-8.0 and pH 2.0-7.0, respectively. At pH 2.0, the degradation half-lives were 19.0 +/- 0.2 h, 1.3 +/- 0.05 h and 2200 +/- 1100 h, respectively. In gastric juice samples of pH 2.0, the degradation half-lives were 15.2 +/- 0.3 h, 1.0 +/- 0.04 h and > or = 800 h, respectively. The half-lives of the drugs in the gastric juice samples of pH 7.0 were all > 68 h. The co-administration of omeprazole with amoxycillin or clarithromycin is likely to increase the chemical stability of amoxycillin and clarithromycin in gastric juice. Clarithromycin degrades rapidly at normal gastric pH (1.0-2.0) but amoxycillin and metronidazole are sufficiently stable at this pH to maintain an antibacterial concentration in the stomach.

1: *J Pharm Sci* 1978 Aug;67(8):1059-66

Related Articles, Books, LinkOut

Physicochemical properties of amphoteric beta-lactam antibiotics I: Stability, solubility, and dissolution behavior of amino penicillins as a function of pH.

Tsuji A, Nakashima E, Hamano S, Yamana T

The degradation rate, solubility, and dissolution rate of amino penicillins, amoxicillin, ampicillin, epicillin, and cyclacillin, were determined quantitatively as a function of pH. In the pH range studied, 0.30-10.50, the degradation of amoxicillin and epicillin followed pseudo-first-order kinetics to give the same type of pH-rate profiles as those of ampicillin and cyclacillin. Cyclacillin anhydrate was the most soluble, followed in order by ampicillin anhydrate, ampicillin trihydrate, amoxicillin trihydrate, and epicillin anhydrate. These pH-solubility profiles showed showed U-shaped curves. The dissolution rate constants from the rotating disk were analyzed by the simultaneous chemical reaction and diffusion models. Their relative bioavailability after a single oral administration was assessed from their physicochemical properties determined in vitro.

PMID: 27624

111
R. Lansdale

6

BIOEQUIVALENCY DEFICIENCIES

ANDA: #65-080 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Amoxicillin [redacted] Tablets, 200 mg and 400 mg

The Division of Bioequivalence has completed its review. The following deficiencies have been identified:

1. Please provide additional dissolution data for both 200 mg and 400 mg strength of test and reference products applying the following testing conditions:

   Apparatus: USP 24 Apparatus II (paddles)
   Paddle Speed: 25, 50, and 75 rpm
   Media: water, 0.1 N HCl, and pH 6.8

   You do not need to repeat dissolution testing in water using Apparatus II at 75 rpm.

2. Please note that it is inappropriate to cite [redacted] next to your product name when there is no corresponding [redacted] for Amoxicillin [redacted] Tablets in the [redacted]

Sincerely yours,

/S/

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-080 (Amendment) SPONSOR :Ranbaxy Laboratories Limited

DRUG AND DOSAGE FORM : Amoxicillin [redacted] Tablets, 200 mg and 400 mg

STRENGTH(S) : 200 mg and 400 mg

TYPES OF STUDIES : SD SDF MULT OTHER X

CLINICAL STUDY SITE(S) : [redacted]

ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY: In single-dose fasting BE study, Amoxicillin [redacted] Tablets, 400 mg, was shown to be bioequivalent to Amoxil[R] Suspension, 400 mg/5ml. A waiver for the 200 mg strength is granted.

Formulation is acceptable.

DISSOLUTION : acceptable

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Carol Y. Kim BRANCH : 3

INITIAL : /S/ DATE : 3/29/01

TEAM LEADER : Barbara M. Davit BRANCH : 3

INITIAL : /S/ DATE : 3/30/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

fw

INITIAL : /S/ DATE : 5/7/2001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-600)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

File 65-080

7/30 I confirmed this was received (unable to locate confirmation sheet) M Anderson 7/30/01

DATE: 7/30/01

TO: Pat Strasser

FROM Mark Anderson

PHONE: 609-720-5617

PHONE: 301-827-5789

FAX: 609-720-1155

FAX: (301) 443-3839

TOTAL NUMBER OF PAGES: 1
(EXCLUDING COVER SHEET)

SPECIAL INSTRUCTIONS:

Copy of BIO comment for ANDA 65-080

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #65-080 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Amoxicillin [redacted] Tablets, 200 mg and 400 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 900 ml of water at 37°C using USP 24 Apparatus II (paddle) at 75 rpm. The test should meet the following specifications:

> Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-080

ADMINISTRATIVE DOCUMENTS

Redacted 2

Page(s) of trade secret and /or confidential commercial information

ANDA APPROVAL SUMMARY

ANDA #: 65-080 **FIRM:** Ranbaxy Laboratories Limited

DRUG PRODUCT: Amoxicillin Tablets for Oral Suspension

DOSAGE: Tablets for Oral Suspension **STRENGTH:** 200 mg and 400 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 1/11/01

BIO STUDY: Acceptable 5/7/01

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are compendial.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION): The container/closure system used in the stability studies is the same as those described in the c/c section.

LABELING: Acceptable **STERILIZATION VALIDATION:** N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): See below

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

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):
Exhibit batches #1080821 (400 mg, ——— tablets) used for stability and bio studies and #1080815 (200 mg, ——— tablets) used for stability studies were manufactured with API from Ranbaxy Laboratories Limited.

Specifications for active ingredient: Under #23A

Specifications for the finished product: Under #28 and #29

CHEMIST: M. Shih /S/ **DATE:** 7/10/03

SUPERVISOR: Richard Adams /S/ **DATE:** 7/11/03

Redacted 2

Page(s) of trade secret and /or confidential commercial information

File
65080

RECORD OF TELEPHONE CONVERSATION

After discussion with Ruth Ganunis and Richard Adams, I called Abha Pant and requested the following be submitted as a Telephone Amendment:

1. We note that you have revised your product labeling to state that a tablet should be dispersed in [redacted] to 2 ounces of water. Please provide data to support dispersion of the tablets in [redacted] of water.

2. Please revise your fineness of dispersion test conditions to represent the most concentrated dispersion conditions provided for the the labeling.

APPEARS THIS WAY
ON ORIGINAL

V:\firmsnz\ranbaxy\telecons\65080.001

DATE:
7/31/02

ANDA NUMBER:
65-080

PRODUCT NAME:
Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg

FIRM NAME:
Ranbaxy Pharmaceuticals

FIRM REPRESENTATIVE:
Abha Pant

PHONE NUMBER:
609-720-5666

FDA REPRESENTATIVES:
Mark Anderson

SIGNATURES:
/S/
Mark Anderson

Redacted 1

Page(s) of trade secret and /or confidential commercial information

Phone: (609) 720-9200 Direct: (609) 720-5609 • Fax (609) 514-9797

FAX

DATE: 5/14/03

#OF PAGES 2
(INCLUDING THIS COVER)

TO: Gary Buehler	CC TO:
COMPANY: OGD	COMPANY:
FAX NUMBER: 301-594-0183	FAX NUMBER:

FROM: Scott Tomsky

MESSAGE:

ANDA - 65-080

Please see the attached Letter regarding the above mentioned ANDA. The original is being sent Overnight via UPS.

If you have any questions or concerns, please do not hesitate to contact me at 609-720-5609.

Thank you!

ANDA 65-080

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

APPLICANT: Ranbaxy Pharmaceuticals, Inc. (US Agent for Ranbaxy Laboratories Limited)

TEL: 609-720-5666

FAX: 609-514-9797

ATTN: Abha Pant

PROJECT MANAGER: 301-827-5849

FROM: Ted Palat

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 29, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for DisperMox (Amoxicillin Tablets for Oral Suspension), 200 mg and 400 mg.

We are pleased to inform you that this application is APPROVED!

8/11/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-080

CORRESPONDENCE

(1)

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT

July 31, 2003

N/AF

FPL

Mark Anderson
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 20855-2773

UPS & FAX

Reference: **ANDA 65-080**
DisperMox™ Amoxicillin Tablets for Oral Suspension
200 mg and 400 mg

Dear Mark:

As per your suggestion Ranbaxy hereby submits Final Printed Labeling for the Package Insert (18 copies) which has been revised to remove the —, bottle pack from the available sizes for our Amoxicillin Chewable Tablets 250 mg, due to the fact that the CBE Supplement has not been approved by the Agency. This is being sent to you only in case this becomes an issue.

Please contact me at 609-720-5609 or Abha Pant at 609-720-5666, if you have any questions regarding this labeling amendment.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (***for***)
Abha Pant
Official U.S. Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 0 1 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

ORIGINAL

July 11, 2003

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 20855-2773

UPS & FAX
LABELING AMENDMENT

Reference: **ANDA 65-080**
DisperMox™ Amoxicillin Tablets for Oral Suspension
200 mg and 400 mg
Response to Labeling Deficiency dated July 9, 2003

Dear Sir/Madam:

Reference is made to pending ANDA 65-080, for DisperMox™ Amoxicillin Tablets for Oral Suspension 200 mg and 400 mg in which Ranbaxy was asked to further revise the labels and the package insert for the above referenced product.

Provided on the following pages are the agencies faxed comments followed by Ranbaxy's response. The labels and the package insert have been revised as requested. Twelve sets of the final printed labeling are included in **Attachment 1** of the **"original"** copy and an additional 6 sets of final printed labeling are in the duplicate copy of this submission. To facilitate review, we have provided a side-by-side labeling comparison of Ranbaxy's revised labeling and previously submitted, with all differences shown with the use of color in **Attachment 2.**

Please contact the undersigned at 609-720-5633 or Abha Pant at 609-720-5666, if you have any questions regarding this labeling amendment.

Sincerely,

Iris Feliciano
Regulatory Labeling Specialist (***for***)
Abha Pant, US Agent, Regulatory Affairs Director

RECEIVED
JUL 14 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX:** (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT
N/AM

June 18, 2003

FAX & UPS OVERNIGHT

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 20855-2773

TELEPHONE AMENDMENT

Reference: Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg
ANDA 65-080

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg.

Reference is also made to the FDA Telephone contact of June 18, 2003. In the telephone call the Agency requested Ranbaxy to provide additional data in order to determine the percent of the label claim for the dose delivered to a subject when a tablet is dispersed in 10mL's of water.

Based on the Agency's request, each individual tablet was dispersed in the recommended amount of water (10 ml and 15 ml, separately) and the dispersion discarded completely. Assay of residual contents sticking to the container (without rinsing) was done and the data for the same is attached herewith. The testing has been completed on 20 tablets for each strength.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
JUN 19 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT

June 5, 2003

N/AM

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 20855-2773

UPS OVERNIGHT

AMENDMENT

Reference: Amoxicillin Tablets for Oral Suspension USP, 200 mg and 400 mg
ANDA 65-080

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin Tablets for Oral Suspension USP, 200 mg and 400 mg.

Reference is also made to the USP 26, Supplement 1, page 2942 (**Attachment 1**), in which the Official monograph has been published for Amoxicillin Tablets for Oral Suspension. This monograph effective April 1, 2003 is reason for this Amendment. We are hereby updating our release and stability specifications for the following:

	Previous Specifications	**Revised Specifications as per USP 26, supp.1**
Assay		
Fineness of Dispersion	Meets the requirements	Meets the requirements*

* the standard test procedure has been updated as per USP 26, supp. 1, in that the test for Fineness of Dispersion has been revised to "place two tablets in 100 mL water", rather than

The revised release and stability specifications are in **Attachment 2**, and the revised Standard test procedure is in **Attachment 3**.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
PHARMACEUTICALS INC.

Gary Buehler
Director, Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

May 14, 2003

NEW CORRESP

NC

Noted
NAI
mtg ≥ pods
group set
for 6/5/03
MA

Reference: ANDA 65-080
Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg

Dear Mr. Buehler,

Reference is made to the pending ANDA 65-080 for Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg.

As you are well aware, the approval of this ANDA has been delayed and we would like to understand the reasons for this delay as all the technical/scientific issues have been addressed with OGD.

Ranbaxy is very concerned that our customers and investors have begun to doubt our credibility as we have been anticipating this approval for some time now. The ANDA was submitted to the Agency November 29, 2000, and accepted for filing on December 4, 2000.

Ranbaxy has worked closely with the Agency, including the Labeling Review Branch to resolve all of the issues which have surfaced due to the fact that this is a new dosage form. We have worked with USP, which has adopted an official monograph in the 1st Supplement of USP 26, effective April 1, 2003 for Amoxicillin Tablets for Oral Suspension. We have incorporated a "Patient Information Sheet", which will provide patients with a clear and easy to follow "Direction for Use" for this new dosage form. In addition, we have developed a "Dear Pharmacist" letter to introduce the new dosage form, and we have provided a toll free number within the letter which can be utilized by the pharmacist to obtain additional "Patient Information Sheets", and /or answer any questions or concerns the pharmacist or the patient may have.

Ranbaxy filed a final labeling response on December 10, 2002, and was led to believe that the application was approvable based on this amendment. Therefore, we are very concerned about the delay in the approval of this product. We hereby request the Agency to APPROVE this application at this time, or Ranbaxy would like to respectfully request to arrange a meeting with Senior OGD officials and other concerned FDA officials to discuss this issue. Please let us know if there is any other information we can provide to help resolve this issue.

If you have any questions, regarding the submission, please call me at (609) 720-5666.

Sincerely,

Abha Pant.

Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAY 15 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

December 10, 2002

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 20855-2773

FAX & UPS OVERNIGHT

TELEPHONE AMENDMENT

NEW CORRESP

Reference: **Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg**
ANDA 65-080

NC

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg.

Reference is also made to the additional information on the packing details for the 60 count bottles of Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg submitted to the Agency on December 9, 2002.

Ranbaxy would like to further state and clarify that we have not packaged any product in a 60 count bottle pack at this time. We commit to providing the necessary information and notification to the Agency post-approval on this container/closure system in the subsequent Annual Report.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
DEC 1 1 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

December 9, 2002

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 20855-2773

FAX & UPS OVERNIGHT

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/am

Reference: Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg
ANDA 65-080

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg.

Reference is also made to the FDA Telephone contacts of December 6, 2002 and December 9, 2002. In the telephone calls the Agency requested that Ranbaxy provide additional information on the packing details for the 60 count bottles of Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg.

Based on the Agency's request, we are including the relevant information for the 60 count bottles. The packaging compositions and manufacturers of the bottles, CRC caps, desiccants and cotton components remain the same as for the other sizes. Please see attached.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
DEC 1 1 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

ORIG AMENDMENT
N/AF

November 21, 2002

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 20855-2773

FAX & UPS OVERNIGHT

Reference: DisperMox™ 200 mg and 400 mg - ANDA 65-080
(Amoxicillin Tablets for Oral Suspension)

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for DisperMox™ (Amoxicillin Tablets for Oral Suspension) 200 mg and 400 mg.

Reference is also made to November 21, 2002 telephone message of from Jaqueline Counsel, OGD labeling, in which Ranbaxy was asked to provide final printed (100%) full size artwork copies for the 200 mg and 400 mg unit-dose cartons.

Twelve sets of the final printed labels are included as Attachment 1.

Sincerely,

Iris Feliciano
Regulatory Affairs Labeling Specialist (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
NOV 2 2 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

November 5, 2002

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 20855-2773

FAX & UPS OVERNIGHT

ORIG AMENDMENT
N/AF

FPL

Reference: DisperMox™ 200 mg and 400 mg - ANDA 65-080
(Amoxicillin Tablets for Oral Suspension)

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080, DisperMox™ 200 mg and 400 mg (Amoxicillin Tablets for Oral Suspension). Reference is also made to the labeling facsimile deficiency, dated October 11, 2002, in which Ranbaxy was asked to further revise the labels and the package insert for the above referenced product.

Due to a typographical error, side panel word " —— ' should be "intended" Ranbaxy Laboratories Limited withdraws the 200 mg and 400 mg 100 unit-dose tablets (10 strips of 10 Unit-Dose Tablets) printed cartons submitted November 1, 2002.

Enclosed, herewith, are the revised six sets of the final printed cartons for the 200 mg and 400 mg 100 unit-dose tablets (10 strips of 10 Unit-Dose Tablets).

Please contact the undersigned at 609-720-5633, or Abha Pant at 609-720-5666, if you have any questions regarding this letter.

Sincerely,

Iris Feliciano
Regulatory Labeling Specialist (*for*)
Abha Pant
U.S. Agent for Ranbaxy Laboratories Ltd.

RECEIVED
NOV 0 6 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

November 1, 2002

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 20855-2773

FAX & UPS OVERNIGHT

TELEPHONE AMENDMENT

ORIG AMENDMENT

N/AF

Reference: DisperMox™ 200 mg and 400 mg - ANDA 65-080
(Amoxicillin Tablets for Oral Suspension)

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for DisperMox™ (Amoxicillin Tablets for Oral Suspension) 200 mg and 400 mg.

Reference is also made to the labeling facsimile deficiency, dated October 11, 2002, in which Ranbaxy was asked to further revise the labels and the package insert for the above referenced product. Reference is also made to the telephone contact of October 29, 2002 between Ranbaxy and Mark Anderson, in which the Agency had provided revisions to the "Directions for Use" of the Tablets for Oral Suspension after requests from Ranbaxy.

Provided on the following pages are the agency's deficiencies followed by Ranbaxy's responses. The labels and the package insert have been revised as requested. Six sets of the final printed revised labels and package insert are included in **Attachment 5**. To facilitate review we have provided a side-by-side labeling comparison with Ranbaxy's revised labeling and previously submitted, with all differences explained and shown with the use of color, in **Attachment 6**.

Please contact the undersigned at 609-720-5633, or Abha Pant at 609-720-5666, if you have any questions regarding this labeling amendment.

Sincerely,

Iris Feliciano

Iris Feliciano
Regulatory Affairs Labeling Specialist (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
NOV 0 4 7002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

August 6, 2002

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 20855-2773

FAX & UPS OVERNIGHT

ORIG AMENDMENT
N/AM

TELEPHONE AMENDMENT

Reference: Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg
ANDA 65-080

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin Tablets for Oral Suspension, 200 mg and 400 mg.

Reference is also made to the FDA Telephone contact of July 31, 2002. In the telephone call the Agency had asked Ranbaxy to generate additional data on Amoxicillin Tablets for Oral Suspension using one tablespoonful of water for dispersion.

Based on the Agency's request, the data for pH, Assay, Related Substances and Fineness of Dispersion has been generated on the current aged samples (24 months and also 12 months) of the exhibit/ ANDA batches. The data has been generated on dispersion using ~ of water at 0-hour and 1-hour of dispersion on samples of both strengths, from all packs of the exhibit batches. The data is provided in **Attachment 1**.

The dispersed tablet is intended to be consumed within 30 minutes of making the dispersion. The data for pH, related substances and assay at 1-hour after dispersing the tablet in water (60 ml and 120 ml) was already submitted on 9 month old samples in our response to minor amendment dated April 06, 2001. As per the Agencys request we have futher generated data using ~ of water (**Refer Attachment 1**). The specifications for Amoxicillin tablets for oral suspension already include the tests for Disintegration Time and Fineness of Dispersion to check the specific characteristics of tablets for oral suspension. Accordingly, the final drug product release specifications remain same as submitted in the original ANDA (**Refer Attachment 2**).

The test for fineness of dispersion was previously done by dispersing two tablets in 100 mL of water. However, based on the Agency's request the data for fineness of dispersion on 24 month old samples has been generated with ~
Accordingly, we have revised the standard test procedure for fineness of dispersion to incorporate this revision **(Refer Attachment 3, page 25)**.

RECEIVED
AUG 0 7 2002
OGD / CDER

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5609. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

May 30, 2002

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 20855-2773

UNITED PARCAL SERVICE

MINOR AMENDMENT
LABELING

ORIG AMENDMENT
N/AM SP

Reference: **ANDA 65-080**
Amoxicillin ' ——— , Tablets
200 mg and 400 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin ' ——— , Tablets, 200 mg and 400 mg.

Reference is also made to the FDA Minor Deficiency letter for labeling dated March 20, 2002. The questions and responses follow in the same order as in the letter. They are attached.

Reference is also made to the telephone contact of May 10, 2002, stating that the term, ——— could not be used in the labeling and the official name would be "tablets for oral suspension". In addition to the labeling comments, the change in the name is also reflected in this amendment.

If you have any questions, regarding the submission, please call me Abha Pant at (609-720-5666).

Sincerely,

Patricia Strasser (for)
Director of Regulatory Affairs
U.S. Agent for Ranbaxy Laboratories Limited.

RECEIVED
JUN 0 3 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

February 13, 2002

ORIG AMENDMENT
N/HF

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

UPS

LABELING AMENDMENT
to ANDA 65-080

Reference: **ANDA 65-080**
Amoxicillin [redacted] Tablets
200 mg and 400 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin [redacted], Tablets, 200 mg and 400 mg.

Reference is also made to the FDA Labeling Deficiency Letter dated December 6, 2001. The questions and responses follow in the same order as in the letter. They are attached.

In the December 6, 2001 labeling deficiency it was stated that OPDRA did not recommend the use of the proprietary name [redacted]. Ranbaxy Laboratories Limited would still prefer to use this name as the primary name and is filing an appeal with this amendment to use the proprietary name [redacted]

If you have any questions, regarding the submission, please call me at (609) 720-5666 or Pat Strasser at (609)-720-5617.

Sincerely,

Pat Strasser (per)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

October 15, 2001

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

UPS

LABELING AMENDMENT
to ANDA 65-080

AP

Reference: **ANDA 65-080**
Amoxicillin [redacted] Tablets
200 mg and 500 mg

Dear Sir/Madam:

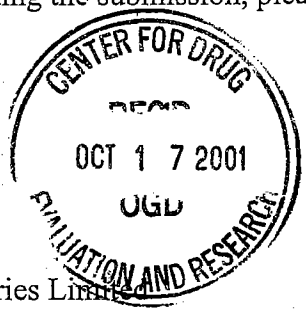
Reference is made to the pending ANDA 65-080 for Amoxicillin [redacted] Tablets, 200 mg and 400 mg.

Reference is also made to the FDA Labeling Deficiency Letter dated September 10, 2001. The questions and responses follow in the same order as in the letter. They are attached.

In addition to the preferred name [redacted], Ranbaxy Laboratories Limited is submitting two additional brand names for consideration.

Field Copy:
We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(5) of this amendment has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions, regarding the submission, please call me at (609) 720-5666 or Pat Strasser at (609)-720-5617.



Sincerely,

Abha Pant.

Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

Noted:
To Clomist
M Anderson
8/22/01

August 15, 2001

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 20855-2773

UPS OVERNIGHT

FAX AMENDMENT

ORIG AMENDMENT
N/FA

Reference: Amoxicillin [redacted] Tablets, 200 mg and 400 mg
ANDA 65-080

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin [redacted] Tablets, 200 mg and 400 mg.

Reference is also made to the FDA Fax Amendment dated July 27, 2001. Reference is also made to the Bioequivalence comments dated July 30, 2001. The questions and responses follow in the same order as in the letter. They are attached.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions regarding this submission please contact me at 609-720-5617 or Shirley Ternyik at 609-720-5612. Thank you.

CENTER FOR DRUGS

Sincerely,

Patricia S. Strasser (for)
Patricia S. Strasser
Manager Regulatory Affairs (for)
Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

NC to Bio

March 27, 2001

NEW CORRESP BIOAVAILABILITY

Division of Bioequivalence
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 20855-2773

UPS OVERNIGHT

NEW CORRESPONDENCE TO BIOEQUIVALENCE

RE: **Amoxicillin [redacted] Tablets, 200 mg and 400 mg**
ANDA 65-080

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin [redacted] Tablets, 200 mg and 400 mg. Reference is also made to the Bioequivalence Amendment dated March 6, 2001 requesting additional dissolution testing and Ranbaxy's response of March 19, 2001. Reference is also made to the telephone contact of March 26, 2001 requesting a correction for page 20.

Page 20 of the response had an incorrect lot number for Ranbaxy's 200 mg [redacted] tablet. The correct lot number is 1080815 and the corrected replacement page is attached.

In addition, it was noted that expiration date given for the Reference Listed Drug, Amoxil® Suspension 400 mg/5mL was reported as August 2001, and the correct expiration date is June 2001. The corrected replacement pages are also attached.

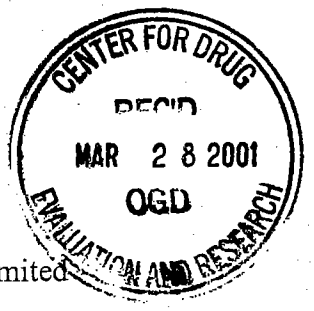
Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions regarding this submission please contact me at 609-720-5617 or Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,

Patricia S. Strasser

Patricia S. Strasser
Manager Regulatory Affairs (for)
Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited



RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

March 19, 2001

N/AB
ORIG AMENDMENT

Division of Bioequivalence
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 20855-2773

UPS OVERNIGHT

BIOEQUIVALENCE AMENDMENT

RE: **Amoxicillin ——— Tablets, 200 mg and 400 mg**
ANDA 65-080

Dear Sir/Madam:

Reference is made to the pending ANDA 65-080 for Amoxicillin ——— Tablets, 200 mg and 400 mg. Reference is also made to the telephone request of February 6, 2001 and the Bioequivalence Amendment dated March 6, 2001 requesting additional dissolution testing.

Attached are the responses to the questions, they follow in the same order as they appear in the Bioequivalence Amendment.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions regarding this submission please contact me at 609-720-5617 or Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,

CENTER FOR DRUG
RECD
MAR 2 0 2001
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EVALUATION AND RESEARCH

Patricia S. Strasser
Manager Regulatory Affairs (for)
Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited

ANDA 65-080

Ranbaxy Pharmaceuticals Inc.
U.S. Agent for Ranbaxy Laboratories Limited
Attention: Shirley Ternyik
600 College Road East
Princeton, NJ 08540

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Amoxicillin [redacted] Tablets, 200 mg and 400 mg

DATE OF APPLICATION: November 29, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 4, 2000

We will correspond with you further after we have had the opportunity to review the application.

In the interim, please submit three separately bound copies of your method validation package. Please submit three copies in separate binders.

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

APPEARS THIS WAY
ON ORIGINAL

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 65-080
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, [illegible] /S/ _____date 12/29/00
HFD-615/EThomas, CSO _____date 12/29/00
Word File V:\Firmsnz\ranbaxy\ltrs&rev\65080.ack
/S/
F/T EEH 12/29/2000
ANDA Acknowledgment Letter!

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

Ack - ISI
12/29/00
505(j)(2)(A)

November 29, 2000

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 20855-2773

UPS

Reference: Amoxicillin ——— Tablets 200 mg and 400 mg
Abbreviated New Drug Application

Dear Sir/Madam:

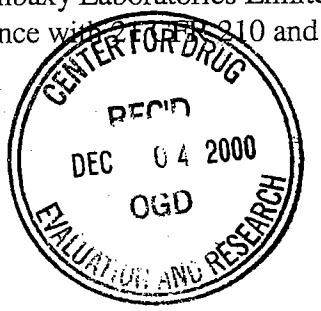
Ranbaxy Laboratories Limited. herewith submits an abbreviated new drug application (ANDA) for Amoxicillin ——— Tablets 200 mg and 400 mg pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The abbreviated new drug application (ANDA) for Amoxicillin ——— Tablets 200mg and 400mg is based on the approved suitability petition (Docket #99P-5450/CP-1) dated June 13, 2000. The subject suitability petition requested for a change in the dosage form from Amoxicillin for oral suspension (powder for reconstitution) to ———, tablets. The approved petition permits this change in dosage form under Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act.

Accordingly, the ANDA refers to the listed drug, Amoxil® (Amoxicillin powder for Oral Suspension) of SmithKline Beecham Pharmaceuticals, published in the 2000 "*Approved Drug Products with Therapeutic Equivalence Evaluations*" (commonly known as the Orange Book), 20th Edition, p. 3-28.

In the applicant's opinion and to the best of applicant's knowledge, no patent claims have been submitted to the FDA. In addition, the applicant is not aware of any marketing exclusivity.

The drug product manufacturer is Ranbaxy Laboratories Limited. Amoxicillin ——— Tablets 200 mg and 400 mg, will be manufactured at Ranbaxy Laboratories Limited's FDA registered and inspected Dewas, India facility in accordance with 21 CFR 210 and 211.



The drug product will also be packaged in bulk, bottles and strip packs at the Dewas, India facility.

The manufacturer of the Amoxicillin trihydrate drug substance used to produce the ANDA batches of drug product is Ranbaxy Laboratories Limited, Toansa, India. The Drug Master File (DMF) No. ——— was filed on March 11, 1998. A sample of the bulk raw material is available and will be provided to the Agency upon request.

The required bioavailability/bioequivalence study was conducted on Amoxicillin Dispersible Tablets 400 mg and Amoxil® for oral suspension 400 mg/5 mL by ——— The study indicates that Amoxicillin ——— Tablets 400 mg are bioequivalent to Amoxil® for oral suspension 400 mg/5 mL. The in-vitro dissolution profiles for Amoxicillin ——— Tablets 200 mg & 400 mg are comparable to those of Amoxil® for oral suspension 200 mg/5 mL and 400 mg/5mL. Therefore, a waiver of in-vivo bioavailability/bioequivalence study requirements for Amoxicillin ——— Tablets 200 mg is requested.

Amoxicillin ——— Tablets 200 mg & 400 mg are stable and a two year expiration dating is requested. The two year expiration dating for these products is supported by one, two and three months accelerated stability data (40°C/75% relative humidity).

The route of administration, indications and usage, route of administration, active ingredient, potency and labeling (except DESCRIPTION and HOW SUPPLIED sections) for Amoxicillin ——— Tablets 200 mg & 400 mg are the same as those for Amoxil® for oral suspension 200 mg/5 mL and 400 mg/5 mL. Dosage is based on the approved suitability petition.

This ANDA is submitted in seven volumes :

Volume I:	Section I through Section V.
Volume II: through Volume IV	Section VI.
Volume V:	Section VII through Section XII
Volume VI:	Section XIII through Section XV
Volume VII:	Section XVI through Section XXII

Ranbaxy Laboratories Limited commits to resolve any issues identified in the methods validation process after approval.

Please contact the undersigned at 609-720-5612 if you have any questions regarding this submission.

Field Copy : We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for the International Operations Group.

Sincerely,

Shirley Ternyik

Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited.