CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
50-784

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA	50-784
PRODUCT	Azithromycin (Zithromax®)
DOSAGE FORM	500 mg film-coated tablets
SUBMISSION DATES:	7/27/01, 11/20/01
SPONSOR	Pfizer, Inc., Groton, CT 06340
TYPE OF SUBMISSION	Original NDA
MEDICAL DIVISION	Anti-Infective Drug Products
REVIEWER	Charles R. Bonapace, Pharm.D.
ACTING TEAM LEADER	Sue-Chih Lee, Ph.D.

I. Executive Summary

The sponsor submitted NDA 50-784 for marketing approval of azithromycin 500 mg tablets for the treatment of acute bacterial exacerbations of chronic bronchitis (AECB). [redacted] The sponsor proposes using azithromycin 500 mg tablets with an accelerated dosing 3-day regimen (500 mg/day × 3 days) in adults in addition to the currently approved 5-day regimen (500 mg on day 1, then 250 mg/day for days 2-5).

To seek approval of the adults accelerated dosing program, two clinical efficacy studies (066-1013 and AZM-NY-93-007) were submitted to support the safety and efficacy of the 3-day dosing regimen in adults. These two studies used the to-be-marketed formulation of 500 mg tablets.

The human pharmacokinetics and bioavailability section contained three pharmacokinetic studies comparing the 3-day and 5-day regimens (066-087, AZM-NY-90-011, and AZM-F-93-004). These studies were previously submitted and reviewed with NDAs 50-670, 50-710, and 50-711 on 12/14/01.

The sponsor also submitted *in vitro* dissolution data to support the request for a waiver of in vivo bioequivalence studies. The similarity factor was greater than 50 using the approved regulatory methods (USP Apparatus 2, 75 RPM, 900 mL, 0.1M phosphate buffer) with 12-unit dissolution profiles comparing 250 mg and 500 mg tablets. Thus, the sponsor's dissolution data meets the requirements for a waiver of in vivo bioequivalence studies.

A. Recommendation

This application was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation III and found to be acceptable from a clinical pharmacology point of view.

/S/

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

/S/

RD/FT Initialed by Sue-Chih Lee, Ph.D., Acting Team Leader

cc:
Division File: NDA 50-784
HFD-520 (CSO/Milstein)
HFD-880 (Division File, Lazor, Lee, Bonapace)
CDR (Clin. Pharm./Biopharm.)

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Azithromycin is an azalide antibiotic, a subclass of the macrolide antibiotics for oral and intravenous administration. Although azithromycin is derived from erythromycin, it differs chemically from erythromycin in that a methyl-substituted nitrogen is incorporated into the lactone ring. Azithromycin acts by binding reversibly to the 23S component of bacterial 50S ribosomal subunits, blocking the translocation reactions of polypeptide chain elongation. Azithromycin is indicated for community acquired pneumonia, acute otitis media, and pharyngitis/tonsillitis in pediatrics and community acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections in adults.

The sponsor proposes an accelerated dosing regimen (3-day regimen) of azithromycin in adults for acute bacterial exacerbations of chronic bronchitis, [redacted]
The approved and proposed dosage regimens of azithromycin in adults are shown below:

Approved 5-day regimen:
500 mg (2 × 250 mg) on day 1, then 250 mg/day for days 2-5

Proposed 3-day regimen:
500 mg/day × 3 days

The sponsor submitted two clinical efficacy studies to support approval of the accelerated dosing program in adults for acute bacterial exacerbations of chronic bronchitis. [redacted] The to-be-marketed formulation of the azithromycin 500 mg tablets were used in each clinical efficacy study.

The sponsor previously submitted three clinical pharmacokinetic studies (066-087, AZM-NY-90-011, and AZM-F-93-004) comparing the 5-day regimen (500 mg on day 1, then 250 mg/day for days 2-5) to the 3-day regimen (500 mg/day × 3 days) of azithromycin in adults. These studies were submitted to support the pediatric efficacy supplements SE-008, SE009, SE-010 for NDAs 50-670, 50-710, and 50-711 on 2/16/01. The results demonstrated that the total exposure ($AUC_{0-\infty}$) was similar between the 5-day and 3-day regimens. Since it is thought that the pharmacodynamic parameter most predictive of azithromycin efficacy based on *in vitro* and animal models is the AUC/MIC ratio, the 5-day and 3-day regimens may have similar clinical efficacy.

In addition, the sponsor has requested a waiver of in vivo bioequivalence studies and has submitted *in vitro* dissolution data comparing the currently marketed 250 mg tablets to 500 mg tablets. Twelve-unit dissolution profiles were determined comparing two 250 mg tablets and a single 500 mg tablet using USP Apparatus 1, 100 RPM, 900 mL, 0.1M phosphate buffer pH 4.5, 6.0, & 7.5 and compared using a similarity factor (f_2). Samples were obtained at 10, 20, 30, 45, and 60 minutes. The % dissolution exceeded [redacted]% by the 10 minute sampling point for phosphate buffer pH 4.5 and 6.0 and the similarity factor could not be calculated. The similarity factor for phosphate buffer pH 7.5 was [redacted]

The approved regulatory method is USP Apparatus 2, 75 RPM, 900 mL 0.1M phosphate buffer pH 6.0. The sponsor performed 12-unit dissolution profiles comparing a single 250 mg, 500 mg, and 600 mg tablets using USP Apparatus 2, 75 RPM, 900 mL, 0.1M phosphate buffer pH 6.0 and 7.5. Phosphate buffer pH 7.5 was requested since it appeared to be more discriminating than phosphate buffer pH 6.0. Samples were obtained at 10, 20, 30, 45, and 60 minutes. The % dissolution exceeded [redacted]% by the 10 minute sampling point for phosphate buffer pH 6.0 and the similarity factor could not be calculated. The similarity factor for phosphate buffer pH 7.5 was [redacted](using the 10, 20, and 30 minute sample points)

comparing 250 mg and 500 mg tablets and ~ (10, 20, 30, and 45 minute sample points) for 600 mg and 500 mg tablets.

The sponsor meets the requirements for granting a waiver of in vivo bioequivalence studies for azithromycin 500 mg tablets based on a similarity factor of greater than 50 using 12-unit dissolution profiles.

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IV. Question-Based Review

A. General Clinical Pharmacology

What is the proposed dosing regimen and route of administration?

The approved dosing regimen for acute bacterial exacerbations of chronic bronchitis, community acquired pneumonia, pharyngitis/tonsillitis, and skin and skin structure infections in adults is oral azithromycin 500 mg on day 1, then 250 mg/day for days 2-5.

The proposed accelerated dosage regimen for acute bacterial exacerbations of chronic bronchitis, in adults is oral azithromycin 500 mg/day for 3 days.

What are the characteristics of the exposure-response relationships for efficacy and safety?

It is thought that the pharmacodynamic parameter most predictive of azithromycin efficacy using *in vitro* and animal models is the ratio of the area under the serum concentration-time curve (AUC) to the organism's minimal inhibitory concentration (MIC), the AUC/MIC ratio. *In vitro* and in vivo animal pharmacodynamic studies provide evidence that administering the same total dose of azithromycin over a shortened duration (5-day vs. 3-day vs. 1-day regimens) should result in similar exposures compared to the approved five day duration and thus, similar efficacy. In addition, it is possible that greater maximum concentration (C_{max}) to MIC ratios (C_{max}/MIC) resulting from administering larger daily doses may provide an additional benefit for organisms that are at the upper limit of susceptibility.

How does the exposure of the 5-day regimen compare to the 3-day regimen in adults?

The sponsor previously submitted studies 066-087, AZM-NY-90-001, and AZM-F-93-004 comparing the pharmacokinetics of azithromycin when administered as 5-day and 3-day regimens in healthy adult subjects. Each study was an open-label, multiple-dose, cross-over study in which subjects received azithromycin 500 mg on day 1 followed by 250 mg/day for 4 days or 500 mg/day for 3 days. The results were reviewed with efficacy supplements SE-008, SE-09, and SE-010 for NDAs 50-670, 50-710, and 50-711 and are summarized below.

Data were not reported by the reviewer from study AZM-NY-90-011 since the sponsor only submitted a summary of the validation data and the accuracy of the analytical assay may be outside the acceptable range. Partial validation data were provided for study AZM-F-93-004; the results of this study were used to support study 066-087. Only two blood samples were obtained on day 2 (3-day regimen) and days 2-4 (5-day regimen) of study 066-087. An estimate of the total exposure ($AUC_{0-\infty}$) was unable to be performed using a non-parametric analysis without incorporating an unacceptable degree of error. The individual concentration-time profiles were fit using a three compartment, oral absorption model with micro constants in WinNonlin and simulations performed with individual parameter estimates.

The $AUC_{0-\infty}$ geometric mean ratio (90% confidence interval) for study AZM-F-93-004 was 0.933 (0.798 to 1.092). The geometric mean ratio (90% confidence interval) for study 066-087 using simulated concentrations was 1.118 (0.962 to 1.299). The 5-day and 3-day regimens were similar based on overall exposure ($AUC_{0-\infty}$) and although the 90% confidence interval exceeded 1.25 for study 066-087 (0.96 to 1.30), it was within 0.80 to 1.25 for study AZM-F-93-004 (0.80 to 1.09). Thus, the 3-day regimen should provide at least the exposure of the 5-day regimen. Since the AUC/MIC appears to be the pharmacodynamic parameter most predictive of azithromycin efficacy and is correlated with clinical

outcome, the proposed 3-day dosing regimen may be expected to have similar clinical outcome as the approved 5-day regimen.

What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics data?

Clinical studies submitted to support acute exacerbations of chronic bronchitis:
Study 0661013 (n=407): Phase 3, randomized, multicenter, double-blind, double-dummy trial comparing the clinical and microbiological efficacy of azithromycin 500 mg daily for 3 days vs. clarithromycin 500 mg BID for 10 days

Clinical studies to support
Study AZM-NY-93-007 (n=203): Phase 3, multicenter, open-label, comparative study to compare the clinical and microbiological efficacy of azithromycin 500 mg daily for 3 days vs. clarithromycin 250 mg BID for 10 days

Note: Study AZM-NY-93-007 was used to support the acute exacerbations of chronic bronchitis indication.

B. General Biopharmaceutics

Based on BCS principles, in what class is this drug and formulation?

Azithromycin has two tertiary amines with assigned pK_a values of 8.1 and 8.8. As expected, the solubility of azithromycin dihydrate increases exponentially with decreasing pH at room temperature as shown in the table below:

pH	Solvent System	Solubility (mg/mL)
6.9	Water[1]	1.1 mg/mL
<7	pH Stat[2]	>100 mg/mL
7.25	pH Stat[2]	100 mg/mL
7.5	0.1 M Phosphate Buffer	35 mg/mL
8	0.1 M Phosphate Buffer	8 mg/mL
9	0.1 M Phosphate Buffer	0.2 mg/mL
10	0.1 M Phosphate Buffer	0.025 mg/mL
11	0.1 M Phosphate Buffer	0.006 mg/mL

1 - Temp 37°C
2 - pH held constant for 10 hrs by automatic addition of H_3PO_4

Azithromycin solubility in 0.1 M phosphate buffer at pH 8.0 is 8 mg/mL. Thus, azithromycin is a high solubility drug since the 500 mg tablet will dissolve in 250 mL of phosphate buffer adjusted between pH 1.0 to 8.0. The absolute bioavailability of azithromycin is approximately %. Although azithromycin is unstable in acidic pH (gastric acid), the AUC of azithromycin was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide and administration of cimetidine two hrs prior to azithromycin had not effect on azithromycin absorption. Thus, the low absolute bioavailability of azithromycin is not the result of instability in the gastrointestinal tract. *In vitro* studies suggest that azithromycin is a P-glycoprotein (P-gp) substrate and its oral bioavailability could be limited by the P-gp efflux pump. It is unknown whether the permeability of azithromycin has been determined experimentally. Thus, azithromycin may be either a high solubility/high permeability drug (BCS Class 1) or a high solubility/low permeability drug (BCS Class 3) even though the absorption is less than %.

What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

Azithromycin 250 mg, 500 mg, and 600 mg film-coated tablets are formulated from the same blend and proportionately similar in composition. The formulation of the 250 mg and 500 mg tablets are shown in Table 1 below.

Table 1. Comparison of azithromycin 250 mg and 500 mg tablet formulations

Ingredient	250 mg Tablet	500 mg Tablet
Azithromycin Dihydrate USP[1]		
Pregelatinized Starch NF		
Calcium Phosphate Dibasic, Anhydrous, Anhydrous USP Diluent[2]		
Croscarmellose Sodium NF		
Purified Water USP[3]	As Required	As Required
Magnesium Stearate / Sodium Lauryl Sulfate		
Pink		
Purified Water USP[3]	As Required	As Required
Purified Water USP[3]	As Required	As Required
Total Weight (mg)	**470.25**	**932.28**

1-Based on a theoretical potency of 95.4%
2-Calcium phosphate dibasic anhydrous weight is adjusted according to small potency changes in the azithromycin dihydrate to maintain a constant tablet weight
3-Evaporated during processing

Although the 250 mg and 500 mg tablets share a common blend, the 250 mg tablets have a of magnesium stearate/sodium lauryl sulfate than the 500 mg tablets. Dr. Andrew Yu, the Chemistry reviewer, considered the discrepancy in magnesium stearate/sodium lauryl sulfate between the 250 mg and 500 mg tablets unlikely to impact the tablet dissolution since . For rework lots, magnesium stearate/sodium lauryl sulfate blend may be of the tablet weight.

The sponsor used the to-be-marketed 500 mg tablets in both clinical studies (study 0661013 and study AZM-NY-93-007) to support the clinical efficacy of azithromycin. Thus, the *in vitro* dissolution data will be used to support the bioequivalence of azithromycin 250 mg and 500 mg tablets and allow two 250 mg tablets to be used in place of a single 500 mg tablet.

What are the results of *in vitro* dissolution studies? Has the sponsor requested a waiver of in vivo bioequivalence studies?

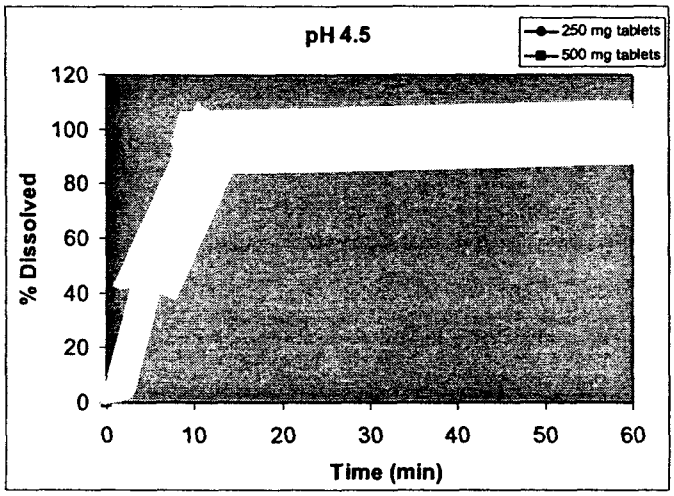
The sponsor has requested a waiver of in vivo bioequivalence studies. The Agency and the sponsor reached an agreement on 6/1/99 that *in vitro* dissolution testing was acceptable to support a waiver of bioequivalence studies using a 12-unit comparative dissolution profiles with similarity factors.

The sponsor submitted *in vitro* dissolution testing using USP Apparatus 1 (rotating basket), 100 RPM, 900 mL, 0.1M phosphate buffers pH 4.5, 6.0, and 7.5 to compare two 250 mg tablets and a single 500 mg tablet. Simulated gastric acid was not chosen as a dissolution medium because azithromycin is not

sufficiently stable at this acidic pH. In addition, water was not chosen because the aqueous solubility of azithromycin is only 1.1 mg/mL.

The dissolution profiles at pH 4.5, 6.0, and 7.5 are shown in Figure 1. The sponsor calculated a similarity factor (f_2) at pH 4.5 and pH 6.0 even though the % dissolution exceeded —% by the first sample. The similarity factor for pH 7.5 was — Since the f_2 value just exceeded 50, the sponsor repeated the dissolution study at pH 7.5 and extended the sampling time to 120 minutes. The similarity factor calculated over 120 min was —

Figure 1. Dissolution profiles comparing two 250 mg tablets and a single 500 mg tablet using USP Apparatus 1, 100 RPM, pH 4.5, 6.0, and 7.5



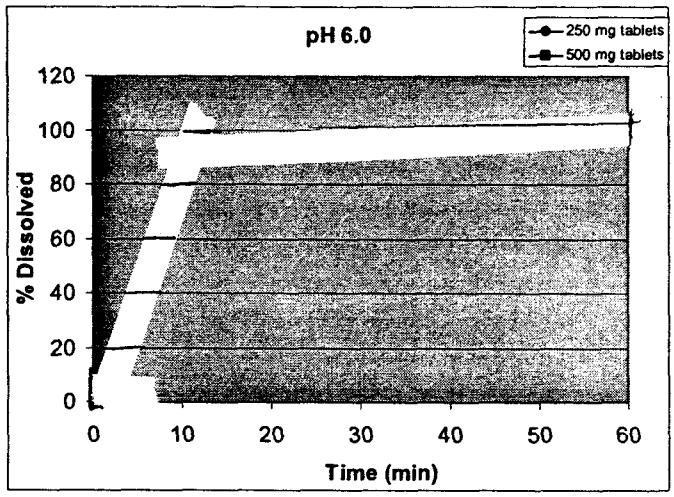
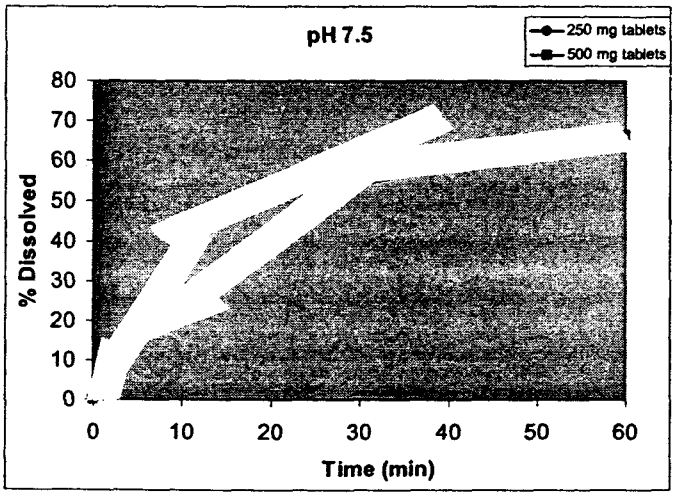
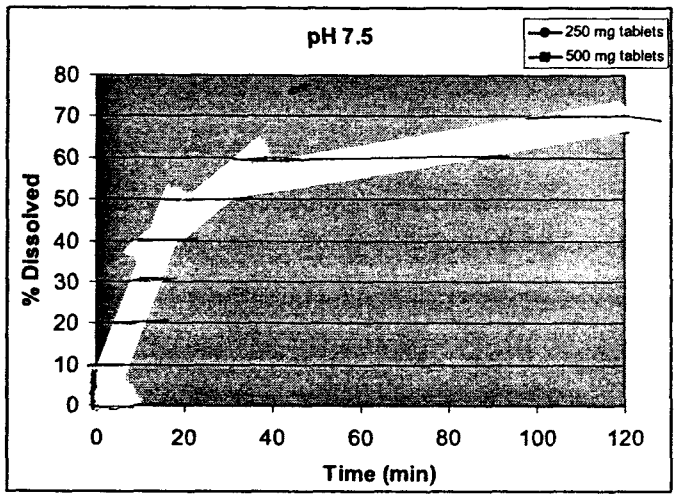


Figure 1 (continued). Dissolution profiles comparing two 250 mg tablets and a single 500 mg tablet using USP Apparatus 1, 100 RPM, pH 4.5, 6.0, and 7.5





The similarity factors provided by the sponsor and calculated by the reviewer for 0.1M phosphate buffer pH 4.5, 6.0 and 7.5 are shown in Table 2. The reviewer was unable to calculate a similarity factor for

0.1M phosphate buffer pH 4.5 and 6.0 since the % dissolution exceeded — % by the first sampling time point.

Table 2. Comparison of similarity factors reported by the sponsor and reviewer comparing two 250 mg tablets vs. a single 500 mg tablet using USP Apparatus 1, 100 RPM

	Similarity factor (f_2)	
Conditions	**Sponsor**	**Reviewer**
pH 4.5, 60 min		NA*
pH 6.0, 60 min		NA*
pH 7.5, 60 min		
pH 7.5, 120 min		NA*

*Not calculated by the reviewer

The accepted regulatory test methods for azithromycin tablets are USP Apparatus 2, 75 RPM, 900 mL, 0.1M phosphate buffer pH 6.0. The sponsor was requested to perform 12-unit dissolution profiles comparing a single 250 mg, 500 mg, and 600 mg tablet using USP Apparatus 2 (paddle), 75 RPM, 0.1 phosphate buffer pH 6.0 and 7.5. The phosphate buffer pH 7.5 was included in the request since the solubility of azithromycin is lowest in alkaline solutions and pH 7.5 buffer may be more discriminating than pH 6.0 buffer.

The dissolution profiles at pH 6.0 and 7.5 are shown in Figures 2 and 3. The similarity factor was calculated between a single 250 mg and 500 mg tablet as well as between a single 600 mg and 500 mg tablet. The sponsor calculated a similarity factor at pH 6.0 even though the % dissolution exceeded —% by the first sample. The reviewer calculated the similarity factor at pH 7.5 using one measurement after — % dissolution for both tablet strengths. The results of the similarity factor are shown in Table 3.

Table 3. Comparison of similarity factors reported by the sponsor and reviewer comparing two 250 mg tablets vs. a single 500 mg tablet using USP Apparatus 1, 100 RPM

	Similarity factor (f_2)	
Condition	**Sponsor**	**Reviewer**
250 mg vs. 500 mg tablets		
pH 6.0		NA*
pH 7.5		
600 mg vs. 500 mg tablets		
pH 6.0		NA*
pH 7.5		

*Not calculated by the reviewer

The coefficient of variation at any pH did not exceed 8.9% for the comparison of 250 mg vs. 500 mg tablets or 600 mg vs. 500 mg tablets.

Based on the similarity of the *in vitro* dissolution profiles, the dissolution characteristics of azithromycin 500 mg tablets are similar to 250 mg tablets and supports granting a waiver of in vivo bioequivalence studies to the sponsor.

Figure 2. The dissolution profiles comparing a single 250 mg and 500 mg tablet at pH 6.0 and 7.5 (USP Apparatus 2, 75 RPM)

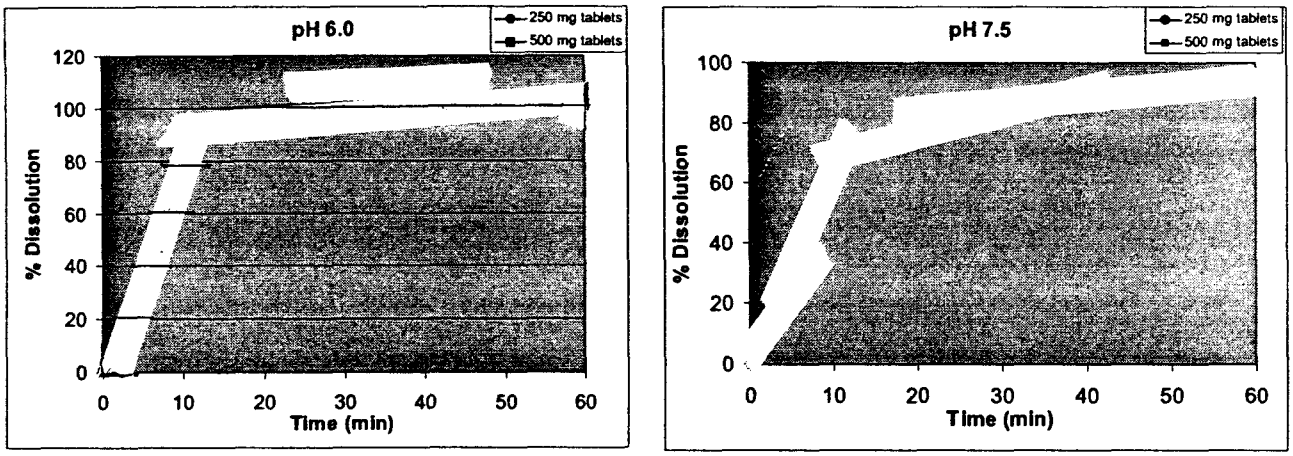
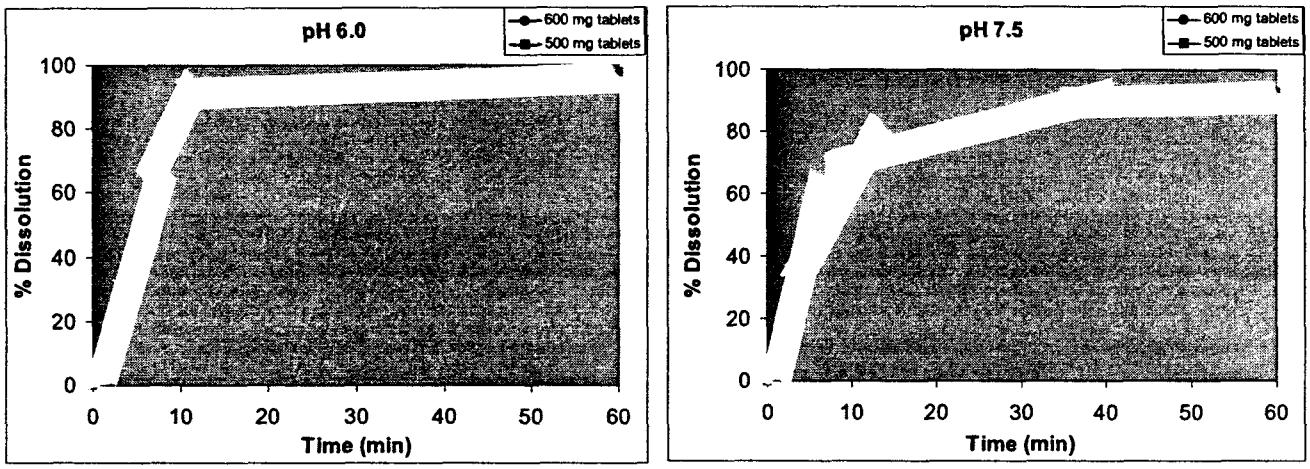


Figure 3. The dissolution profiles comparing a single 600 mg and 500 mg tablet at pH 6.0 and 7.5 (USP Apparatus 2, 75 RPM)



The recommended dissolution conditions for azithromycin 500 mg tablets are the same as azithromycin 250 mg and 600 mg tablets: USP Apparatus 2 (paddle) at 75 rpm, in 900 ml of pH 6.0 0.1 M phosphate buffer at 37°C ± 0.5°C. The recommended specification for azithromycin 500 mg tablets is Q= ▬ % in 30 minutes.

1 pages redacted from this section of the approval package consisted of draft labeling

VI. Appendix A. Proposed Label

See attached label

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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5/13/02 01:23:41 PM
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