nDA50-7

AP Ltr
AE Ltrs
SBA memo
mOR
Bio
Pharm. memos
Chem

EA + Fans.
micro

Ap Ltr
AE LtRs
SBA memos

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-711

JUL 18 1996

Robert B. Clark
Senior Associate Director
Regulatory Affairs Division
Pfizer Incorporated
235 East 42nd Street
New York, New York 10017-5755

Dear Mr. Clark:

Please refer to your February 15, 1994 new drug application (NDA) submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for ZITHROMAX ® (azithromycin) 250 mg Tablets.

We acknowledge receipt of your amendments dated September 26, 1994, November 21, 1995, March 25, 1996, May 2, 1996, and June 19, 1996.

We also note our approvable letters dated February 14, 1995, and May 22, 1996.

This new drug application provides for pharmacokinetic data to demonstrate that azithromycin tablets are bioequivalent to the currently marketed capsule formulation.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling submitted on May 2, 1996. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on May 2, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-711. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in the May 22, 1996 approvable letter and agreed upon as per your letter dated June 19, 1996. These commitments, along with any completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. Jose Cintron, Project Manager, at 301-827-2125.

Sincerely yours,

David W Feigal Jr 7-17-96

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Orig NDA 50-711
HFD-520/Div.File
HFD-2/MLumpkin
HFD-830/ESheinin
HFD-40/DDMAC
HFD-613
HFZ-400
HFD-80
DISTRICT OFFICE
HF-2/Medwatch (labeling)
HFD-735
HFD-021/JTreacy
HFD-520/MO/GGirardi
HFD-520/TLPHARM/ROsterberg
HFD-520/PHARM/MAdeyemo 7/18/96
HFD-520/TLCHEM/SRoy
HFD-520/CHEM/JTimper 7-15-96
HFD-520/TLBIOPHARM/FPelsor
HFD-520/BIOPHARM/HSun 7/19/96
HFD-520/TLMICRO/ASheldon
HFD-520/MICRO/PDionne
HFD-520/TLSTAT/DLin
HFD-520/PMS/JCintron
HFD-520/PMS/FVLeSane/7-12-96 7-12-96

Concurrence Only:
HFD-520/Acting Div.Dir./DFeigal
HFD-520/TLMO/MAlbuerne/MA 7/19/96
HFD-520/CPMS/JBone 7/17/96

50-711.AP

APPROVAL with Phase 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-711

MAY 22 1996

Robert B. Clark
Senior Associate Director
Regulatory Affairs Division
Pfizer Incorporated
235 East 42nd Street
New York, New York 10017-5755

Dear Mr. Clark:

Please refer to your February 15, 1994 new drug application (NDA) submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for ZITHROMAX ® (azithromycin) 250 mg Tablets.

We acknowledge receipt of your amendments dated November 21, 1995; March 25, 1996, and May 2, 1996 .

We also note our approvable letter dated February 14, 1995.

This new drug application provides for pharmacokinetic data to demonstrate that azithromycin tablets are bioequivalent to the currently marketed capsule formulation.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information:

BIOPHARMACEUTICS:

1. Conduct dissolution studies in the proposed media at both 75 rpm and 50 rpm paddle speed for the tablet formulation. The dissolution test should be conducted on 12 units each of the whole tablets. The lot used in this dissolution test should be the same as the lot used for conducting dissolution test at 100 rpm (lot # ED-B-387-Z92).

   At this time, as an interim dissolution test, the dissolution specification should be changed to Q % in minutes at 100 rpm instead of proposed Q % in minutes at 100 rpm.

Sufficient sampling times should be included to generate a complete dissolution profile. Upon review of these data, a final dissolution specification for the tablet should be proposed.

CHEMISTRY:

2. Revise the appropriate Chemistry, Manufacturing, and Control sections (CMC) for this 250 mg tablet when the pending NDA 50-730 for the 600 mg tablet is approved.

In addition, please submit sixteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material. The labeling should be identical in content to the draft labeling submitted on May 2, 1996.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Mr. Jose Cintron, Project Manager, at 301-827-2125.

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

cc: Orig NDA 50-711
HFD-520/Div.File
HFD-2/MLumpkin
HFD-101/LCarter
HFD-104/DFeigal
HFD-830/ESheinin
HFD-40/DDMAC
HFD-613
HFZ-400
HFD-80
DISTRICT OFFICE
HF-2/Medwatch (labeling)
HFD-735
HFD-021/JTreacy
HFD-520/MO/GGirardi
HFD-520/PHARM/MAdeyemo
HFD-520/CHEM/JTimper
HFD-520/BIOPHARM/HSun
HFD-520/MICRO/PDionne
HFD-520/TLSTAT/DLin
HFD-520/PMS/JCintron
HFD-520/PMS/FVLeSane/4-16-96/5-22-96

Concurrence Only:
HFD-520/Dir./MFanning
HFD-520/TLMO/MAlbuerne. 5/22/96
HFD-520/CPMS/JBona 5/22/96
HFD-540/Dir.ODE IV/DFeigal 5-22-96

50-711.AE

APPROVABLE (AE)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-711

FEB 14 1995

Charles A. Ritrovato, Pharm.D.
Associate Director II
Regulatory Affairs-Liaison
Pfizer Inc.
Eastern Point Road
Groton, CT 06340

Dear Dr. Ritrovato:

Please refer to your February 15, 1994 new drug application (NDA) submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for ZITHROMAX® (azithromycin) 250-mg Tablets.

We acknowledge receipt of your additional communication dated September 26, 1994.

This new drug application provides for pharmacokinetic data to demonstrate that azithromycin tablets are bioequivalent to the currently marketed capsule formulation.

We have completed the review of this application, as amended, and it is approvable. Before the application may be approved, however, we request that you revise the package insert as indicated in the January 27, 1995 approvable letter for NDA 50-710.

In addition, the CLINICAL PHARMACOLOGY section should be revised as follows:

1. Line 34 should read:

2. Insert the following pharmacokinetic/bioequivalence information regarding the tablet formulation starting with line 51:

3. Line 124, the statement should be rewritten as follows:

Please note that any advertising or promotional labeling for ZITHROMAX® (azithromycin) Tablets will be considered false and misleading under Section 502 of the Act if it utilizes in vitro microbiologic data to imply clinical efficacy or to imply clinical superiority over other drug products if such indications or clinical superiority have not been established in adequate and well-controlled clinical trials. *In vitro* microbiologic data establish in vitro microbiologic activity. Appropriate use of such data in advertising and promotional labeling requires a balanced presentation of how such data should be interpreted in view of the human pharmacokinetic properties and the established clinical efficacy of these drug products.

In addition, any advertising or promotional labeling for ZITHROMAX® (azithromycin) Tablets will be considered false and misleading under Section 502 of the Act if it attempts to minimize, by print size or presentation emphasis, the fact that clinical data from adequate and well-controlled trials are not available establishing efficacy of this drug product in treating diseases due to the organisms contained in the "not clinically supported" (i.e., the second) grouping of organisms in the *Microbiology* subsection of the drug product labeling.

Finally, any advertisement or promotional labeling for ZITHROMAX® (azithromycin) Tablets will be considered false and misleading under the Act if it does not include the entire **INDICATIONS AND USAGE AND DOSAGE AND ADMINISTRATION** sections of the labeling when referring to the indications or dosing regimens for which this product is approved. The "NOTES" and other added statements in these sections are considered integral parts of the approved indication and dosing regimens and may not be deleted or edited.

Also, in advertising or promotional labeling, the "NOTES" and other added statements may not be spatially separated from the wording in the initial part of the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION sections so as to minimize their impact. Such information must be presented in advertising or promotional pieces in at least the same print size and with at least the same impact as any other information from this section of the labeling.

This guidance constitutes notice of activities that may be considered to be violations of the Act. Failure to comply with this guidance may result in regulatory action without further notice.

Please submit, in quadruplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Anti-Infective Drug Products, and the remaining copies to the Division of Drug Marketing, Advertising, and Communications, HFD-240, Room 17B-06, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FDA 2253 for this submission; that form is for routine use, not proposed materials. Please be advised that, should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

Please also be advised that the establishment inspections have not yet been completed. We cannot approve this application until satisfactory Establishment Inspection Reports have been received for all facilities involved in the manufacture and packaging of the bulk drug and the drug product.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial response will not be processed as a major amendment ("user fee resubmission"), and, therefore, the user fee review clock for the "resubmission" will not be activated.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of this invoice.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions concerning this application, please contact Ms. Frances LeSane, Project Manager, at 301-443-0257

Sincerely yours,

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 50-711
HFD-520 Div. File
HF-2 (with draft labeling)
HFA-100 (If user fee application)
HFC-130/JAllen
HFD-5/THassall (If user fee application)
HFD-82
HFD-473
HFD-500
HFD-735
HFD-240
HFD-520/MO/NMoledina 2/13/95
HFD/520/Micro/PDionne PAD 2/13/95
HFD-520/Pharm/MAdeyemo 2/13/95
HFD-520/Chem/JTimper JMT 2/13/95
HFD-426/Biopharm/HSun 2/13/95
HFD-520/PMS/FLeSane/1-24-95/2-10-95/2-13-95

Concurrence Only:
HFD/520/Act Div Dir/LGavriloyich
HFD-520/SMO/MAlbuerne 2/13/95
HFD/520/SPharm/ROsterberg 2/13/95
HFD/520/SChem/SRoy 2/13/95 2/13/95
HFD/520/SMicro/ASheldon 2/11/95
HFD-713/SBiometrics/RHarkins
HFD-426/SBiopharm/FPelsor 2/13/95
HFD-520/SPM/JBona 2/13/95

APPROVABLE

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 12, 1996

TO: David W. Feigal, M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

FROM: Frances V. LeSane, Project Manager
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Summary Basis of Approval for NDA 50-711, Zithromax® (azithromycin) 250 mg Tablets.

The following reviews will serve as the Summary Basis of Approval for Zithromax® (azithromycin) 250 mg Tablets.

Medical review dated January 24, 1995.
Statistical review cross-referenced from NDA 50-670 azithromycin capsules approved 11-1-91.
Biopharm review dated January 27, 1995.
Pharmacology reviews cross-referenced from NDA 50-670 azithromycin capsules approved 11-1-91 and NDA 50-710 approved 10-19-95.
Chemistry review dated April 8, 1994, June 21, 1996.
Microbiology review dated April 26, 1994.

Note Phase 4 commitments in the May 22, 1996 approvable letter agreed upon by sponsor June 19, 1996.

cc:
Orig NDA 50-711
HFD-520/Div. File
HFD-520/TLMO/MAlbuerne
HFD-520/MO/GGirardi
HFD-713/TLSTAT/DLin
HFD-880/TLBIOPHARM/FPelsor
HFD-880/BIOPHARM/HSun
HFD-520/TLPHARM/ROsterberg
HFD-520/PHARM/MAdeyemo
HFD-520/TLCHEM/SRoy
HFD-520/CHEM/JTimper

HFD-520/TLMICRO/ASheldon
HFD-520/MICRO/HSilver
HFD-520/PMS/JCintron
HFD-520/PMS/FLeSane/7-12-96

MoR

MEDICAL OFFICER'S REVIEW OF NDA 50-711

Date Submitted:	February 15, 1994.
Date Assigned:	February 18, 1994.
MOR Initiated:	January 24, 1995.

APPLICANT: Pfizer Central Research
Eastern Point road
Groton, CT 06304

DRUG: **Generic:** Azithromycin
Trade: Zithromax

DOSAGE FORM: 250 mg tablets

MATERIAL REVIEWED: Bioequivalent studies/Food studies

BACKGROUND:

This NDA contains data to demonstrate that azithromycin tablets are bioequivalent to the currently marketed capsule formulation. The NDA also presents data from food effect studies to demonstrate that the effect of food on the bioavailability of azithromycin is a formulation dependent phenomena.

Medical Officer's Review

Since there are no clinical data submitted for review, a summary of the Biopharmaceutics Review by Dr. He Sun (Refer to his review dated January 27, 1995) is presented below.

In the submission there were two pivotal studies, **#066-042-599**, a bioequivalence study comparing the 250 mg tablet formulation to the commercially available 250 mg capsule; and study **#066-055-54C**, a food effect study on the bioavailablity of the tablet. There were six additional studies (4 US studies and 2 Non-US) submitted to demonstrate that azithromycin bioavailability is not inherently affected by food and that the effect of food is formulation-dependent. The four US studies have adequate data for review and are acceptable, while the two Non-US studies are incomplete. The data from two pivotal studies and 4 food effect studies support the labeling change requested by the applicant.

The overall conclusions drawn by Dr. He Sun, the biopharmaceutics reviewer of this NDA are:

- Study #066-042-599 examined the bioequivalence of the proposed 250 mg tablet formulation of azithromycin to the present commercially available 250 mg capsule formulation. The results demonstrated that the relative bioavailability was 105% with 90% confidence limits on the tablet to capsule AUC ratio of 99-113% and C_{max} 96-121%. Both sets of confidence limits fell within the criteria for bioequivalence of 80-120%. **Thus, the conclusion drawn was that the proposed 250 mg azithromycin tablet was bioequivalent to the current commercial 250 mg azithromycin capsule.**

- The food effect study #066-055-54C with 12 volunteers **demonstrated that a** standard breakfast containing at least 30 grams of fat, **did not affect the** bioavailability of azithromycin from the proposed 250 mg tablets. **Thus, the conclusion drawn was that the bioavailability of azithromycin administered as two 250-mg tablets was not changed by a high fat meal. These results demonstrate that the 250 mg tablet may be given without restrictions relative to the ingestion of meals.**

- The other 4 US studies compared the bioavailability of different azithromycin formulations with regard to food. **The conclusion drawn was that the effect of food on the bioavailability of azithromycin is dependent upon the formulation.**

The following labeling changes are recommended by the biopharmaceutics reviewer, Dr. He Sun (Refer to the attachment):

1. Line 34 to line 44, the data presented are for the capsule formulation. When the labeling is changed for the tablet formulation, line 34 should read as '

2. Insert the following pharmacokinetic/bioequivalence information regarding the tablet formulation starting from line 51:

3. The statement "Food does not affect the absorption of azithromycin" should be rewritten to state:

OVERALL RECOMMENDATIONS:

According to the biopharmaceutics reviewer, Dr. He Sun, this NDA contains data which have demonstrated that the 250-mg tablet is bioequivalent to the commercially available 250-mg capsule. Thus, the application is approvable pending revision of the labeling to incorporate the food effect statement as recommended by the biopharmaceutics reviewer and revised by Dr. Albuerne (SMO) and Dr. Moledina (MO) and additional revisions pending approval of the suspension formulation labeling.

Nasim Moledina

Nasim Moledina, M.D.

cc orig NDA
HFD-235
HFD-520
HFD-340
HFD-520/MO/NMoledina
HFD-520/PMS/FLeSane
HFD-520/Micro/PDionne
HFD-520/Pharm/Adeyemo
HFD-426
50711/nm/1-24-95/rev2-9-95 2/11/95

Concurrence Only:
HFD-520/ActingDivDir/LGavrilovich
HFD-520/SMO/MSAlbuerne
2/9/95

Bio

JAN 27 1995

NDA: 50,711		**SUBMISSION DATE:**	Feb. 15, 1994 April 29, 1994 Sept. 26, 1994
PRODUCT:	Azithromycin Tablet **(ZITHROMAX)**		
SPONSOR:	Pfizer Central Research. Eastern Point Road Groton, CT 06340		
TYPE OF SUBMISSION:	Original NDA, 3S	**REVIEWER:**	HE SUN, Ph.D.

BIOPHARMACEUTICS REVIEW

NDA 50,711

I. SYNOPSIS

Azithromycin capsule was approved on November 1, 1991 (NDA 50,670). The sponsor submitted this New Drug Application (NDA 50,711) to support a new tablet formulation (FID #GOO267AA) which is formulated to replace the capsule formulation.

In the submission, one study (#066-042-599) was conducted to establish the bioequivalence of this new 250 mg tablet formulation to the commercial 250 mg capsules. Another study (#066-055-54C) was performed to assess the effect of food upon the bioavailability of azithromycin tablet. Six additional studies (#066-041-503, #066-046-599, #066-050-29C, #066-057-54C, #066-206, AZM-NY-89-0) are presented in this submission to demonstrate that azithromycin bioavailability is not inherently affected by food and that the effect of food is formulation-dependent.

The results of included BE, BA studies well support the following statements:

1. The new 250 mg azithromycin tablet formulation is bioequivalent to the present commercial capsule, when administered to volunteers in the fasted state.

2. The extent of bioavailability of the new tablet formulation of azithromycin is unchanged by coadministration with food.

3. The effect of food on the bioavailability of azithromycin is formulation dependent.

II. RECOMMENDATION

1. **The two main studies, #066-042-599, Bioequivalence Study, and #066-055-54C, Effect of Food on the Bioavailability of Tablet, are acceptable to the Division of Biopharmaceutics. These two studies support the proposed labeling.**

2. **The additional six food effect studies were not used to support the proposed labeling. In which, four U.S. studies (#066-041-503, #066-046-599, #066-050-29C, and #066-057-54C) are completed and acceptable. These studies support the statement that the food effect on azithromycin absorption is formulation depended. Two non-US studies (#066-206, #AZM-NY-89-0) are incomplete. However, they do not affect the acceptance of the submission.**

3. **Although the bioavailabilities/bioequivalence studies, presented in this submission, were conducted in healthy male volunteers, the sponsor has evaluated the effect of gender on the pharmacokinetics of azithromycin in previous NDA submissions.**

4. **Overall, the sponsor's conclusions are supported by studies included. The Pharmacokinetics and Biopharmaceutics Section of NDA 50,711 is acceptable to the Division of Biopharmaceutics.**

5. **The dissolution study is incomplete. As an interim dissolution test, the sponsor should change the dissolution specification to Q % in minutes at 100 rpm instead of proposed Q % in minutes at 100 rpm.**

6. **The sponsor should be informed comments #1-3.**

7. **The final label should be submitted for review.**

TABLE OF CONTENTS:

III. BACKGROUND

Azithromycin is an azalide, a subclass of macrolide antibiotic. Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentration in tissue than in plasma or serum. Plasma concentration of azithromycin declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. The high values for apparent steady-state volume of distribution (31.1 L/kg) and plasma clearance (630 ml/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues.

Azithromycin capsules previously received marketing approval in the U.S. on November 1, 1991 (NDA 50,670) as a capsule dosage form for the treatment of respiratory tract, skin and skin structure infections, and chlamydia trachomatis genitourinary infections in patients 16 years of age and older. A majority of the technical information contained in NDA 50,670, such as in vitro microbiology data, chemistry, manufacturing and control data pertaining to azithromycin drug substance, and nonclinical pharmacology and toxicology data is directly applicable to the current application and is therefore incorporated by cross-reference. This submission seeks to replace the commercial capsules with a new tablet formulation (FID #GOO267AA).

The formulations used in these studies were described in Section 6 (Human Pharmacokinetics and Bioavailability Section) of this NDA.

In all six studies conducted by Pfizer Central Research in the United States (#066-042-599, #066-055-54C, #066-041-503, #066-046-599, #066-050-29C, #066-057-54C), concentrations of azithromycin in serum were determined with an HPLC assay with amperometric electrochemical detection. The method is described in detail in the assay reports appended to study reports in Section 6, HUMAN PHARMACOKINETICS AND BIOAVAILABILITY, of this NDA.

Studies performed outside the USA (AZM-NY-89-0) by other Pfizer Divisions also utilized HPLC assays with electrochemical detection.

Four azithromycin oral formulations were submitted by the sponsor to date: the oral capsule (NDA 50,670, approved on Nov. 1, 1991); the 1 gram single dose Packet (NDA 50,693, approved on Sept. 28, 1994); the pediatric suspension formulation (NDA 50,710) and the current tablet formulation. Dr Ruth Stevens found that the 1 gram single dose packet suspension was equivalent in the extent of absorption (AUC 90%CI: 97%-102.1%) but not equivalent in rate of absorption (Cmax 90%CI: 102.3%-125.6%). Dr. Ene Ette found that food increased the rate and extent of absorption of azithromycin from the 1 gram single dose packet by 46% and 14%, respectively. Dr. He Sun found studies for the pediatric suspension formulation are acceptable and food effect essentially is the same as for the 1 gram single dose packet suspension. The new tablet formulation is listed in Section IV.

IV. DRUG FORMULATION

The new tablet formulation is listed in the following page.

D.2.A Composition

Each tablet contains azithromycin dihydrate equivalent to 250 mg of azithromycin. The tablets also contain: pregelatinized starch (binder); calcium phosphate, dibasic, anhydrous (diluent); croscarmellose sodium (disintegrant); and magnesium stearate/sodium lauryl sulfate, 90/10 blend (lubricant and wetting agent). The tablet blend is granulated with purified water which is evaporated during processing. Compressed tablet cores are film-coated with pink Opadry II® dispersed in purified water. This water is also evaporated during processing. The quantitative compositions of the tablet blend and film-coated tablets are:

Tablet Core Ingredients	mg/tablet
Azithromycin Dihydrate	
Pregelatinized Starch	
Calcium Phosphate Dibasic, Anhydrous	
Croscarmellose Sodium	
Magnesium Stearate/Sodium Lauryl Sulfate 90/10 Blend	

(1) Equivalent to 250 mg azithromycin based on a theoretical potency of 95.4%

Tablet cores are coated with pink Opadry II® with an intended coverage of [redacted] mg per tablet. Total weight of film-coated tablets [redacted] mg.

D.2.B Manufacturing and Packaging

Azithromycin 250 mg film-coated tablets will be manufactured at either of the following two plant sites:

Pfizer Pharmaceuticals
Brooklyn Plant
630 Flushing Avenue
Brooklyn, NY 11026

Pfizer Pharmaceuticals
P.O. Box 628
KM 58.2 Road #2
Barceloneta, Puerto Rico 00617-0628

V. SUMMARY OF STUDIES

A overall summary of studies are tableted in page 6 and 7.

1. Bioequivalence Study

Clinical Study #066-042-599

Phase I study to examine the bioequivalence of azithromycin commercial 250 mg capsules and 250 mg tablet.

This was an open, randomized, two-way crossover study to examine the bioequivalence of azithromycin commercial capsules and the 250 mg tablets. Thirty-six (36) fasted, healthy, male volunteers received two 250 mg commercial capsules (Lot #F311) and two 250 mg tablets (FID #G00267AA, Lot #ED-B-387-Z92). The doses were separated by two weeks. Blood samples were collected for times up to 120 hours post-dose for preparation of serum, which was frozen at -70°C until assay by HPLC with electrochemical detection. Pharmacokinetic parameters (AUC_{0-72}, C_{max}, T_{max}) were determined. The results are:

	Capsule	Tablet	90% CI*
AUC 0-72 ug-hr/ml	4.08 (1.194)	4.26 (1.183)	(99-113%)
Cmax (ug/ml)	0.482 (0.191)	0.512 (0.210)	(96-121%)
Tmax (hours)	2.1 (0.8)	2.2 (0.9)	

* Based on log transformed data.

Both sets of confidence limits fell within the criteria for bioequivalence of 80 to 125%. Thus, the two formulations were bioequivalent.

2. Effect of Food on Bioavailability of the Tablet Formulation

Clinical Study #066-055-54C

An open study of Azithromycin serum concentration following oral administration of 250 mg tablets with and without food.

This was an open, randomized, 2x2 crossover study to assess the effect of food on the serum concentrations of azithromycin resulting from the oral administration of two 250 mg film-coated tablets (FID #G00267AA, ED-B-387-Z92). 12 Subjects ranged in age from 21 to 36 years (mean age 26.4 years) and in weight from 54.9 to 90.7 kg (mean weight 75.8 kg) were enrolled in the study. Subjects were randomly assigned to receive two 250 mg film-coated tablets either after an 12 hours overnight fast or after a standard meal high in fat content (two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk) on day 1. On day 15, subjects were administered azithromycin under the alternate treatment conditions. All doses were taken after an overnight fast of at least 12 hours, and were taken with 240 ml of water alone, or with 240 ml of

water after the standard meal. Subjects refrained from eating, lying down, or drinking caffeinated beverages for four hours after each dose, at which time they were provided identical standard meals. Serum samples were collected up to 96 hours after each dose of azithromycin. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC_{0-48}, C_{max}, T_{max}).

The results are listed at following:

	Fasted	Fed	90% CI
Relative Bioavailability (%)	–	96.3	
AUC_{0-48} ug-hr/ml	2.491 (0.642)	2.399 (0.678)	(82.2-113.4%)
C_{max} (ug/ml)	0.336 (0.081)	0.412 (0.194)	(88.1-145.8%)
T_{max} (hours)	2.1 (0.7)	2.3 (0.8)	

Results show that azithromycin was well tolerated, with only a single episode of mild diarrhea reported. The bioavailability of the 500 mg of azithromycin from two 250 mg film-coated tablets was not reduced by administration with a high fat (>20 gram fat) meal.

3. Effect of Food on Bioavailability of Other Formulations (Supportive studies)

Clinical Study #066-041-503

PHASE I PHARMACOKINETIC STUDY COMPARING AZITHROMYCIN 250 MG CAPSULES VERSUS ORAL SOLUTION GIVEN WITH AND WITHOUT FOOD

The purpose of this study was to assess the effects of formulation dissolution and the effects of administration under fed and fasted conditions on the pharmacokinetics of azithromycin. This was an open label, randomized, four-way crossover study of single 500 mg doses of azithromycin administered orally as 2x250 mg commercial capsules and as a solution. 12 subjects ranged in age from 20 to 44 years (mean age 29.9 years) and in weight from 62.1 to 89.8 kg (mean weight 71.9 kg) were enrolled. The individual doses were 2x250 mg capsules (commercial lot #F311), fed and fasting, and as an oral solution (FID #FY-91-092), fed and fasting on days 1, 15, 29, and 43. Subjects fasted overnight for 10-12 hours prior to each dose or standard breakfast. Serum samples collected up to 96 hours after each azithromycin administration were analyzed for azithromycin content. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC_{0-48}, C_{max}, and T_{max}).

Pharmacokinetic Parameter Values are:
Mean (Standard Deviation)

	500mg Solution		2x250 mg Capsules	
	Fasted	Fed	Fasted	Fed
AUC_{0-48} (ug-hr/ml)	3.20(0.70)	2.94(0.74)	2.57(0.82)	2.11(0.73)
C_{max} (ug/ml)	0.517(0.194)	0.502(0.232)	0.357(0.106)	0.276(0.149)
T_{max} (hours)	1.21(0.62)	2.25(0.87)	2.18(1.08)	3.83(1.19)

	Solution (Fed/Fast)	Capsule (Fed/Fast)	Capsule (Fast)/ Solution (Fast)
Relative Bioavailability	92	82	80
AUC_{0-48} geometric mean ratio	90.0	80.4	78.4
(90% CI)	(75.4-107.3)	(67.0-96.40)	(65.4-94.1)
C_{max} geometric mean ratio	92.5	70.0	70.2
(90% CI)	(70.8-120.9)	(53.1-92.3)	(53.3-92.5)

Results indicate that azithromycin capsules were about % bioavailable compared to the azithromycin administered as a solution. The time to peak serum concentration was longer after the capsule than after the solution.

Concomitant administration of azithromycin with a high-fat breakfast decreased the bioavailability, as measured by AUC_{0-48}, approximately 18% and 8% for the capsules and solution, respectively. T_{max} was prolonged by food.

No subjects discontinued the study. Two subjects had mild to moderate side effects (headache, headache and abdominal pain) which resolved without additional treatment.

Clinical Study #066-046-599

A PILOT STUDY OF THE PERFORMANCE OF AN ENTERIC DOSAGE FORM OF AZITHROMYCIN ADMINISTERED WITH AND WITHOUT FOOD IN NORMAL VOLUNTEERS

The purpose of this study was to determine the absolute bioavailability of an enteric coated formulation of azithromycin in fasted and fed normal volunteers after oral administration. This study was designed as an open, randomized, three period, three treatment crossover study in which 12 subjects were administered a single 500 mg dose of azithromycin as an intravenous infusion in the fasting state, as an 2x250 mg capsules containing an enteric coated bead formulation in the fasting state, or as an enteric coated formulation after a standard meal. Serum samples collected immediately prior to, and 0.5, 1, 2, 3, 4, 6, 8, 12,18, 24, 48, 72, 96, and 120 hours after each dose were analyzed for azithromycin content. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC_{0-48}, C_{max}, Tmax).

	Pharmacokinetic Parameter Values are: Mean (Standard Deviation)		
	Intravenous (Fasting)	Enteric Coated (Fasting)	Enteric Coated (Fed)
AUC_{0-48}(ug-hr/ml)	8.50 (1.32)	3.30 (0.73)	1.66 (0.90)
C_{max} (ug/ml)	---	0.295 (0.086)	0.193 (0.145)
T_{max}(hours)		3.3 (1.5)	5.6 (1.8)

Bioavailability (Ratio %, (90% Confidence Limits))

AUC_{0-48}	Fasting vs IV	38.4%	(30.3%, 48.5%)
	Fed vs IV	17.6%	(13.9%, 22.3%)
	Fed vs Fasting	46.0%	(36.3%, 58.2%)
C_{max}	Fed vs Fasting	54.2%	(35.6%, 82.6%)

The results from the pharmacokinetic analysis indicate that, following oral administration of an enteric coated bead formulation of azithromycin to fasted healthy volunteers, the bioavailability was about 38%. When the same formulation was administered to fed volunteers, the bioavailability was reduced to about 18%. The bioavailability of azithromycin in fed subjects relative to fasted subjects was about 50%. Thus, the standard high-fat breakfast substantially reduced the bioavailability of azithromycin in the enteric-coated beads.

Side effects were all mild and included pruritus, diarrhea, dyspepsia, nausea, injection site reaction, and taste perversion. Laboratory tests were performed at screening only. No subjects discontinued from the study. There were no serious adverse events.

Clinical Study #066-050-29C

PHASE I STUDY COMPARING AZITHROMYCIN SERUM CONCENTRATIONS FOLLOWING ADMINISTRATION OF 500 MG OF ORAL SUSPENSION IN CONJUNCTION WITH MEALS OF VARYING COMPOSITION

This was an open-label, randomized three period, three treatment crossover study of azithromycin serum concentrations following administration of 500 mg of azithromycin as an oral suspension to six healthy male volunteers under fasting conditions, immediately following ingestion of a standard meal, and immediately following a light meal consisting only of cereal and milk. Serum samples were to be collected immediately prior to and at specified times up to 96 hours after each dose of azithromycin for the determination of pharmacokinetic values. Vital signs and side effects were to be monitored throughout the study. 40 mg/ml suspension (FID# G00007AA) administered orally as a single 500 mg dose on three occasions (fasted, standard breakfast, light breakfast).

		Fasted	Standard Breakfast	Light Breakfast
AUC_{0-48} ug-hr/ml		2.194 (0-542)	2.216 (0-590)	2.325 (0.692)
C_{max} (ug/ml)		0.312 (0.092)	0.325 (0.091)	0.253 (0.051)
T_{max} (hours)		1.8 (0.8)	1.8 (0.8)	2.5 (0.8)
geometric mean ratio (90%CI)	AUC		100.7(79.1-128.2)	102(81.8-132.6)
	C_{max}		104(74.3-146.6)	83.0(59.1-116.6)

Compared to the fasting state, the ingestion of either a standard high-fat or light breakfast caused no apparent changes in the mean extent of absorption of azithromycin after oral administration. Azithromycin was well tolerated. There were no side effects or serious adverse events.

Clinical Study #066-057-54C

A PHASE I OPEN, RANDOMIZED STUDY OF THE CLINICAL PHARMACOLOGY OF AZITHROMYCIN AFTER 1 GRAM OF THE SACHET WITH AND WITHOUT FOOD COMPARED WITH THE INTRAVENOUS FORMULATION IN NORMAL HEALTHY SUBJECTS

This was an open, randomized three treatment, three period crossover study of the effect of food on the serum concentrations and absolute bioavailability Of azithromycin after oral administration of the 1000 mg sachet. Azithromycin was administered on three separate occasions as a 1000 mg intravenous infusion, as a 1000 mg sachet after an overnight fast, and as the 1000 mg sachet immediately after a high fat breakfast on days 1, 15, and 29. Serum samples collected immediately prior to and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 72, 96, and 120 hours after each oral ingestion or after the start of the intravenous infusion were analyzed for azithromycin content. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC_{0-72}, C_{max}, T_{max}, absolute oral bioavailability, and relative bioavailability). 12 Subjects ranged in age from 18 to 42 years (mean age 27.6 years) and in weight from 62.6 to 86.2 kg (mean weight 74.5 kg). The intravenous infusion was infused over a 1 hour period.

	Sachet Fed	Sachet Fasted	Intravenous Infusion
AUC0-72 ug.hr/ml	7.37 (2.12)	6.49 (1.54)	14.76 (2.84)
Cmax (ug/ml)	1.05 (0.40)	0.75 (0.42)	–
Tmax (hours)	2.04 (0.69)	1.46 (0.69)	
Absolute Bioavailability	49.9%	44.0%	
Relative Bioavailability	113.5%	–	

The ratio of AUC_{0-72} sachet-fed to AUC_{0-72} sachet-fasted determined using geometric means was 112.1%. The 90% confidence interval on the ratio ranged from 99.2% to 126.7%. The ratio of Cmax Sachet-fed to Cmax Sachet-fasted using geometric means was 146.2%. The 90% confidence interval on the ratio ranged from 115.8% to 184.6%.

The administration of the azithromycin sachet immediately after a high fat breakfast resulted in increased systemic exposures and peak azithromycin serum concentrations relative to administration without food. The mean relative bioavailability (fed/fasting) was 113.5%. The mean absolute oral bioavailabilities were similar (50% fed, 44% fasting).

Clinical Study #066-206.

THE EFFECT OF FOOD ON THE PLASMA PHARMACOKINETICS OF A SINGLE ORAL DOSE Of AZITHROMYCIN

This was an open label , randomized, two-way crossover with 18 days between each period. A single 500 mg dose of 2 azithromycin capsules was administered on two occasions, to healthy volunteers,

once after a 12 hour fast and once after a standard meal, and plasma samples were withdrawn at intervals up to 24 hours after each dose. Laboratory safety tests were monitored before dosing and 24 and 72 hours after dosing with clinical examinations performed after each dose. The results are as follows:

1.	PK Parameters Mean (SD)	Fasting	Non-Fasting
	C_{max} (ng/ml)	314 (122.5)	153 (37.4)
	T_{max} (hr)	2.6 (1.29)	3.4 (1.5)
	AUC_{0-24} (ng.h/ml)	1347 (495, n=10)	776 (299, n=5)
2.	Safety:	Fasting	Non-Fasting
	No. of subjects with treatment related Side-effects	1/11	0/11

The administration of azithromycin capsules to volunteers in the non-fasting state resulted in statistically and clinically significantly lower C_{max} values (p=0.004). Detectable plasma levels were found at sufficient time points for AUC_{0-24} calculations in only 5/11 subjects in the fed state, so formal statistical analysis was not possible. It is concluded that absorption is reduced in the non-fasting state. Azithromycin was otherwise well tolerated. Laboratory data showed rises in CPK levels in 2 subjects that were possibly treatment related.

Clincial Study AZM-NY-89-0 (conducted by Pfizer-Mack R&D, 7918 Illertissen, Germany)

THE EFFECT OF A LIGHT BREAKFAST ON THE BIOAVAILABILITY OF AZITHROMYCIN CAPSULES, SIMILAR TO THE PRESENT COMMERCIAL CAPSULES.

This was an open, randomized, two-way crossover study to examine the effect of a light breakfast on the bioavailability of azithromycin capsules, similar to the present commercial capsules. Twelve healthy, male volunteers each received two 1000 mg oral doses of azithromycin in four 250 mg capsules (FID #YY-89-051), once following an overnight (12 hr) fast and once following a light breakfast of two rolls with butter and jam and approximately 300 ml of coffee or tea with milk, ingested immediately prior to the doses. The treatments were separated by an interval of two weeks. Blood was collected for times up to 46.5 hours post-dose for preparation of serum, which was frozen until assay for azithromycin by HPLC with electrochemical detection and by bioassay. Urine samples were also collected for intervals up to 46.5 hours post-dose and assayed for azithromycin by HPLC-EC and bioassay. Since the results were similar for the two assays, only HPLC assay results are reported here. The lower limit of quantification of the HPLC assay was 0.01 ug/ml in serum and 0.060 ug/ml in urine. The data were analyzed with a two-way, repeat measures ANOVA. The 90% confidence bounds on the differences in mean AUC, C_{max}, T_{max} and urinary recovery between treatments were calculated.

Mean values of $AUC_{0-46.5}$ were 4.53 ug*hr/ml following the overnight fast and 3.37 ug*hr/ml following the light breakfast. The mean relative bioavailability was 74%. Mean C_{max} was 0.71 ug/ml

following the overnight fast and 0.59 ug/ml following the light breakfast. The ratio of mean C_{max} values was 84%. Mean T_{max} was 2.3 hr following the fast and 3.1 hr following the light breakfast. The 90% confidence limits on the difference in AUCs (AUC_{fed} - AUC_{fasted}), expressed as a percentage of the observed mean following the overnight fast, were -48% and -3%. The corresponding limits on the difference in C_{max} were -38% and +5%. The mean recoveries of azithromycin in urine were 5.1% and 3.8% following the overnight fast and the light breakfast, respectively. Thus, the bioavailability of azithromycin in capsules was reduced by coadministration with a light breakfast.

VI. OVERALL SUMMARY AND CONCLUSION

Study #066-042-599 examined the bioequivalence of the proposed 250 mg tablet formulation of azithromycin and the present commercial formulation. The relative bioavailability was 105% with 90% confidence limits on the tablet to capsule AUC ratio of 99-113% and C_{max} 96-121%. Both sets of confidence limits fell within the criteria for bioequivalence of 80 to 125%. Thus, the proposed 250 mg tablet formulation was bioequivalent to the current commercial 250 mg capsule.

A further study (#066-055-54C) with 12 volunteers showed that administration of a standard breakfast, containing at least 30 grams of fat, did not affect the bioavailability of azithromycin from the proposed commercial 250 mg tablets. The geometric mean relative bioavailability, comparing the AUC following the standard meal with the AUC following an overnight fast, was 97% with 90% confidence limits on the fed to fasted ratio of 82% and 113%. Thus, the bioavailability of azithromycin administered as two 250 mg tablets was not decreased by administration immediately following a high-fat meal.

The effects of food on the bioavailability of azithromycin from several formulations were examined in six studies. Relative bioavailabilities ranged from less than or equal to 50% for two formulations (research capsule Study #066-206; enteric-coated beads - Study #066-046-599) to values close to 100% for 500 mg in solution (Study #066-041-503), 500 mg from a powder for oral suspension (Study #066-050-29C) and a 1000 mg sachet (Study #066-057-54C). Examination of the effect of food on the bioavailability of the present commercial capsule showed a moderate effect, with a high-fat breakfast yielding a relative bioavailability of 82% in Study #066-041-503 and a light breakfast producing a relative bioavailability of 74% for a 1000 mg dose in Study AZM-NY-89-0. Thus, the effect of food on bioavailability is dependent upon the formulation.

These results demonstrate that the proposed 250 mg azithromycin tablets will produce serum concentrations in man equal to those produced by the present commercial capsules and that the tablets may be given without restrictions relative to the ingestion of meals.

Protocol No. (Country)	Study Objective	Study Design	Number of Subjects enrolled/ completed	Treatment	Study Conclusion*	FID Number	Lot Number (Date of Manufacture)
066-042-599 (USA)	Bioequivalence of commercial capsule	Two-way single dose crossover and proposed tablet	36/36	2 x 250 mg tablet	-	G00267AA	EC-B-387-Z92 (1/93)
			36/36	2 x 250 mg commercial capsule		commercial material	F311
066-056-54C (USA)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover	12/12	2 x 250 mg tablet, fasted.	-	G00267AA	EC-B-387-Z92 (1/93)
			12/12	2 x 250 mg tablet, fed[a]		G00267AA	EC-B-387-Z92 (1/93)
066-041-503 (USA)	Compare serum levels in fed and fasted	Four-way single dose crossover subjects	12/12	500 mg solution fasted.		YY-91-092	EC-G-209-891 (10/91)
			12/12	500 mg solution fed[a].		YY-91-092	EC-G-209-891 (10/91)
			12/11	2 x 250 mg capsule fasted.		commercial material	F311 (8/91)
			12/12	2 x 250 mg capsule fed[a].		commercial material	F311 (8/91)
066-046-599 (USA)	Absolute bioavail of enteric dose. Serum levels in fed and fasted subjects.	Three-way single dose crossover.	12/12	1000 mg IV	-	YY-91-092	EC-G-321-Z91 (1/92)
			12/12	500 mg enteric beads, fasted.		G00243AA	EC-G-349-Y92 (11/92)
			12/12	500 mg enteric beads, fed[a].		G00243AA	EC-G-349-Y92 (11/92)
066-050-29C (USA)	Compare serum levels in fed and fasted subjects.	Three-way single dose crossover	6/6	500 mg oral solution, fasted.	-	G00007AA	EC-B-092-491 (7/91)
			6/6	500 mg oral solution, fed[a].		G00007AA	EC-B-092-491 (7/91)
			6/6	500 mg oral solution, fed[b].		G00007AA	EC-B-092-491 (7/91)
066-057-54C (USA)	Absolute bioavail of sachet. Serum levels in fed and fasted subjects.	Three-way single dose crossover	12/12	1000 mg IV, fasted	-	YY-91-092	EC-G-321-Z91 (1/92)
			12/12	1000 mg oral sachet, fasted.	-	G00047AA	EC-P-156-691 (7/91)
			12/12	1000 mg oral sachet, fed[a].		G00047AA	EC-P-156-691 (7/91)
066-206 (Belgium)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover	11/10	2 x 250 mg capsule, fasted.	-	YY-88-008	855-19 (2/88)
			11/10	2 x 250 mg capsule, fed[a].		YY-88-008	855-19 (2/88)
AZM-NY-89-0 (Germany)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover.	12/12	4 x 250 mg capsule, fasted.	-	YY-89-051	EC-G-170-789 (8/89)
			12/12	4 x 250 mg capsule, fed[a].		YY-89-051	EC-G-170-789 (8/89)

* Please refer to Section F.1 (Human Pharmacokinetics and Bioavailability Summary).

a High-fat breakfast containing at least 30 grams of fat.

b Cereal and milk.

c Light breakfast of rolls with butter and jam and coffee or tea

Study	Dosage Form	Dose (mg) Treatment	C_{max} (µg/mL)	T_{max} (hr)	AUC^1 (µg hr/mL)	Urinary Excretion[2] (% of Dose)
Bioequivalence of 250 mg commercial capsule and proposed 250 mg tablet						
066-042-560	Oral 250 mg commercial capsule	500 mg	0.402 (40)	2.1 (16)	4.07[0-72] (29)	
	Oral 250 mg tablet	500 mg	0.513 (41)	2.5 (43)	4.280[0-72] (28)	
Effect of food on proposed 250 mg tablet formulation						
066-053-54C	Oral 250 mg tablet	500 mg fasted	0.336 (24)	2.1 (33)	2.491[0-48] (36)	
	Oral 250 mg tablet	500 mg fed[3]	0.412 (47)	2.3 (35)	2.969[0-48] (28)	
Effect of food on other formulations						
066-041-503	Oral solution	500 mg fasted	0.517 (38)	1.2 (51)	3.20[0-48] (22)	
	Oral solution	500 mg fed[3]	0.502 (39)	2.3 (25)	2.84[0-48] (23)	
	Oral 250 mg capsule	500 mg fasted	0.357 (20)	2.2 (50)	2.67[0-48] (32)	
	Oral 250 mg capsule	500 mg fed[3]	0.276 (54)	3.8 (31)	2.11[0-48] (36)	
066-046-559	1 hr IV infusion	1000 mg	3.22 (16)	0.9 (22)	8.50[0-48] (18)	
	Enteric-coated beads	500 mg fasted	0.285 (29)	3.5 (45)	3.50[0-48] (22)	
	Enteric-coated beads	500 mg fed[3]	0.193 (75)	5.6 (32)	1.86[0-48] (54)	
066-050-29C	Oral POS	500 mg fasted	0.312 (28)	1.8 (44)	2.19[0-48] (35)	
	Oral POS	500 mg fed[3]	0.335 (28)	1.8 (44)	2.21[0-48] (27)	
	Oral POS	500 mg fed[3]	0.269 (28)	2.8 (32)	2.32[0-48] (30)	
066-057-54C	1 hr IV infusion	1000 mg			14.78[0-72] (19)	
	Oral Sachet	1000 mg fasted	0.749 (57)	1.5 (47)	5.45[0-72] (34)	
	Oral sachet	1000 mg fed[3]	1.052 (28)	2.0 (34)	7.37[0-72] (29)	
066-206	Oral 250 mg capsule	500 mg fasted	0.314 (38)	2.8 (50)	1.347[0-48] (57)	
	Oral 250 mg capsule	500 mg fed[3]	0.183 (34)	5.4 (44)	0.779[0-48] (59)	
AZM-NY-89-0	Oral 250 mg capsule	1000 mg fasted	0.705 (21)	2.3 (33)	4.53[0-48.5] (32)	8.1[0-72] (40)
	Oral 250 mg capsule	1000 mg fed[3]	0.550 (32)	5.1 (44)	3.57[0-48.5],[0-72] (42)	(55)

1 measured over the specified interval.
a High-fat breakfast containing at least 30 grams of fat.
b Cereal and milk.
c Light breakfast of rolls with butter and jam and coffee or tea.

Food effects from NDA 50,711

	C_{max}	AUC	T_{max}
Tablet	↑	↔	↔
solution	↔	↔	↑
Caparlex ①	↓	↓	↑
Caparlex ③	↓	↓	↑
Caparlex ②	↓	↓	↑
Enteric-coated beads	↓	↓	↑
oral solution			
High-fat	↔	↔	↔
light milk	↓	↔	↑
Sachet	↑	↑	↑ or ↔ (4.5 vs. 24 hr)

VII. DISSOLUTION TEST

A dissolution rate test is employed to measure the in vitro dissolution rate of 250 mg tablets and commercial capsules. The method uses USP Apparatus 2 (paddles) rotating at 100 rpm in 900 ml of pH 6.0 phosphate buffer held at 37°C±0.5°C. The pH 6.0, 0.1 M phosphate buffer was chosen to assure drug solubility exceeded sink conditions and to assure optimum stability of azithromycin in the dissolution medium. The drug has a solubility of approximately 39 mg/ml in the phosphate buffer at 37°C. This dissolution test for tablet is similar to that used for the approved azithromycin capsules except that trypsin, which is included to aid dissolution of the gelatin capsule shell, is not added to the dissolution medium for the film-coated tablets. Aliquot of the dissolution media were collected at 15, 30, and 45 minute and were analyzed using an HPLC procedure.

Other media considered during the development of the dissolution rate included simulated gastric fluid and water. Simulated gastric fluid was not chosen as the dissolution medium because azithromycin is not sufficiently stable at this acidic pH for such a test. Water was not chosen because the aqueous solubility of azithromycin is only 1.1 mg/ml.

	tablet lot ED-B-387-Z92			Capsule lot F311		
	15'	30'	45'	15'	30'	45'
Mean	99	100	100	99	100	100
low	95	97	98	93	97	9797
HIGH	100	102	101	103	102	102
%rsd	1.3	1.7	0.9	2.6	1.5	1.6

The sponsor proposed a specification at Q= % in minutes which is the same as that approved for azithromycin capsules in NDA 50,670

SPECIFIC COMMENTS

1. Studies #066-042-599, #066-055-54C, #066-041-503 and #066-046-599 are acceptable to the Division of Biopharmaceutics. Study #066-057-54C was reviewed and accepted to the Division of Biopharmaceutics (NDA 50,693, Supplement, reviewer Dr. E. Ette).

   Reports for studies #066-050-29C, #066-206, AZM-NY-89-0 were not completed as indicated in comments #2. However, these deficiencies do not affect the acceptance of the submission.

2. For study #066-050-29C, Food Effect on Oral Suspension, the sample size (6 subjects total) is too small to conclude that food does not affect the absorption of azithromycin delivered from the suspension. Sampling time up to 24 hr is too short for a drug with a half-life of 63 hours. (please refer to NDA 50,710, reviewer, Dr. H. Sun). I noted that the sponsor submitted a study protocol to IND (reviewer Dr. H. Sun) which is a duplicate of this study with 28 subjects. Samples will be collected up to 120 hours (Study reported in NDA 50,710 and was accepted. Reviewer, Dr. H SUN).

3. The dissolution study is incomplete. As a phase IV commitment, the sponsor should conduct dissolution studies in the proposed media at 50 rpm paddle speed for the tablet formulation. The dissolution testing should be conducted on 12 units each of whole and broken (1/2) tablets. Sufficient sampling times should be included to generate complete dissolution profile. Upon review of these data, a final dissolution specification for the tablet should be proposed.

LABELING:

(These comments are based on the available proposed labeling for the tablets formulation, see attachment)

1. Line 34 to line 44, the data presented are for capsule formulation. When the labeling is changed for the tablet formulation, line 34 should be read as

2. Insert pharmacokinetic/bioequivalence information regarding the tablet formulation starting from line 51. recommendation:

3. Line 124, proposed labeling

4. From a biopharmaceutics standpoint, it is clear that the tablet formulation behaves different in the presence of food than the capsule. It is clear that the tablet formulation is intended to be administered without regard to meals. The sponsor's data are sufficient to support this claim.

NOTE REGARDING RECOMMENDATIONS ON LABELING

It is learned (1/18/95) that the sponsor planned to replace the capsule formulation with the tablet and planned to combine the labeling for tablet with 1 gm packet and pediatric suspension. The following comments and recommendations have been presented in ZITHROMAX labeling meetings held on Jan.18, and Jan. 26, 1995, respectively. Separate Labeling review have been completed and may be referenced (reviewer Dr. He Sun, completed Jan. 26, 1995).

1. The entire section of Clinical Pharmacology should be rewritten. Mixing information related to different formulations, especially mixing the clinical pharmacology information for adults and children, is very confusing. Information for adults and children must be clearly separated. This applies to all related sections such as: Indications and Usage, Contradictions, Precautions, Dosage Administration and etc. It is recommended that (1) make a separate label for

the pediatric suspension formulation, or (2) have a separate part of labeling for pediatric suspension following the parts of label for adult formulations, or (3) have separate paragraphs for pediatric suspension after each paragraph describing clinical pharmacology information for adults.

(Separate paragraphs for pediatric suspension after each paragraph describing adult clinical pharmacology information was accepted by both the Labeling meeting held Jan. 20, 1995 and the sponsor).

2. For food effect on the absorption of pediatric suspension, reports of study 050 and 059 were submitted in NDA 50,710 and were reviewed. The conclusions of these two studies are different. Study 050 shows that food does not affect the absorption of Azithromycin from the pediatric suspension which is the base for the current proposed labeling. However, study 059 (which replaced study 050) indicated a significant increase of Cmax (56%) when pediatric suspension was given with food to 28 adults healthy volunteers, and only study 059 was accepted to the Division of Biopharmaceutics. The labeling should be based on the results of study 059 of NDA 50,710. Corrections regarding food effect in all sections should be made. Suggestions are as follows:

In clinical pharmacology section:

In other sections:

3. It is required to clearly state that clinical pharmacology information in pediatric patient is very limited. Available pharmacokinetic parameters after oral pediatric suspension formulation should be listed in Clinical Pharmacology Section. The pediatric information should be separate from adults.

(The recommendations were accepted by the labeling meeting held Jan., 20, 1995).

1/27/95

He Sun, Ph.D.
Pharmacokinetics Evaluation Branch II

RD/FT Initialed by Frank Pelsor, Pharm. D.

Biopharm-Day Jan. 26, 1995. Attendees: Drs. Malinowski, ChenM, and Sun.

cc: NDA 50,711, HFD-520 (Clinical, Parker), HFD-427(ChenML, Pelsor), HFD-426(Fleischer), Chron, Drug, HFD-19(FOI), HFD-340(Viswanathan), Reviewer.

APPENDEX

BIOPHARMCEUTICS REVIW

NDA 50,711

1. Bioequivalence Study

Clinical Study #066-042-599

PHASE I STUDY TO EXAMINE THE BIOEQUIVALENCE OF AZITHROMYCIN COMMERCIAL CAPSULES AND 250 MG TABLETS, WHICH IS THE SUBJECT OF THE SUBMISSION.

Principal Investigator:

A. STUDY DESIGN:

This was an open, randomized, two-way crossover study to examine the bioequivalence of azithromycin commercial capsules and the 250 mg tablets. Serum samples collected immediately prior to and 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96 and 120 hours after each dose of azithromycin were analyzed for azithromycin content. Thirty-six fasted, healthy, male volunteers received two 250 mg commercial capsules (Lot #F311) and two 250 mg tablets (FID #GOO267AA, Lot #ED-B-387-Z92). The doses were separated by two weeks. Blood samples were collected for times up to 120 hours post-dose for preparation of serum, which was frozen at -70C until assay by HPLC with electrochemical detection. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC0-72, Cmax, Tmax)This was an open, randomized, two-way crossover study.

B. SUBJECTS:

Entered treatment	36
Assessed for pharmacokinetics	36
assessed for side effects	36

Subjects ranged in age from years (mean age 22.7 years) and in weight from kg (mean weight 74.6 kg)

C. Assay:

HPLC with amperometric electrochemical detection.

LLQ

Assay range
Linearity
Within-day Precision
Between-day Precision
Accuracy
Specificities

D. STATISTICS:

The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratios between treatments of Cmax and of AUC.

E. RESULTS:

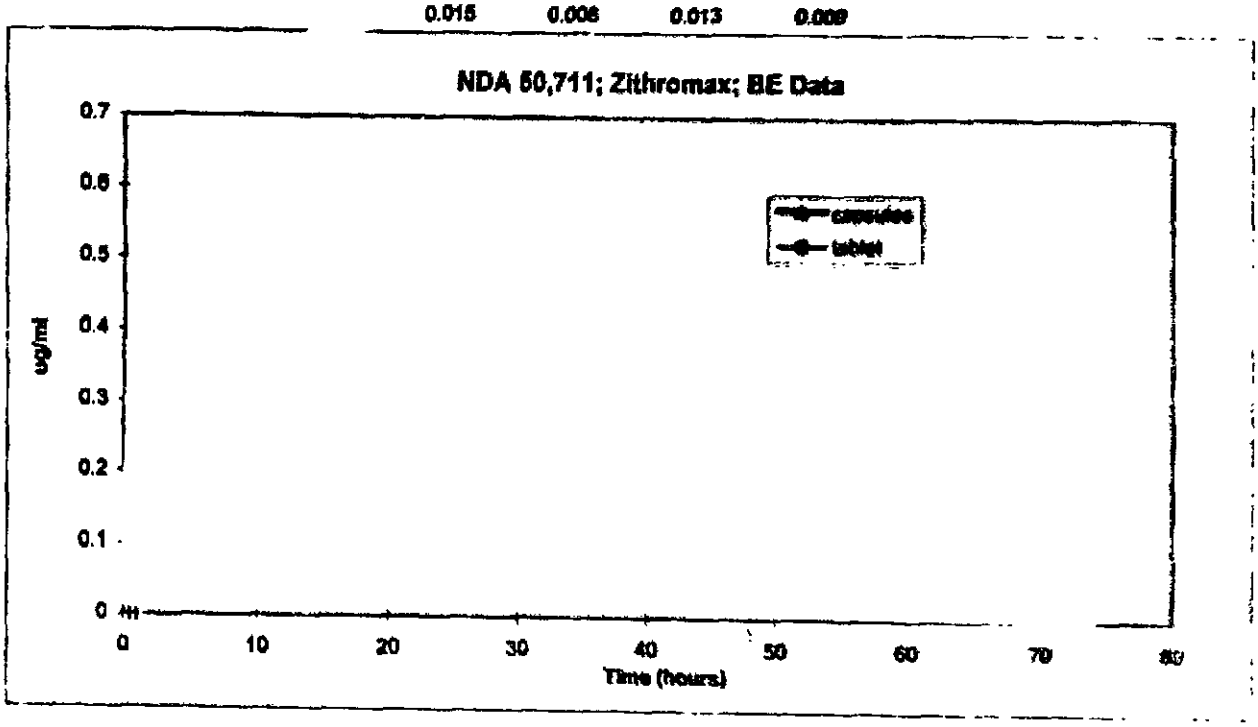
1. PHARMACOKINETICS (Values are Mean (SD))

	Capsule	Tablet	90% CI
AUC 0-72 ug-hr/ml	4.08 (1.194)	4.26 (1.183)	(99-113%)
Cmax (ug/ml)	0.482 (0.191)	0.512 (0.210)	(96-121%)
Tmax (hours)	2.1 (0.8)	2.2 (0.9)	

The mean values of AUC0-72 were 4.26 ug*hr/ml for the tablets and 4.08 ug*hr/ml for the capsules. The relative bioavailability was 105%. The 90% confidence limits on the tablet to capsule geometric mean ratio were 99% and 113%. The mean values of Cmax were 0.512 ug/ml for the tablet and 0.482 ug/ml for the capsule. The 90% confidence limits of the tablet to capsule geometric mean ratio were 96% and 121 %. The mean values of Tmax were similar (2.2 hr for the tablets and 2.1 hr for the capsules). Both sets of confidence limits fell within the criteria for bioequivalence of 80 to 125%. Thus, the two formulations were bioequivalent.

Comparing serum azithromycin concentration in healthy male volunteers following oral administration of two 250 mg capsules and two 250 mg new tablets. (Reviewer H.SUN)

Time	capsules	SD	tablet	SD
	0.069	0.061	0.052	0.102
	0.192	0.226	0.188	0.238
	0.309	0.23	0.307	0.249
	0.267	0.099	0.335	0.124
	0.213	0.063	0.229	0.074
	0.165	0.064	0.191	0.054
	0.117	0.039	0.122	0.036
	0.076	0.019	0.08	0.022
	0.053	0.015	0.056	0.017
	0.047	0.014	0.049	0.013
	0.026	0.008	0.027	0.009
	0.015	0.006	0.013	0.009



Serum concentration at 2 hours and later are significantly greater than zero. There are no statistical significant differnce in serum drug concentrations at 2 hours and later for Capsule and Tablet. The Cmax for capsule ranged from ug/ml and from ug/ml for Tablet. Tmax ranged from 1 hour to 4 hours with 27/36 appeared between 2-3 hours for Capsule and 26/36 appeared between 2-3 hours for Tablet.

Overall there are no different in serum concentration between these two formulations

2. Effect of Food on Bioavailability of the Tablet Formulation

Clinical Study #066-055-54C

AN OPEN STUDY OF AZITHROMYCIN SERUM CONCENTRATIONS FOLLOWING ORAL ADMINISTRATION OF 250 MG TABLETS WITH AND WITHOUT FOOD

PRINCIPAL INVESTIGATOR:

A. STUDY DESIGN:

This was an open, randomized, 2x2 crossover study to assess the effect of food on the serum concentrations of azithromycin resulting from the oral administration of two 250 mg film-coated tablets. More specifically, the serum concentrations were used to compare the bioavailability of azithromycin in 250 mg film-coated tablets when taken with and without food. Serum samples collected immediately prior to and 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hours after each dose of azithromycin were analyzed for azithromycin content. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC0-48, Cmax, Tmax).

B. SUBJECTS:

Entered treatment	12
Assessed for pharmacokinetics	12
assessed for side effects	12

Subjects ranged in age from 21 to 36 years (mean age 26.4 years) and in weight from 54.9 to 90.7 kg (mean weight 75.8 kg).

C DRUG ADMINISTRATION:

Subjects received single 500 mg oral doses of azithromycin on days 1 and 15. Subjects were randomly assigned to receive two 250 mg film-coated tablets (FID# G00267AA) either after an overnight fast or after a standard meal high in fat content (two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk) on day 1. On day 15, subjects were administered azithromycin under the alternate treatment conditions. All doses were taken after an overnight fast of at least 12 hours, and were taken with 240 ml of water alone, or with 240 ml of water after the standard meal. Subjects refrained from eating, lying down, or drinking caffeinated beverages for four hours after each dose, at which time they were provided identical standard meals.

D. RESULTS:

I. PHARMACOKINETICS (Values are Mean (SD))

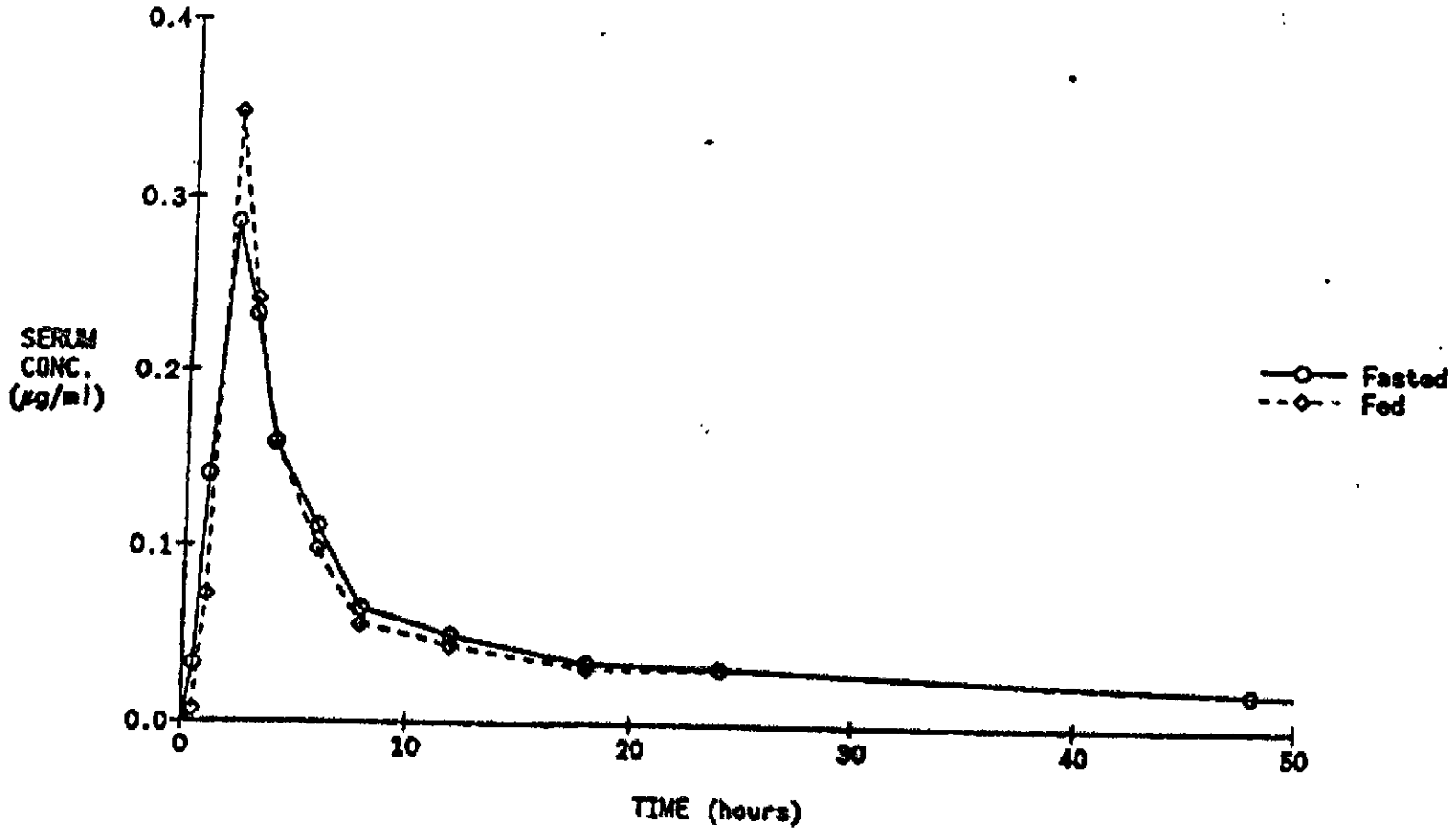
	Fasted	Fed	90% CI
Relative Bioavailability (%)	–	96.6	
AUC 0-48 ug-hr/ml	2.491 (0.642)	2.399 (0.678)	(82.2-113.4%)
Cmax (ug/ml)	0.336 (0.081)	0.412 (0.194)	(88.1-145.8%)
Tmax (hours)	2.1 (0.7)	2.3 (0.8)	

The ratio of geometric mean AUC0-48 values was 96.6% with corresponding 90% confidence interval of 82.2% to 113.4% (Table 4), which lies within the 80% to 125% range. The ratio of geometric mean Cmax values was 113.4% with the corresponding 90% confidence interval of 88.1% to 145.8% (Table 4), which does not lie within the 80% to 125% range.

E. CONCLUSIONS:

Azithromycin was well tolerated, with only a single episode of mild diarrhea reported. The bioavailability of the 500 mg of azithromycin from two 250 mg film-coated tablets was not reduced by administration with a high fat (>20 gram fat) meal.

Figure 3. Mean Serum Concentrations of Azithromycin Following Oral Administration of Two 250 mg Tablets to 12 Volunteers After an Overnight Fast and After a Fatty Breakfast (Study #066-055-54C, Dr. Levy, NMRC)



Data truncated at 50 hr to improve visualization.

3. Effect of Food on Bioavailability of Other Formulations

Clinical Study #066-041-503

PHASE I PHARMACOKINETIC STUDY COMPARING AZITHROMYCIN 250 MG CAPSULES VERSUS ORAL SOLUTION GIVEN WITH AND WITHOUT FOOD

PRINCIPAL INVESTIGATOR:

A. STUDY DESIGN:

The purpose of this study was to assess the effects of formulation dissolution and the effects of administration under fed and fasted conditions on the pharmacokinetics of azithromycin. This was an open label, randomized, four-way crossover study of single 500 mg doses of azithromycin administered orally as 2x250 mg commercial capsules and as a solution. Serum samples collected immediately prior to and 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hours after each azithromycin administration were analyzed for azithromycin content. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC0-48, Cmax, and Tmax).

B. SUBJECTS:

Entered treatment	12
Assessed for pharmacokinetics	12
Assessed for side effects	12

Subjects ranged in age from 20 to 44 years (mean age 29.9 years) and in weight from 62.1 to 89.8 kg (mean weight 71.9 kg).

C. DRUG ADMINISTRATION:

A computer generated randomization was used to determine the individual subjects sequence of dosing on days 1, 15, 29, and 43. There were four separate 500 mg doses administered to each subject. The individual doses were 2x250 mg capsules (commercial lot #F311), fed and fasting, and as an oral solution (FID* YY-91-092), fed and fasting. Subjects fasted overnight for 10-12 hours prior to each dose or standard breakfast. The standard breakfast was to consist of two eggs fried in one tablespoon of butter, two strips of bacon, two ounces of ham, two pieces of toast with butter and jelly, and eight ounces of whole milk. Subjects continued fasting for four hours after each dose, at which time they were provided identical standard meals.

D. Assay:

HPLC with amperometric electrochemical detection.

LLQ
Assay range
Linearity
Within-day Precision
Between-day Precision
Accuracy
Specificities

E. RESULTS:

1. PHARMACOKINETICS

Parameter Values are listed as Mean (Standard Deviation)

	500mg Solution		2x250 mg Capsules	
	Fasted	Fed	Fasted	Fed
AUC0-48 (ug-hr/ml)	3.20(0.70)	2.94(0.74)	2.57(0.82)	2.11(0.73)
Cmax (ug/ml)	0.517(0.194)	0.502(0.232)	0.357(0.106)	0.276(0.149)
Tmax (hours)	1.21(0.62)	2.25(0.87)	2.18(1.08)	3.83(1.19)

	Solution (Fed/Fast)	Capsule (Fed/Fast)	Capsule (Fast)/ Solution (Fast)
Relative Bioavailability	92	82	80
AUC geometric mean ratio (90% CI)	90.0 (75.4-107.3)	80.4 (67.0-96.40)	78.4 (65.4-94.1)
Cmax geometric mean ratio (90% CI)	92.5 (70.8-120.9)	70.0 (53.1-92.3)	70.2 (53.3-92.5)

The ratio of geometric means of AUCfasted for the capsule to AUCfasted for the solutions was 78.4%, with 90% confidence limits of 65.4% to 94.1 %. The ratio of the geometric means of AUCfed to AUCfasted for the solution was 90.0%, with 90% confidence limits of 75.4% to 107.3%. The ratio of geometric means of AUCfed to AUCfasted for the capsule was 80.4%, with 90% confidence limits of 67.0% to 96.4%.

The ratio of geometric means of Cmax following the capsule under fasting conditions to Cmax following the solution under fasting conditions was 70.2%, with 90% confidence limits of 53.3% to 92.5%. The ratio of geometric means of Cmax for the solution, fed to Cmax for the solution, fasting was 92.5%, with confidence limits of 70.8% to 120.9%. The ratio of geometric means of Cmax for the capsule, fed to Cmax for the capsule, fasting was 70.0% with 90% confidence limits of 53.1 % to 92.3%.

No subjects were discontinued from the study and there were no serious adverse events reported.

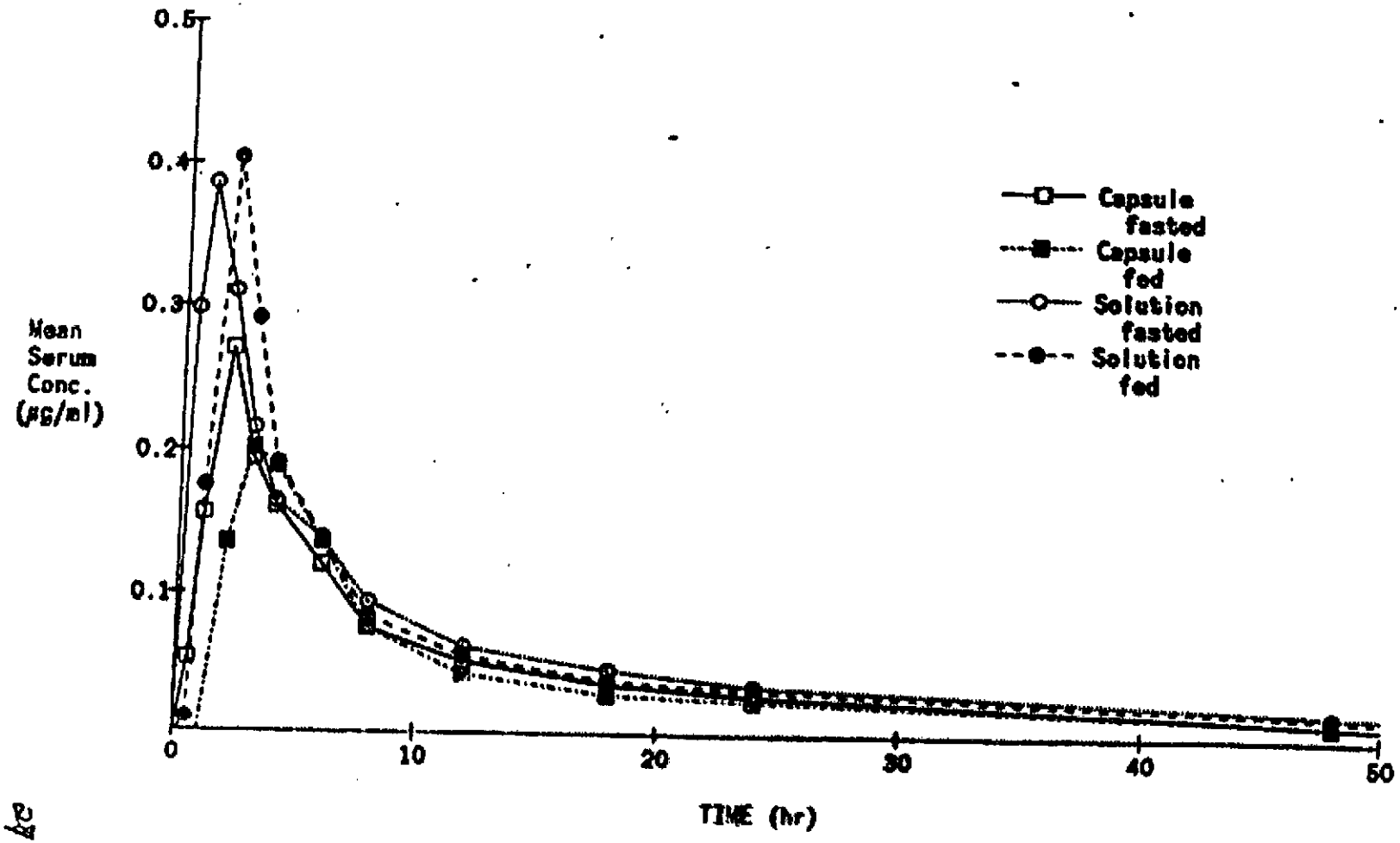
F. CONCLUSIONS:

In this study, azithromycin capsules were about 80% bioavailable compared to the azithromycin administered as a solution. The time to peak serum concentration was longer after the capsule than after the solution.

Concomitant administration of azithromycin with a high-fat breakfast decreased the bioavailability, as measured by AUC0-48, approximately 18% and 8% for the capsules and solution, respectively. Tmax was prolonged by food.

No subjects discontinued the study. Two subjects had mild to moderate side effects (headache, headache and abdominal pain) which resolved without additional treatment.

Figure 5. Mean Serum Concentrations of Azithromycin Following Oral Administration of Solutions or Capsules to Fed and Fasted Subjects (Study #066-041-503, Dr. Zinny)



Clinical Study #066-046-599

A PILOT STUDY OF THE PERFORMANCE OF AN ENTERIC DOSAGE FORM OF AZITHROMYCIN ADMINISTERED WITH AND WITHOUT FOOD IN NORMAL VOLUNTEERS

PRINCIPAL INVESTIGATOR

A. STUDY DESIGN:

The purpose of this study was to determine the absolute bioavailability of an enteric coated formulation of azithromycin in fasted and fed normal volunteers after oral administration. This study was designed as an open, randomized, three period, three treatment crossover study in which subjects were administered a single 500 mg dose of azithromycin as an intravenous infusion in the fasting state, as an enteric coated formulation in the fasting state, or as an enteric coated formulation after a standard meal. Serum samples collected immediately prior to, and 0.5, 1, 2, 3, 4, 6, 8, 12,18, 24, 48, 72, 96, and 120 hours after each dose were analyzed for azithromycin content. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC0-48, Cmax, Tmax).

B. SUBJECTS:

Entered treatment	12
Assessed for pharmacokinetics	12
Assessed for safety	12

Subjects ranged in age from 20 to 38 years(mean age 29.0 years) and in weight from 68.0 to 88.9 kg (mean weight 75.8 kg).

C. DRUG ADMINISTRATION:

Subjects were randomly allocated to receive each of three treatment regimens of 500 mg azithromycin (intravenous infusion in a fasted state, oral administration in a fasted state, oral administration in a fed state) at 15 day intervals. Oral administration was as 2 x 250 mg capsules containing an enteric coated bead formulation of azithromycin. All subjects fasted for 10 - 12 hours prior to dosing. Subjects dosed under fed conditions received a standard meal just prior to dosing and fasted for four hours after dosing. Subjects dosed under fasting conditions continued to fast for four hours after drug administration and then received an identical meal.

D. Assay:

HPLC with amperometric electrochemical detection.

LLQ
Assay range
Linearity
Within-day Precision
Between-day Precision
Accuracy
Specificities

E. RESULTS:

1. PHARMACOKINETICS(Values are Mean(SD),n=12)

	Intravenous (Fasting)	Enteric Coated (Fasting)	Enteric Coated (Fed)
AUC0-48(ug-hr/ml)	8.50 (1.32)	3.30 (0.73)	1.66 (0.90)
Cmax(ug/ml)	---	0.295 (0.086)	0.193 (0.145)
Tmax(hours)		3.3 (1.5)	5.6 (1.8)

Bioavailability (Ratio %, (90% Confidence Limits))

AUC0-48	Fasting vs IV	38.4%	(30.3%, 48.5%)
	Fed vs IV	17.6%	(13.9%, 22.3%)
	Fed vs Fasting	46.0%	(36.3%, 58.2%)
Cmax	Fed vs Fasting	54.2%	(35.6%, 82.6%)

2. SAFETY

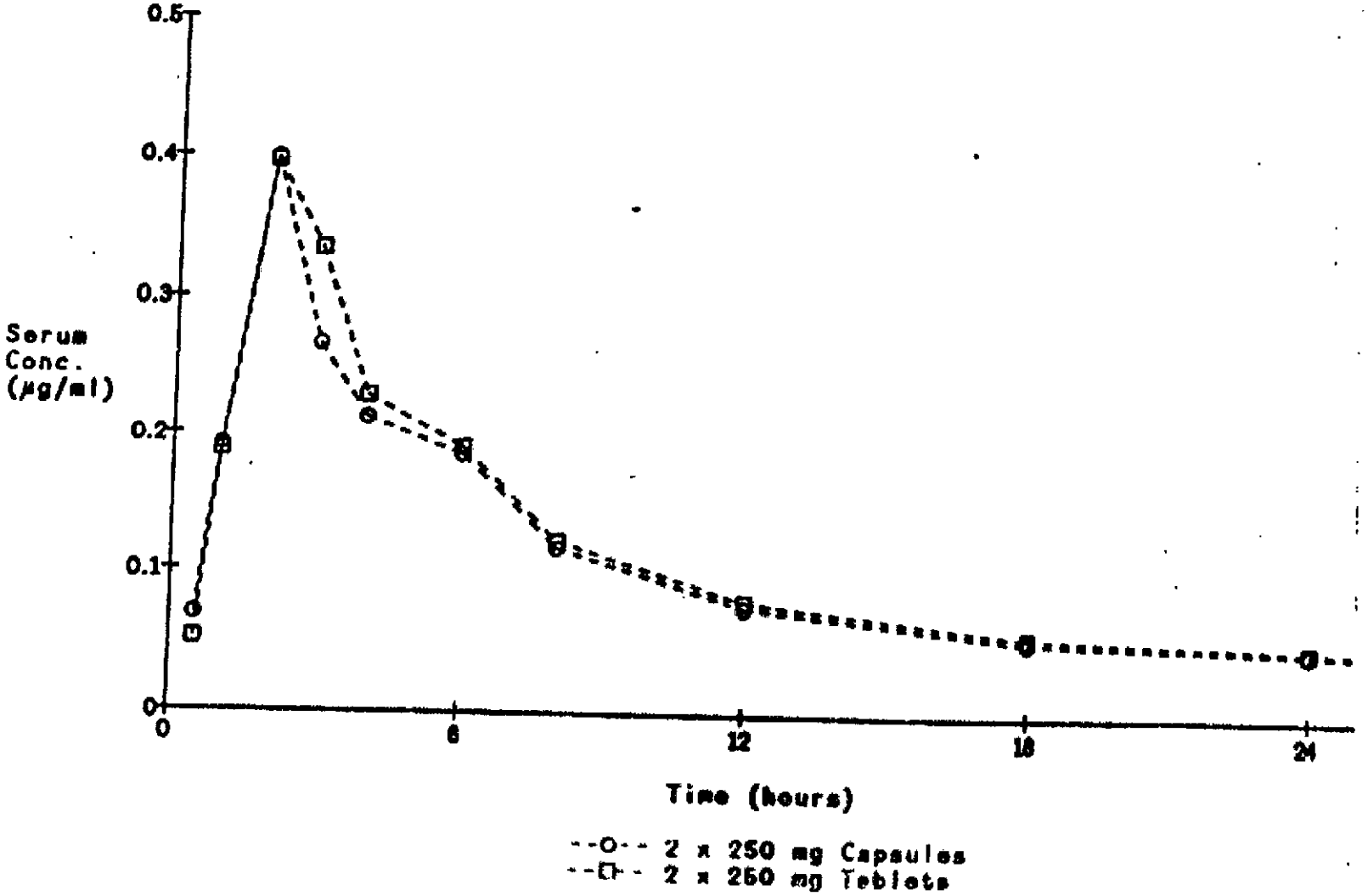
	intravenous (Fasting)	Enteric Coated (Fasting)	Enteric Coated (Fed)
No. of Subjects with Treatment-related Side Effects	7/12	1/12	0/12

Side effects were all mild and included pruritus, diarrhea, dyspepsia, nausea, injection site reaction, and taste perversion. Laboratory tests were performed at screening only. No subjects discontinued from the study. There were no serious adverse events.

E. CONCLUSIONS:

The results from the pharmacokinetic analysis indicate that, following oral administration of an enteric coated bead formulation of azithromycin to fasted healthy volunteers, the bioavailability was about 38%. When the same formulation was administered to fed volunteers, the bioavailability was reduced to about 18%. The bioavailability of azithromycin in fed subjects relative to fasted subjects was about 50%. Thus, the standard high-fat breakfast substantially reduced the bioavailability of azithromycin in the enteric-coated beads.

Figure 3. Mean Azithromycin Serum Concentrations Following Oral Administration of Two 250 mg Capsules and Two 250 mg Tablets to Healthy, Male Volunteers (Clinical Study #066-042-599, Pharmaco Dynamics, Inc., Austin, TX)



Clinical Study #066-050-29C

PHASE I STUDY COMPARING AZITHROMYCIN SERUM CONCENTRATIONS FOLLOWING ADMINISTRATION OF 500 MG OF ORAL SUSPENSION IN CONJUNCTION WITH MEALS OF VARYING COMPOSITION

PRINCIPAL INVESTIGATOR:

A. STUDY DESIGN:

This was an open-label, randomized three period, three treatment crossover study of azithromycin serum concentrations following administration of 500 mg of azithromycin as an oral suspension to six healthy male volunteers under fasting conditions, immediately following ingestion of a standard meal, and immediately following a light meal consisting only of cereal and milk. Serum samples were to be collected immediately prior to and at specified times up to 96 hours after each dose of azithromycin for the determination of pharmacokinetic values. Vital signs and side effects were to be monitored throughout the study.

B. SUBJECTS:

Entered treatment	6
Assessed for pharmacokinetics	6
Assessed for side effects	6

C. DRUG ADMINISTRATION:

40 mg/ml suspension (FID# G00007AA) administered orally as a single 500 mg dose on three occasions (fasted, standard breakfast, light breakfast).

D. Assay:

HPLC with amperometric electrochemical detection.

LLQ
Assay range
Linearity
Within-day Precision
Between-day Precision
Accuracy
Specificities

E. RESULTS:

1. PHARMACOKINETICS (Values are Mean (SD))

		Fasted	Standard Breakfast	Light Breakfast
AUC 0-48 ug-hr/ml		2.194 (0-542)	2.216 (0-590)	2.325 (0.692)
Cmax (ug/ml)		0.312 (0.092)	0.325 (0.091)	0.253 (0.051)
Tmax (hours)		1.8 (0.8)	1.8 (0.8)	2.5 (0.8)
geometric mean ratio (90%CI)	AUC		100.7(79.1-128.2)	102(81.8-132.6)
	Cmax		104(74.3-146.6)	83.0(59.1-116.6)

The ratio of AUC0-48 after the light breakfast to AUC0-48 under fasting conditions determined using geometric means was 104.2%. The 90% confidence interval on the ratio ranged from 81.8% to 132.6%. The ratio of AUC0-48 after the standard high-fat breakfast to AUC0-48 under fasting conditions determined using geometric means was 100.7%. The 90% confidence interval on the ratio ranged from 79.1 % to 128.2%. The ratio of Cmax after the light meal to Cmax under fasting conditions using geometric means was 83.0%. The 90% confidence interval on the ratio ranged from 59.1 % to 116.6%. The ratio of Cmax after the standard high-fat breakfast to Cmax under fasting conditions using geometric means was 104.4%. The 90% confidence interval on the ratio ranged from 74.3% to 146.6%.

2. SAFETY

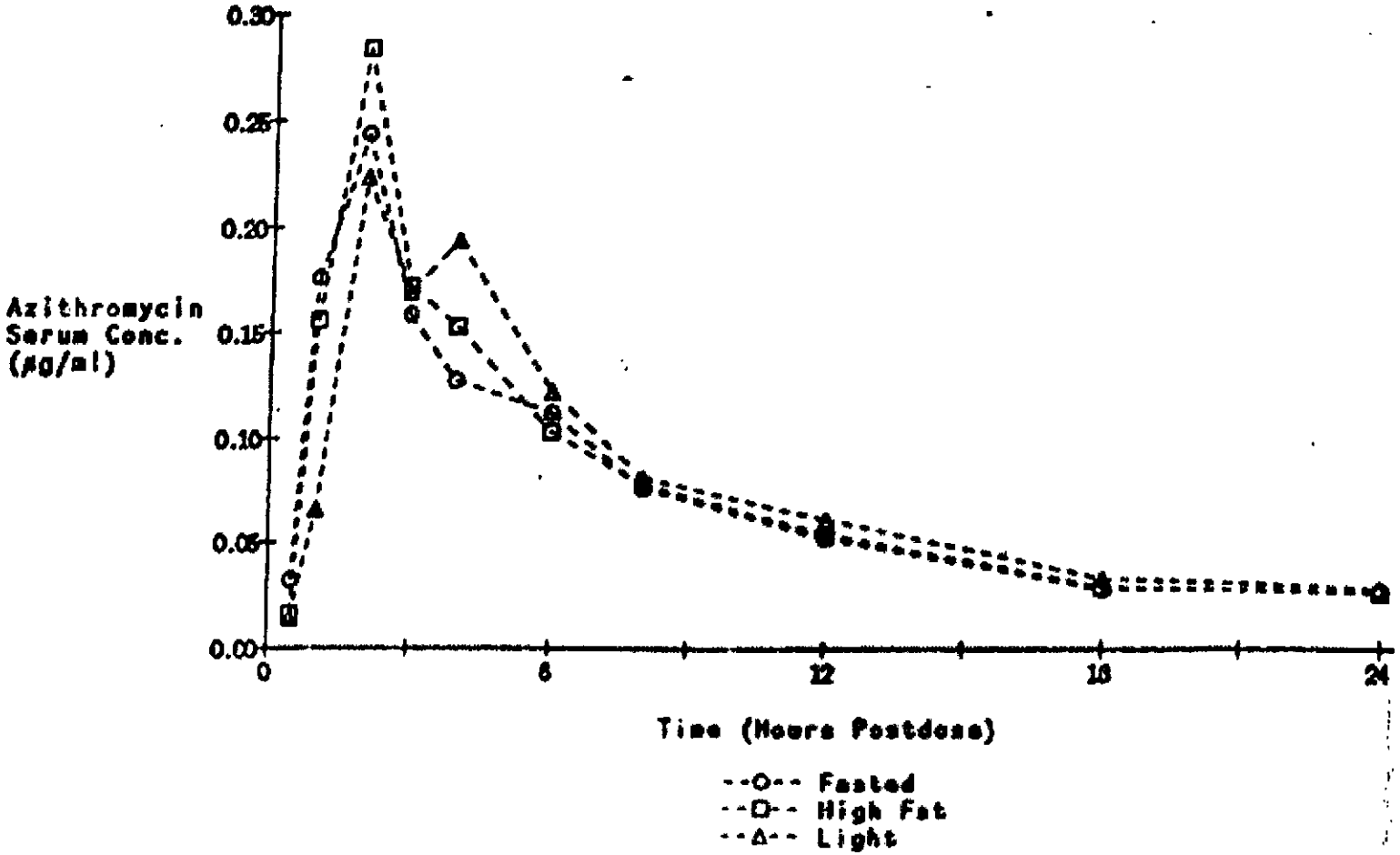
There were no side effects or serious adverse events reported.

F. CONCLUSIONS:

Compared to the fasting state, the ingestion of either a standard high-fat or light breakfast caused no apparent changes in the mean extent of absorption of azithromycin after oral administration.

Azithromycin was well tolerated. There were no side effects or serious adverse events.

Figure 4. Mean Serum Concentrations of Azithromycin Following Oral Administration of 500 mg in Suspension to Healthy, Male Volunteers Who Had Fasted Overnight or Ingested a High Fat or Light Breakfast
(Clinical Study #066-050-29C, Dr. Zinny, M.T.R.A., Boston, MA)



Clinical Study #066-057-54C

A PHASE I OPEN, RANDOMIZED STUDY OF THE CLINICAL PHARMACOLOGY OF AZITHROMYCIN AFTER 1 GRAM OF THE SACHET WITH AND WITHOUT FOOD COMPARED WITH THE INTRAVENOUS FORMULATION IN NORMAL HEALTHY SUBJECTS

PRINCIPAL INVESTIGATOR:

A. STUDY DESIGN:

This was an open, randomized three treatment, three period crossover study of the effect of food on the serum concentrations and absolute bioavailability of azithromycin after oral administration of the 1000 mg sachet. Azithromycin was administered on three separate occasions as a 1000 mg intravenous infusion, as a 1000 mg sachet after an overnight fast, and as the 1000 mg sachet immediately after a high fat breakfast. Serum samples collected immediately prior to and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 72, 96, and 120 hours after each oral ingestion or after the start of the intravenous infusion were analyzed for azithromycin content. Serum azithromycin concentrations were used to estimate pharmacokinetic parameters (AUC_{0-72}, C_{max}, T_{max}, absolute oral bioavailability, and relative bioavailability).

B. SUBJECTS:

Entered treatment	12
Assessed for pharmacokinetics	12
Assessed for side effects	12

Subjects ranged in age from 18 to 42 years (mean age 27.6 years) and in weight from 62.6 to 86.2 kg (mean weight 74.5 kg).

C. DRUG ADMINISTRATION:

Single 1000 mg doses of azithromycin were administered to each subject in an open fashion at approximately 0800 on days 1, 15, and 29. Doses were administered either orally as the sachet (FID# G00047AA) or as an intravenous infusion (FID# YY-91-092) according to a computer generated randomization. The intravenous infusion was administered after fasting overnight and was infused over a 1-hour period. The sachet was administered either immediately after a high fat breakfast (two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk) or after an overnight fast. Subjects refrained from eating, lying down, or drinking caffeinated beverages for four hours after each dose, at which time they were provided identical standard meals.

D. Assay:

HPLC with amperometric electrochemical detection.

LLQ
Assay range
Linearity
Within-day Precision
Between-day Precision
Accuracy
Specificities

E. RESULTS:

1. PHARMACOKINETICS (values are Mean(Standard Deviation), n=12)

	Sachet Fed	Sachet Fasted	Intravenous Infusion
AUC0-72 ug.hr/ml	7.37 (2.12)	6.49 (1.54)	14.76 (2.84)
Cmax (ug/ml)	1.05 (0.40)	0.75 (0.42)	–
Tmax (hours)	2.04 (0.69)	1.46 (0.69)	
Absolute Bioavailability	49.9%	44.0%	
Relative Bioavailability	113.5%	–	

The ratio of AUC0-72 sachet-fed to AUC0-72 Sachet-fasted determined using geometric means was 112.1%. The 90% confidence interval on the ratio ranged from 99.2% to 126.7% The ratio of Cmax Sachet-fed to Cmax Sachet-fasted using geometric means was 146.2%. The 90% confidence interval on the ratio ranged from 115.8% to 184.6%.

2. SAFETY

NO. OF SUBJECTS WITH TREATMENT-RELATED:	Sachet Fed	Sachet Fasted	Intravenous Infusion
SIDE EFFECTS	6/12	4/12	5/12
LABORATORY TEST ABNORMALITIES	0/12	0/12	0/12

No subjects were discontinued from the study and there were no serious adverse events.

F. CONCLUSIONS:

The administration of the azithromycin sachet immediately after a high fat breakfast resulted in increased systemic exposures and peak azithromycin serum concentrations relative to administration without food. The mean relative bioavailability (fed/fasting) was 113.5%. The mean absolute oral bioavailabilities were similar (50% fed, 44% fasting).

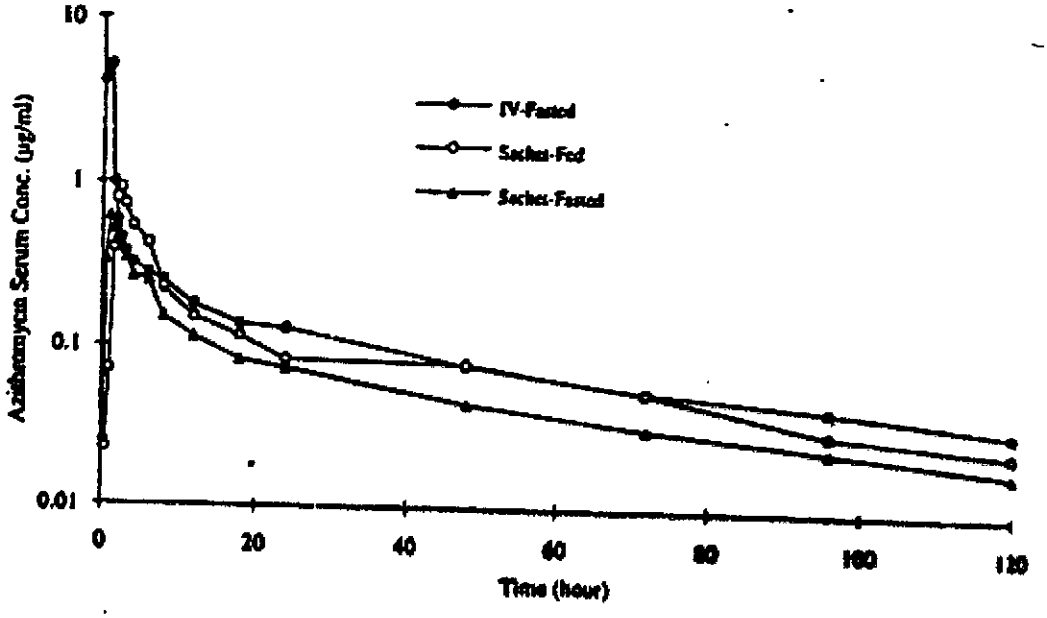


Figure 4. Mean Serum Concentrations of Azithromycin following Oral Administration of 1000 mg as a Single-Dose Sachet under both the Fed and Fasted Conditions, and after a 60-Minute Intravenous Infusion of 1000 mg in the Fasting State.
(Clinical Study #066-057-54C, Dr. Levy, National Medical Research Corp., Hartford, CT)

Study #066-206.

THE EFFECT OF FOOD ON THE PLASMA PHARMACOKINETICS OF A SINGLE ORAL DOSE Of AZITHROMYCIN

Principal Investigator:

A. STUDY DESIGN:

This was an open label , randomized, two-way crossover with 18 days between each period. A single dose of azithromycin was administered on two occasions, to healthy volunteers, once after a hour fast and once after a standard meal, and plasma samples were withdrawn at intervals up to 24 hours after each dose. Each subject received azithromycin 500mg (2 x 250mg capsules) on two occasions. Laboratory safety tests were monitored before dosing and 24 and 72 hours after dosing with clinical examinations performed after each dose.

B. Assay:

HPLC method. Full report of assay was not submitted

C. RESULTS:

1.	Pharmacokinetics	Fasting	Non-Fasting
	Mean values:		
	Cmax (ng/ml)	314 (122.5)	153 (37.4)
	Tmax (hr)	2.6 (1.29)	3.4 (1.5)
	AUC0-24 (ng.h/ml)	1347 (495, n=10)	776 (299, n=5)

2.	Safety:	Fasting	Non-Fasting
	No. of subjects with treatment related Side-effects	1/11 (0)	0/11
3.	Lab. Test Abnormalities	2/11 (0)	1/11 (0)

Note: ( ) Resulting in withdrawal from study.

D. CONCLUSIONS:

The administration of azithromycin capsules to volunteers in the non-fasting state resulted in statistically and clinically significantly lower Cmax values (p=0.004). Detectable plasma levels were found at sufficient time points for AUC0-24 calculations in only 5/11 subjects in the fed state, so formal statistical analysis was not possible. It is concluded that absorption is reduced in the non-fasting state. Azithromycin was otherwise well tolerated. Laboratory data showed rises in CPK levels in 2 subjects that were possibly treatment related.

Study 206

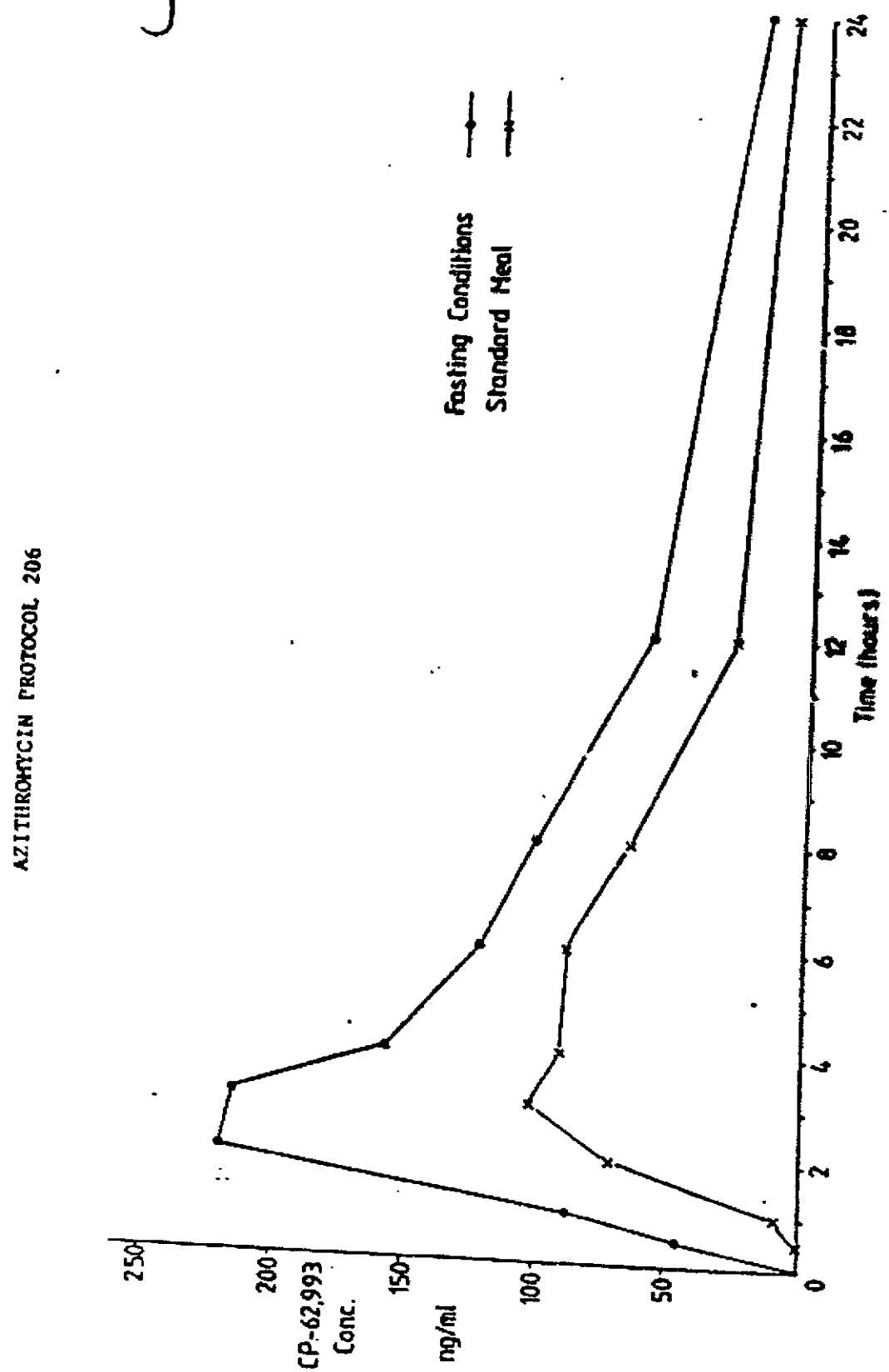


Figure 1. Plots of mean plasma CP-62,993 concentrations from 0-24 hours after oral administration of 500mg under fasting conditions and after a standard meal

Study AZM-NY-89-0 (conducted by Pfizer-Mack, illertissen, Germany)

THE EFFECT OF A LIGHT BREAKFAST ON THE BIOAVAILABILITY OF AZITHROMYCIN CAPSULES, SIMILAR TO THE PRESENT COMMERCIAL CAPSULES.

Principle Investigator:

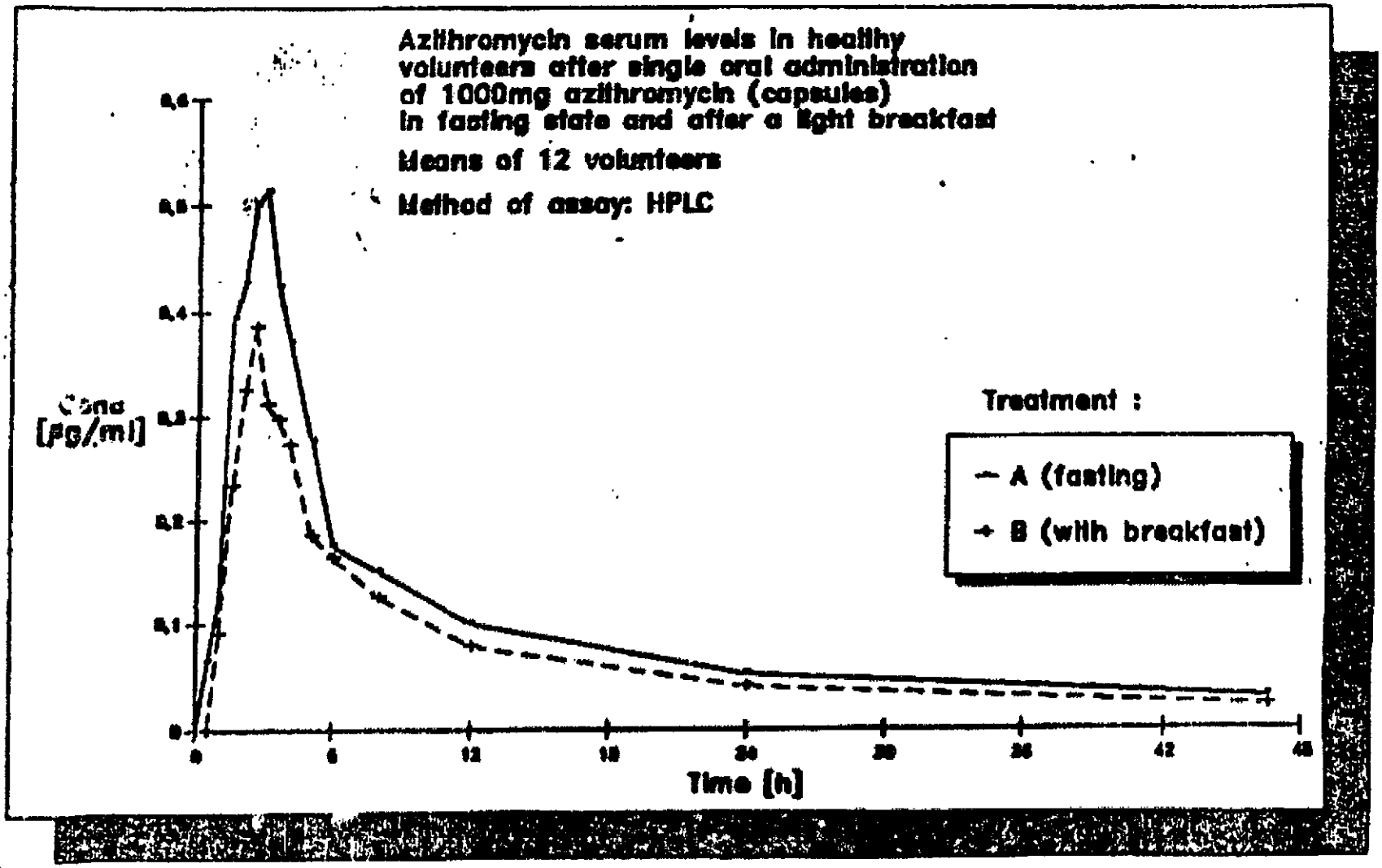
A. STUDY DESIGN:

This was an open, randomized, two-way crossover study to examine the effect of a light breakfast on the bioavailability of azithromycin capsules, similar to the present commercial capsules. Twelve healthy, male volunteers each received two 1000 mg oral doses of azithromycin in four 250 mg capsules (FID #YY-89-051), once following an overnight (12 hr) fast and once following a light breakfast of two rolls with butter and jam and approximately 300 ml of coffee or tea with milk, ingested immediately prior to the doses. The treatments were separated by an interval of two weeks. Blood was collected for times up to 46.5 hours post-dose for preparation of serum, which was frozen until assay for azithromycin by HPLC with electrochemical detection and by bioassay. Urine samples were also collected for intervals up to 46.5 hours post-dose and assayed for azithromycin by HPLC-EC and bioassay. Since the results were similar for the two assays, only HPLC assay results are reported here. The lower limit of quantification of the HPLC assay was 0.01 ug/ml in serum and 0.060 ug/ml in urine. The data were analyzed with a two-way, repeat measures ANOVA. The 90% confidence bounds on the differences in mean AUC, Cmax, Tmax, and urinary recovery between treatments were calculated.

B. RESULTS:

Mean values of AUC0-46.5 were 4.53 ug*hr/ml following the overnight fast and 3.37 ug*hr/ml following the light breakfast. The mean relative bioavailability was 74%. Mean Cmax was 0.71 ug/ml following the overnight fast and 0.59 ug/ml following the light breakfast. The ratio of mean Cmax values was 84%. Mean Tmax was 2.3 hr following the fast and 3.1 hr following the light breakfast. The 90% confidence limits on the difference in AUCs (AUCfed - AUCfasted), expressed as a percentage of the observed mean following the overnight fast, were -48% and -3%. The corresponding limits on the difference in Cmax were -38% and +5%. The mean recoveries of azithromycin in urine were 5.1% and 3.8% following the overnight fast and the light breakfast, respectively. Thus, the bioavailability of azithromycin in capsules was reduced by coadministration with a light breakfast.

Figure 2


Azithromycin serum levels in healthy volunteers after single oral administration of 1000mg azithromycin (capsules) in fasting state and after a light breakfast
Means of 12 volunteers
Method of assay: HPLC
Conc [µg/ml]
Time [h]
Treatment :
A (fasting)
B (with breakfast)

IV. OVERALL SUMMARY AND CONCLUSION

Study #066-042-599 examined the bioequivalence of the proposed 250 mg tablet formulation of azithromycin and the present commercial formulation. The geometric mean relative bioavailability was 105% with 90% confidence limits on the tablet to capsule AUC ratio of 99% and 113%. Thus, the proposed 250 mg tablet formulation was bioequivalent to the current commercial 250 mg capsule.

A further study (#066-055-54C) with 12 volunteers showed that administration of a standard breakfast, containing at least 30 grams of fat, did not affect the bioavailability of azithromycin from the proposed commercial 250 mg tablets. The geometric mean relative bioavailability, comparing the AUC following the standard meal with the AUC following an overnight fast, was 97% with 90% confidence limits on the fed to fasted ratio of 82% and 113%. Thus, the bioavailability of azithromycin administered as two 250 mg tablets was not decreased by administration immediately following a high-fat meal.

The effects of food on the bioavailability of azithromycin from several formulations were examined in six studies. Relative bioavailabilities ranged from less than or equal to 50% for two formulations (research capsule Study #066-206; enteric-coated beads - Study #066-046-599) to values close to 100% for 500 mg in solution (Study #066-041-503), 500 mg from a powder for oral suspension (Study #066-050-29C) and a 1000 mg sachet (Study #066-057-54C). Examination of the effect of food on the bioavailability of the present commercial capsule showed a moderate effect, with a high-fat breakfast yielding a relative bioavailability of 82% in Study #066-041-503 and a light breakfast producing a relative bioavailability of 74% for a 1000 mg dose in Study AZM-NY-89-0. Thus, the effect of food on bioavailability is dependent upon the formulation.

These results demonstrate that the proposed 250 mg azithromycin tablets will produce serum concentrations in man equal to those produced by the present commercial capsules and that the tablets may be given without restrictions relative to the ingestion of meals.

V. DISSOLUTION TEST

A dissolution rate test is employed to measure the in vitro dissolution rate of 250 mg tablets and commercial capsules. The method uses USP Apparatus 2 (paddles) rotating at 100 rpm in 900 ml of pH 6.0 phosphate buffer held at 37°C±0.5°C. The pH 6.0, 0.1 M phosphate buffer was chosen to assure drug solubility exceeded sink conditions and to assure optimum stability of azithromycin in the dissolution medium. The drug has a solubility of approximately 39 mg/ml in the phosphate buffer at 37°C. This dissolution test for tablet is similar to that used for the approved azithromycin capsules except that trypsin, which is included to aid dissolution of the gelatin capsule shell, is not added to the dissolution medium for the film-coated tablets. Aliquot of the dissolution media were collected at 15, 30, and 45 minutes and were analyzed using an HPLC procedure.

Other media considered during the development of the dissolution rate included simulated

gastric fluid and water. Simulated gastric fluid was not chosen as the dissolution medium because azithromycin is not sufficiently stable at this acidic pH for such a test. Water was not chosen because the aqueous solubility of azithromycin is only 1.1 mg/ml.

	Tablet lot ED-B-387-Z92			Capsule lot F311		
	15'	30'	45'	15'	30'	45'
Mean	99	100	100	99	100	100
low	95	97	98	93	97	9797
HIGH	100	102	101	103	102	102
CV%	1.3	1.7	0.9	2.6	1.5	1.6

The proposed specification was set at Q % in minutes which is the same as that approved for azithromycin capsules in NDA 50,670.

Pharm. memos

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation & Research

Date: *February 8, 1995*

To: *NDA 50-711*

From: *Oluwadare M. Adeyemo, Ph.D.* OMA 2/8/95
Pharmacologist, HFD-520

Subject: *NDA 50-711, Azithromycin Tablets*

Through: *Robert E. Osterberg, Ph.D.* REO 2/9/95 10 2/11 95
Supervisory Pharmacologist, HFD-520

No new preclinical studies were submitted in support of this NDA 50-711. All referenced preclinical studies in support of NDA 50-711 were previously reviewed and considered adequate in connection with NDAs 50-670 & 50-710.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation & Research

Date: April 28, 1994

To: NDA 50-711 Files

From: Oluwadare M. Adeyemo, Ph.D.
Pharmacologist, HFD-520

Subject: NDA 50-711, Azithromycin Tablets

Through: Robert E. Osterberg, Ph.D. concur 4/29/94
Supervisory Pharmacologist, HFD-520

No new preclinical studies were submitted in support of this NDA 50-711. All referenced preclinical studies in support of NDA 50-711 were previously reviewed and considered adequate in connection with INDs and NDAs 50-670 & 50-710. I do not expect any significant differences in safety and pharmacokinetic parameters between the capsule and tablet formulations.

Therefore, from the standpoint of pharmacology and toxicology, NDA 50-711 is fileable.

Chem

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : February 8, 1995

TO : NDA 50-711 file, Zithromax Tablets, 250mg

FROM : Suva B. Roy, Ph. D. SBR 2/8/95
Acting Supervisory Chemist (HFD-520)
Division of Anti-Infective Drug Products

SUBJECT : Recommendation in CMC reviews

The CMC review recommendation may be changed from not approvable, to approvable pending satisfactory GMP inspections.

The sponsor has adequately addressed all sections of the CMC. Methods validation by our New York District Laboratories and GMP inspection of the manufacturing facilities by our compliance branch are still outstanding. Completion of methods validation is not essential before the issuance of the final approval letter. However, satisfactory GMP inspection would be necessary for the final approval action. An approvable letter may be issued at this time.

APR 8 1994

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-711 CHEM.REVIEW #: 1 REVIEW DATE: 3/16/94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
ORIGINAL	2-15-94	2-16-94	3-16-94

NAME & ADDRESS OF APPLICANT:

Pfizer Inc.
Eastern Point Road
Groton, CT 06340
(203) 441-4100

CONTACT:
Charles A. Ritrovato, Pharm. D. Associate Director II, Regulatory Affairs, Liaison

DRUG PRODUCT NAME

Proprietary: Zithromax
Established: Azithromycin dihydrate
Code #: CP-62,993

PHARMACOLOGICAL CATEGORY/INDICATION:
Azalide Antibiotic

DOSAGE FORM: Tablets

STRENGTHS: 250 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Azithromycin USP, $C_{38}H_{72}N_2O_{12}$; 729.00

(1) 1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl]oxy]-, [2R*-(2R*,3S*,4R*,5R*,8R*,10R*,11R*,12R*, 13S*, 14R*)]-;

(2) (2R,3S,4R,5R,8R,10R,11R,12R, 13S, 14R)-13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one;

(3) 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.

CAS-83905-01-5; CAS-117772-70-0 (dihydrate).

SUPPORTING DOCUMENTS:

NDA 50-670; IND

DMF DMF DMF DMF DMF DMF DMF DMF

RELATED DOCUMENTS: n/a

MF NDA 50-693; NDA 50-710; IND IND

CONSULTS: n/a

REMARKS/COMMENTS:

Chemistry items contained in NDA 50-670 which pertain to this NDA 50-710 are not repeated in this submission; information is taken from that NDA 50-670 in this review.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable with regard to chemistry, manufacturing, and controls. Methods validation (drug product) and the establishment inspections are outstanding.

JT/L 3-16-94
J. Timper, Review Chemist

cc: Org. NDA 50-711
HFD-520/Division File
HFD-520/SBRoy/Acting SUPVCHEM 3/22/94
HFD-520/Timper/CHEM 3/16/94
HFD-520/Lizambri/MO
HFD-520/Adeyemo/Pharm
HFD-520/Silver/MICRO 3/8/94
HFD-520/Dillon-Parker/CSO
HFD-102/CKumkumian [#1 only]
HFC-130/JAllen

micro

APR 26 1994

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Clinical Microbiological Review

NDA #: 50-711 **REVIEW #:** #1 **REVIEW DATE:** 11-APR-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	15-FEB-94	16-FEB-94	07-APR-94

NAME & ADDRESS OF APPLICANT:

PFIZER CENTRAL RESEARCH
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME
Proprietary: ZITHROMAX® Tablets
Nonproprietary/USAN: Azithromycin Tablets

ANDA Suitability Petition/DESI/Patent Status:

Not Applicable

PHARMACOLOGICAL CATEGORY/INDICATION: Antibacterial (macrolide)

DOSAGE FORM: Tablet
STRENGTHS: 250 milligrams
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L*-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D*-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

Molecular Formula: $C_{38}H_{72}N_2O_{12}\bullet 2H_2O$

Molecular Weight: 785.0

SUPPORTING DOCUMENTS: NDA 50-670 (azithromycin capsule--approved November 1, 1991)

RELATED DOCUMENTS: IND

CONSULTS: None

REMARKS/COMMENTS:

There is no Microbiology Section in this application. All Microbiology is referenced to NDA 50-670 for azithromycin capsules. No new microbiology data has been submitted.

No microbiological testing is performed on the finished tablets and this is satisfactory. All raw materials are USP or NF, except for (a film-coating ingredient). USP Microbial Limits Testing is performed on pregelatinized starch and the magnesium stearate used in the tablets as directed in USP<61>. The purified water, USP meets the bacteriological purity standards of 40 CFR 141.14. The microbiological testing of the raw materials is satisfactory.

Since we have made minor revisions in the Microbiology Section of labels since the capsule NDA was approved the Microbiology section of the label should be revised as follows:

Microbiology:

Pages 3-5
Deleted

References

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

CONCLUSIONS & RECOMMENDATIONS:

The product should be approved with the above microbiology labeling.

Peter A. Dionne
Peter A. Dionne
Review Microbiologist

cc: Orig. NDA 50-711
HFD-520/Division File
HFD-520/MO/Moledina
HFD-520/Pharm/Adeyemo
HFD-520/Chem/Timper
HFD-520/CSO/Dillon-Parker
HFD-520/Micro/Dionne/03/22/94

Concurrence Only:
HFD-520/ActingDir/LGavrilovich
HFD-520/SMicro/ATSheldon
RD 4/14/94
Fmea 4/15/94
4/26/94

WAITING FOR COMPANY TO SEND IN AN UPDATE.

BY CROSS-REFERENCE FROM NDA 50-670

FINDING OF NO SIGNIFICANT IMPACT

NDA 50-670

ZITHROMAX (azithromycin)

Pfizer Central Research has made a New Drug Application for Zithromax (azithromycin) a macrolide systemic antibiotic. Chemically, azithromycin is 9-deoxo-9a-aza-9a-methyl-9a-homo-erythromycin A. Zithromax capsules are formulated to contain 250 mg azithromycin.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Azithromycin, Pfizer has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Any residues of Azithromycin or its major metabolites entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

CC: Original NDA 50-670
Philip Chao HFD-362
Fonsi File 50670

DEC 17 1991
DATE

Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

12/12/91
DATE

Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Environmental assesement for Zithromax.
Package Insert

Food and Drug Administration

[Docket No. 92N-0166]

Environmental Assessments and Findings of No Significant Impact

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that it has received environmental assessments (EA's) and issued findings of no significant impact (FONSI's) relating to the approval of new drug applications (NDA's) for the following products: Cefzil (cefprozil) tablets and powder; Lorabid (loracarbef) powder and capsules; Maxicon (flumazenil) injection; Mivacron (mivacurium chloride) injection and infusion; and Zithromax (azithromycin) capsules. FDA is publishing this notice under section 102 of the National Environmental Policy Act (42 U.S.C. 4332), 21 CFR 25.41(b), and 40 CFR 1506.6.

ADDRESSES: The EA's and FONSI's may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Center for Drug Evaluation and Research (HFD-344), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-295-8049.

SUPPLEMENTARY INFORMATION: The National Environmental Policy Act (NEPA) requires all Federal agencies to "use all practicable means and measures, including financial and technical assistance, in a manner calculated to foster and promote the general welfare, to create and maintain conditions under which man and nature can exist in productive harmony, and fulfill the social, economic, and other requirements of present and future generations of Americans." (See 42 U.S.C. 4331(a).) Under NEPA, all Federal agencies must prepare detailed statements assessing the possible environmental impact of, and alternatives to, major Federal actions significantly affecting the environment, and such statements are to be made available to the public. (See 42 U.S.C. 4332, 21 CFR 25.41(b), and 40 CFR 1506.6.)

FDA implements NEPA through its regulations at 21 CFR part 25. Under those regulations, the approval of an NDA usually constitutes an action that ordinarily requires the preparation of an EA. (See 21 CFR 25.22(a)(14).)

FDA recently approved NDA's pertaining to the following products: Cefzil (cefprozil), NDA 50-664 (tablet) and NDA 50-665 (powder); Lorabid (loracarbef), NDA 50-667 (powder) and NDA 50-668 (capsule); Maxicon (flumazenil), NDA 20-072; Mivacron (mivacurium chloride), NDA 20-098; and Zithromax (azithromycin), NDA 50-670.

The agency has reviewed the EA's submitted for each NDA and has prepared a FONSI for each. No environmental impact statements, therefore, are necessary. This notice announces that the EA's and FONSI's for these human drug products may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: June 12, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 92-14429 Filed 6-18-92; 8:45 am]

BILLING CODE 4160-01-F

FDA Corres.

NDA 50-730

JUN 12 1996

Pfizer Central Research
Attention: Ron Trust, Ph.D.
Eastern Point Road
Groton, CT 06340

Dear Dr. Trust:

Please refer to your December 22, 1995 new drug application submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Zithromax® (Azithromycin) 600 mg tablets.

We acknowledge receipt of your amendments dated:

February 2, 1996	April 24, 1996	May 15, 1996
February 15, 1996	April 30, 1996	May 23, 1996
March 13, 1996	May 8, 1996(2)	May 28, 1996
March 15, 1996	May 9, 1996	June 4, 1996
March 25, 1996	May 10, 1996	June 6, 1996
April 1, 1996	May 21, 1996 (3)	June 7, 1996
April 10, 1996	May 17, 1996	

This new drug application provides for the use of Zithromax® 600 mg tablets in the prophylaxis of disseminated Mycobacterium Avium Complex (MAC) infections in HIV-infected patients.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the June 7, 1996 draft labeling. Accordingly, the application is approved effective on the date of this letter.

Please consider the following recommendations:

1. You should collect information on the susceptibility of breakthrough Mycobacterium avium complex (MAC) isolates during prophylaxis of disseminated MAC infection as well as response to subsequent treatment of disseminated MAC, so that when sufficient information is available to define resistance to azithromycin in MAC, you can assess the impact and significance of prophylactic therapy on the occurrence of resistance.

2. You should collect additional information on the safety profile of azithromycin as used in the management of children with underlying HIV infections.

3. There is a potential that the pediatric suspension will be used by adult patients who have difficulty swallowing the 600 mg tablets. Please submit any available data that may assist in assessing comparability of the bioavailability of the pediatric suspension and 600 mg tablet.

The final printed labeling (FPL) must be identical to the June 7, 1996 draft labeling with the incorporation of the following changes (as discussed June 10, 1996):

1. Confidence intervals in the clinical trials section of the label should be expressed as percentages.

2. Lines 848 to 861 should be eliminated.

Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit twenty copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-730. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

We remind you of your Phase 4 commitment as discussed during your June 10, 1996 telephone conference with Ms. Hubbard of this Division. These commitments, along with the completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to

this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitment".

You should provide data from from DATRI 001, part b, to assess the drug interaction between azithromycin and rifabutin in HIV-positive patients, as soon as the information becomes available.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Under section 736 (a) (1) (B) (ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lisa Hubbard, R.Ph., Consumer Safety Officer, at (301) 827-2335.

Sincerely yours,

6-12-96

David W. Feigal, Jr., M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

concurrence:
HFD-530/DDir/DFreeman 6/14/96
HFD-530/SMO/MGoldberger 6/6/96
HFD-530/MO/RRoca 6.6.96
HFD-530/MO/JKorvick for JK 6.12.96
HFD-530/TL/CChen 6/7/96
HFD-530/Chem/NSchmuff 6/6/96
HFD-530/TL/JRamsey 6/12/96
HFD-530/Micro/LGosey 6/7/96
HFD-530/TL/JJenkins 6/7/96
HFD-530/Biopharm/CSahajwalla 6/7/96
HFD-725/TL/LKammerman 6/7/96
HFD-725/Stat/AMuhly AEM
HFD-725/Harkens cc only
HFD-725/Shores cc only
HFD-530/SCSO/ADeCicco 6.12.96
HFD-530/CSO/LHubbard 6/12/96

cc:
HFD-530/NDA 50-730
HFD-530/Division file
HFD-80
HFD-710
HFD-220
HFD-230
HFD-500
HFD-530/DDir/DFreeman
HFD-530/SMO/MGoldberger
HFD-530/MO/RRoca
HFD-530/MO/JKorvick
HFD-530/TL/CChen
HFD-530/Chem/NSchmuff
HFD-530/TL/JRamsey
HFD-530/Micro/LGosey
HFD-530/TL/JJenkins
HFD-530/Biopharm/CSahajwalla
HFD-715/TL/LKammerman
HFD-715/Stat/AMuhly
HFD-725/Harkens
HFD-725/Shores
HFD-530/SCSO/ADeCicco
HFD-530/CSO/LHubbard
~~HFD-615~~

AF (Approval Letter)

DV

Memorandum of a Telephone Conversation
June 3, 1996 7:10 a.m.

Between

Eric B. Sheinin, FDA and

Dennis Casey, Pfizer

Dennis Casey called to follow-up on the telephone conference held Friday, May 31, 1996, concerning Pfizer's pending NDAs for azithromycin. The following issues were discussed:

1. FDA's request that there be a specific target for magnesium stearate, and not and allowed range, in the proposed formulation. Pfizer now understands our position on why we do not want a range. They never intended to operate in a manner that would allow them to formulate at one level one day and, due to operating conditions, different levels on subsequent manufacturing rungs. They merely wanted the flexibility to optimize the formulation as they gain experience with the product, post-approval. They understand that we may have seen instances where companies try to change the formulation within a range on a day-to-day basis because they are unable to manufacture at a set target. They will agree to a target of 2% for the magnesium stearate content of the 250 and 600 mg tablets. If they need to optimize the formulation they will change the target under SUPAC-IR and will submit the required documentation spelled out in the guidance. Based on the data they have developed thus far, they would like to be able to include the addition of magnesium stearate, up to 3% maximum, in their proposed rework procedure.

I indicated that I thought this would be acceptable.

2. They will expand on the rework procedure submitted to us by FAX on May 31, 1996. In particular they will include more information regarding the weight variation. They do not mean to imply that an unacceptable weight variation is related to variation in the uniformity of the tablet blend. This will have been checked during in-process control monitoring and will have been found within limits. A problem with the variation in the tablet weight is indicative of a tableting problem, most likely with the tablet press. Pfizer will provide an explanation along these lines in a revised rework proposal. Further, they do not intend that the batches would be reworked on a regular basis.

I indicated that this should be acceptable.

3. Pfizer will be submitting additional stability data on drug

product manufactured at the 2% magnesium stearate level. It should be sent out today.

4. He apologized if it appeared that Pfizer was being contentious during our conference call on Friday, May 31.

5. In regard to evolving policies within the Center, he asked if there could be some forum where the industry would have the opportunity to have input into our decisions. I indicated that the Agency, and CDER in particular, is much more open to industry input then ever before and that I thought such a forum would be possible.

6. Pfizer will provide us with updated information on the formulation and the rework procedure.

Eric B. Sheinin

Eric B. Sheinin, Ph.D.

cc: NDA 50-730 / 50-733
HFD-530 / Div Files
HFD-530 / Ray / Trimper / LeLane
HFD-530 / Chen / Schnaa / Hubbard / Rogol

ZITHROMAX®
MAC PROPHYLAXIS
NDA-50-730

Response to FDA Comments

Dated 21 May 1996

NDA 50-730 CMC Issues (Preface to CMC Questions)

On 5/13/96 a meeting was held between the CMC reviewers of various azithromycin NDAs and their Team Leader's from HFD-530 (Division of Antiviral Drug Products) and HFD-520 (Division of Anti-Infective Drug Products), along with the Division Director of the Division of New Drug Chemistry III. As a result of that meeting, for NDA 50-730 we have the following requests and comments.

It should be noted however, that changes made to NDA 50-730 need to be done in concert, as applicable, with applications approved, or pending in HFD-520, *i.e.*, NDAs 50-670, 50-693, 50-710, 50-711, and 50-733.

Method validations are currently on hold for NDA 50-710, 50-711, and 50-733 until resolution of impurities in the drug substance and drug product cited above can be resolved and/or amended.

Pfizer Response:

NOTE

In a follow-up teleconference between FDA and Pfizer on 28 May 1996, it was agreed that the changes made to NDA 50-730 through negotiations regarding the Chemistry, Manufacturing and Controls documentation will only be incorporated into the "approvable" NDA for azithromycin 250 mg tablets (NDA 50-711). This is also referenced in the 22 May 1996 correspondence (approvable letter) from HFD-520 (Division of Anti-Infective Drug Products) to Pfizer regarding NDA 50-711.

FDA Comment 1:

For the drug substance, azithromycin dihydrate, in addition to the specifications for 'Azithromycin, USP,' please add a control for impurities as in NDA 50-670.

Pfizer Response 1:

The drug substance, azithromycin dihydrate, will be tested and released in accordance with the specifications presented in approved NDA-50-670.

FDA Comment 2:

Please provide single target value for the magnesium stearate / sodium lauryl sulfate component. The requested % range, based on the weight of the tablet blend, is not acceptable. Although it is reported that studies were conducted on materials containing this component at the extremes of this range, these data are not included in the application. Submitted batch records for the four stability lots indicate that in each case % of this mixture was used, relative to the total combined weight of azithromycin dihydrate, starch, calcium phosphate and croscarmellose.

Pfizer Response 2:

Based on the discussions during the 5/31/96 and the follow-up telecon on 6/3/96 pertaining to the information facsimiled to FDA on 5/31/96, Pfizer will agree to the following to resolve this issue:

Target lubricant level = %
Maximum lubricant for rework batches = %

Pfizer is committing to operate the process on a routine basis at a single target value (%) as requested by the Agency. As also discussed, if it is necessary to rework a batch (infrequently) under the conditions of the approved rework protocol, the lubricant level of the reworked batch could be increased up to a maximum level of %

In addition, as requested during the telecons on 5/31/96 and 6/3/96, the accelerated stability data from the % lubricant level validation study is also being submitted and is attached on the following pages. It should be noted that at the time of manufacture of this lot (1993), it was Pfizer practice to place lubrication validation study lots on 12 week accelerated stability. The dissolution rate testing performed during this stability study was carried out at 100 rpm.

As a result of our recent discussions with FDA, we have also tested retained samples of this lot. The lot was tested according to our current dissolution rate method. However the paddle speed was set at 75 rpm. The results of this dissolution rate testing (12 units tested) are as follows:

	Dissolution Rate Profile			
Lot Number	minutes	minutes	minutes	minutes
ED-G-302-993	98	99	99	99

Table 1. STABILITY TESTING FOR AZITHROMYCIN FILM-COATED TABLETS - 600mg at 2% Lube Level

Formulated Lot No.: ED-G-302-993
Container: 60cc Wheaton HDPE bottle
Closure: 33 mm/400 Kerr CR with liner retention

Stability Lot No:G-302-993-02C-030A
Date Started: 11/28/93
Bottle Count: 30/bottle

Storage Condition		Appearance	Azithromycin[1] mg/Tab	%LC	mg/g	%Ret	Purity Evaluation By TLC[2] System 1 %CP-64,434[6]	System 2 vs 5°C	System 3 %CP-66,458[7]	% [3] Water	% Dissolved[4] Avg (Range)	Hardness kp [5] Avg (Range)
0 wk	Initial	As described[8]	595	99	532	-	<0.7%	NEB	<0.3%	3.6	101	25.9(
12 wk	15°C/50%RH	NSC	593	99	517	97	<0.7%	NSC	ND	3.4[8]	101	27.2
	30°C/35%RH	NSC	588	98	512	96	<0.7%	NSC	ND	3.4	103	26.4
	40°C/30%RH	NSC	588	98	521	98	<0.7%	NSC	ND	3.3	101	25.9
	40°C/75%RH	NSC	590	98	520	98	<0.7%	NSC	ND	3.6	99	24.6
	50°C/20%RH	NSC	589	98	515	97	<0.7%	NSC	ND	3.2	101	26.5
	Light Cabinet	NSC	587	98	517	97	<0.7%	NSC	ND	3.3	98	25.8

Footnotes are provided on the following page.

Footnotes to Table 1.

(1) Azithromycin content determined by A 129.0
% LC = (mg/Tab/label claim potency) x 100
mg/g = (mg/Tab/tablet weight)
%Rel = Assay (mg/g) at time T/initial x100; calculated on an "as is" basis. Initial values were the average of ten tablets; the subsequent stability values were the average of three tablets.

(2) System 1: Hexane-ethyl acetate-diethylamine, (150:50:20,v/v); Detected with vanillin.
System 2: Methyl ethyl ketone-acetic acid-water, (6:1:1,v/v); Detected with vanillin.
System 3: Ethyl acetate-methyl ethyl ketone-formic acid-water, (3:3:1:1,v/v); Detected with Dragendorff's.

(3) Water determined by W 1.0.

(4) Dissolution determined by Six tablets tested, average and range reported after minutes.

(5) Ten tablets tested, average and range reported.

(6) N-demethylazithromycin

(7) Desosaminylazithromycin

(8) Average of two determinations.

(9) 13/32" X 3/4" modified oval, compound cup, upper scored, lower engraved, white film-coated tablets.

NSC = No significant change when compared to 5°C control.
NEB = No extraneous bands.
ND = None detected.

FDA Comment 3:

Please identify which in-process controls will be used routinely for commercial production batches. The batch records contain several blend sampling steps not mentioned in section 4.3 "In-Process Controls."

Pfizer Response 3:

The in-process control tests and specifications that will be used routinely for commercial production batches are described on pages 3 069 and 3 070 of NDA 50-730. These tests include appearance, potency and blend uniformity at the blend stage and weight variation, appearance and hardness at the tablet core stage.

The batch records which were provided in Section 3.III.D of NDA 50-730 (pp. 319 ff.) contain additional in-process control tests that were utilized for qualification studies.

FDA Comment 4:

Please either withdraw the rework procedure or provide appropriate supporting data to justify the rework procedure. If the latter, describe specific conditions under which the rework would be applicable and specific blend characteristics to be achieved by these processes.

Pfizer Response 4:

Based on the discussions during the May 31, 1996 and the follow-up telecon on June 3, 1996 pertaining to information facsimiled to FDA on May 31, 1996 , we are providing additional clarification and rationale for the rework of tablet cores due to weight variation and friability.

Weight Variation

The primary reason for reworking the tablet cores due to weight variation could be based on the mechanical operations of the tablet press or the powder flow of the compounded blend. As the tablet press operates, it is possible that the tablet punch may fail to fully retract resulting in a decreased volume of blend which would fill the cavity prior to compression. After completing the compression cycle, a tablet would be manufactured potentially outside of the approved in-process control specification for weight variation.

In addition to the mechanical operations of the tablet press, it is possible that in rare cases the powder flow of the compounded blend may result in under filling the cavities in the tablet press. As discussed earlier, under charging the cavity could potentially result in manufacturing a tablet outside of the approved in-process control specification for weight variations.

Friability

Friability is related to the manufacturing of the tablet cores and their resulting hardness. Factors leading to the manufacture of soft tablets have been described under the weight variation rationale. A "soft" tablet core may have acceptable physical appearance at the core stage, however during the film coating process friability may occur. The resulting film coated tablet could potentially fail the physical appearance specification if erosion occurs during film coating. In addition, during commercial manufacturing in which the film coating pans are charged with an increased number of tablets friability may be experienced due to the increase tablet mass in the pan.

FDA Comment 5:

Please commit to developing a validated method and specification for individual and total impurities in the drug product. In the application, it is argued that there is no evidence for the increase of any impurity a) during manufacture, and b) during stability studies. No data on bearing on point "a" are included or referenced in this application. The TLC assays for CP-64,436 and CP-66,458 are incapable of quantifying changes in these impurities below the listed limits. We recommend spotting additional lower levels of the impurity standard. Please consider the possibility of an HPLC method as the validation study for the azithromycin assay suggests that this method might also be suitable for this purpose.

Pfizer Response 5:

Pfizer will commit to developing an appropriately validated method and specification for individual and total impurities in the drug product. Pfizer will also commit to provide this information to FDA within six months of approval of the application.

NDA 50-730 CMC Issues

On 5/13/96 a meeting was held between the CMC reviewers of various azithromycin NDAs and their Team Leader's from HFD-530 (Division of Antiviral Drug Products)and HFD-520 (Division of Anti-Infective Drug Products), along with the Division Director of the Division of New Drug Chemistry III. As a result of that meeting, for NDA 50-730 we have the following requests and comments.

It should be noted however, that changes made to NDA 50-730 need to be done in concert, as applicable, with applications approved, or pending in HFD-520, , i.e., NDAs 50-670, 50-693, 50-710, 50-711, and 50-733.

Method validations are currently on hold for NDA 50-710, 50-711, and 50-733 until resolution of impurities in the drug substance and drug product cited above can be resolved and/or amended.

1) For the drug substance, azithromycin dihydrate, in addition to the specifications for 'Azithromycin, USP,' please add a control for impurities as in NDA 50-670.

2) Please provide single target value for the magnesium stearate / sodium lauryl sulfate component. The requested % range, based on the weight of the tablet blend, is not acceptable. Although it is reported that studies were conducted on materials containing this component at the extremes of this range, these data are not included in the application. Submitted batch records for the four stability lots indicate that in each case % of this mixture was used, relative to the total combined weight of azithromycin dihydrate, starch, calcium phosphate and crosscarmellose.

3) Please identify which in-process controls will be used routinely for commercial production batches. The batch records contain several blend sampling steps not mentioned in section 4.3 "In-Process Controls."

4) Please either withdraw the rework procedure or provide appropriate supporting data to justify the rework procedure. If the latter, describe specific conditions under which the rework would be applicable and specific blend characteristics to be achieved by these processes.

5) Please commit to developing a validated method and specification for individual and total impurities in the drug product. In the application, it is argued that there is no evidence for the increase of any impurity a) during manufacture, and b) during stability studies. No data on bearing on point "a" are included or referenced in this application. The TLC assays for CP-64,436 and CP-66,458 are incapable of quantifying changes in these impurities below the listed limits. We recommend spotting additional lower levels of the impurity standard. Please consider the possibility of an HPLC method, as the validation study for the azithromycin assay suggests that this method might also be suitable for this purpose.

Concurrence: CChen/Team Leader, HFD-530 CBC 5/21/96

SRoy/Team Leader, HFD-520 [signature] 5/21/96

ESheinin/Div Director, DNDC III [signature] 5-21-96

CC: CChen/Team Leader, HFD-530
SRoy/Team Leader, HFD-520
ESheinin/Div Director, DNDC III
NSchmuff/HFD-530
JTimper/HFD-520
BShetty/HFD-520

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 20, 1996

FROM: Frances V. LeSane
Project Manager, HFD-520
Division of Anti-Infective Drug Products
301-827-2125
301-827-2327 (FAX)

SUBJECT: NDA 50-711 Revised Phase 4 Commitments.

TO: Robert B. Clark
Senior Associate Director
Regulatory Affairs Division
Pfizer Incorporated
235 East 42nd Street
New York, New York 10017-5755

Please refer to your February 15, 1994 new drug application and our approvable letter dated February 14, 1995 for ZITHROMAX® (azithromycin) 250 mg Tablets.

We also acknowledge receipt of your amendments dated November 21, 1995, March 25, 1996, and May 2, 1996

Before this application may be approved, however, it will be necessary for you to agree to conduct the following.

BIOPHARMACEUTICS:

A phase 4 commitment to support approval of ZITHROMAX® (azithromycin) 250 mg Tablets in regards to the incomplete dissolution study.

1. Conduct dissolution studies in the proposed media at both 75 rpm and 50 rpm paddle speed for the tablet formulation. The dissolution test should be conducted on 12 units each of the whole tablets. The lot used in this dissolution test should be the same as the lot used for conducting dissolution test at 100 rpm (lot # ED-B-387-Z92).

At this time, as an interim dissolution test, the dissolution specification should be changed to Q % in minutes at 100 rpm instead of proposed Q % in minutes at 100 rpm.

Sufficient sampling times should be included to generate a complete dissolution profile. Upon review of these data, a final dissolution specification for the tablet should be proposed.

CHEMISTRY:

2. Please provide a phase 4 commitment to revise the appropriate Chemistry, Manufacturing, and Control sections (CMC) for this 250 mg tablet when the pending NDA 50-730 for the 600 mg tablet is approved.

If in agreement, please fax us your commitment to the phase 4 request.

NDA 50-711

Charles A. Ritrovato, Pharm.D.
Associate Director
Regulatory Affairs Liaison
Pfizer, Incorporated
Eastern Point Road
Groton, CT 06340

MAR 17 1994

Dear Dr. Ritrovato:

We have received your new drug application (NDA) submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Product: Azithromycin

Date of Application: February 15, 1994

Date of Receipt: February 17, 1994

Our Reference Number: NDA 50-711

Unless we find the application not acceptable for filing, the filing date will be April 16, 1994.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact Ms. Maureen Dillon-Parker, Project Manager, at 301-443-6797.

Sincerely yours,

RD 3-17-94

Patricia L. DeSantis
Acting Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation II

cc:
ORIG. NDA 50-711
HFD-520/SMO/MAlbuerne
HFD-520/PHARM/ROsterberg
HFD-520/CHEM/TDeCamp
HFD-520/micro/ASheldon
HFD-520/CSO/MDillon-Parker
KKonkolewski/3/14/94 MP 3/15/94
F/T:
ACKNOWLEDGMENT LETTER

CHRONOLOGY FOR NDA 50-711

2-14-95 Approvable letter to Sponsor.

11-21-95 Received draft labeling from PFIZER. noting changes concerning FOOD as indicated in NDA 50-710 for the oral suspension approved 10-19-95.

3-20-96 Meeting with Bob Clark, to discuss labeling issues. At this meeting I gave him revision to the label.

3-25-96 Received the changes incorporated in the final draft labeling from sponsor.

4-26-96 Memo to sponsor concerning the PHASE 4 commitment for Biopharm note wording because this was note relayed in the approvable letter.

Conduct dissolution studies in the proposed media at both 75 rpm and 50 rpm paddle speed for the tablet formulation. The dissolution test should be conducted on 12 units each of the whole tablets. The lot used in this dissolution test should be the same as the lot used for conducting dissolution test at 100 rpm (lot # ED-B-387-Z92).

At this time, as an interim dissolution test, the dissolution specification should be changed to
Q % in minutes at 100 rpm instead of proposed
Q % in minutes at 100 rpm.

Sufficient sampling times should be included to generate a complete dissolution profile. Upon review of these data, a final dissolution specification for the tablet should be proposed.

In the CLINICAL PHARMACOLOGY section, the second paragraph should be revised to read:

5-2-96	Commitment from sponsor concerning the Phase 4 and labeling request.
5-7-96	In-House meeting to discuss the interim dissolution with HFD-530. Note fax dated 5-3-96. In this meeting, our BIOPHARM Team Leader will check with his supervisor to see if we can accept the same interim dissolution as HFD 530.
5-15-96	Call to sponsor, note - At this time, as an interim dissolution test, the dissolution specification should be changed to Q % in minutes at 100 rpm instead of proposed Q % in minutes at 100 rpm.
5-20-96	Fax to sponsor - please provide a phase 4 commitment to revise the appropriate Chemistry, Manufacturing, and Control sections (CMC) for this 250 mg tablet when the pending NDA 50-730 for the 600 mg tablet is approved.
5-21-96	In-house meeting with HFD-530 and HFD-520, note agenda.
	Fax sent to sponsor for CMC issues:
	For HFD-520 wait to see if PFIZER will accept the phase 4 for chemistry so we can issue an approval on 5-22-96.

Azithromycin Suspension

NDA 50-710

Richard Lizambri, M. D.
Division of Anti-infective Drug Products

Azithromycin Previous Experience

Azithromycin Capsules NDA 50-670

Approval Date	November 1, 1991
Class of Drug	Azalide (A subclass of Macrolide)
Approval Age	Adults

Current Indications

1. Respiratory Tract Infections
   Acute Exacerbation of Chronic Bronchitis
   Community Acquired Pneumonia of Mild Severity
   Streptococcal Pharyngitis/Tonsillitis (As alternative to first line therapy)

2. Skin and Skin Structure

3. *Chlamydia trachomatis* infections of the GU tract

Azithromycin Previous Experience

Azithromycin Capsules NDA 50-670

Dosage

All indications except *Chlamydia*, 500 mg as a single dose on day 1 followed by 250 mg on days 2 through 5.

Half-life

Approximately 68 hours with a polyphasic decline. With the recommended loading dose, C_{max} and C_{min} remained unchanged on days 2 through 5 of therapy. Without a loading dose, C_{min} required 5 to 7 days to reach a steady state. The prolonged half-life appeared to be due to tissue uptake and rerelease.

Azithromycin Previous Experience

Azithromycin Capsules NDA 50-670

Pharmacokinetics

The pharmacokinetics of azithromycin capsules can be further illustrated by a comparison of the concentration of the drug in tissue vs. plasma. Two 250-mg capsules were given 12 hours apart.

Tissue	Time after dose (hours)	Tissue Conc µg/g	Plasma Conc µg/mL	Ratio
Tonsil	9-18	4.5	0.03	>100
Tonsil	180 (approximately 1 week)	0.9	0.006	>100

Azithromycin Previous Experience

Organism (No. of Strains)	% of Strains Inhibited	MIC µg/mL	
		Azithromycin	Erythromycin
Haemophilus influenzae (70)	50	0.39	1.56
	90	0.78	3.12
Branhamella catarrhalis (17)	50	≤0.015	0.03
	90	0.03	0.06
Streptococcus pneumoniae (10)	50	≤0.025	≤0.025
	90	0.05	≤0.025
Streptococcus pyogenes (17)	50	0.1	≤0.025
	90	0.1	≤0.025
Streptococcus pyogenes Erythromycin Resistant (7)	50	>50	6.25
	90		>50

Azithromycin Suspension

NDA 50-710

Indications Requested

Otitis Media — Four Studies

Dosage 10 mg/kg on the first treatment day followed by 5 mg/kg daily for 4 more days

Pharyngitis — Three Studies

Dosage 12 mg/kg daily for 5 days

Age Requested: Removal of Age Restriction

Azithromycin Suspension

NDA 50-710

Pharmacokinetics
This was studied only at a dosage of 10 mg/kg on the first treatment day followed by 5 mg/kg daily for 4 more days. The Cmax and AUC(0-24) were 1.7 times higher in the 6 to 15 year-old children vs. the 1 to 4-year old children. The values in the younger children were similar to those seen with the usual adult dose.

A pharmacokinetic study was not performed at the dose of 12 mg/kg daily for 5 days.

Azithromycin Suspension NDA 50-710

Otitis Media Efficacy Data

Four Trials, All Domestic

All Trials Used the Dosage 10 mg/kg on the first treatment day followed by 5 mg/kg daily for 4 more days

Study 134
Double-Blind Comparative trial vs. Augmentin
341 Azithromycin Patients, 336 Augmentin Patients

Study 128
Open Label Comparative trial vs. Augmentin
Baseline Tympanocentesis Performed
85 Azithromycin Patients, 84 Augmentin Patients

Study 178
Open Label Comparative trial vs. Augmentin
263 Azithromycin Patients, 264 Augmentin Patients

Study 176
Open Label Non-Comparative trial
Baseline Tympanocentesis Performed
201 Azithromycin Patients

Additional Information in four foreign studies, 322, 334, 337, and 394

Azithromycin Suspension

NDA 50-710

Pharyngitis Efficacy Data

Three Trials, All Domestic

All Trials Used the Dosage 12 mg/kg daily for 5 days

Study 163

Double-Blind Comparative trial vs. Penicillin V
223 Azithromycin Patients, 227 Penicillin V Patients

Study 163Z

Double-Blind Comparative trial vs. Penicillin V
26 Azithromycin Patients, 24 Penicillin V Patients

Study 175

Double-Blind Comparative trial vs. Penicillin V
173 Azithromycin Patients, 169 Penicillin V Patients

Two Earlier trials, Study 126 and Study 126Z, were conducted at a dose of 10 mg/kg on the first treatment day followed by 5 mg/kg daily for 4 more days. Apparently, due to a lack of efficacy, the applicant's consultants suggested the higher dose used in studies 163, 163Z, and 175.

Azithromycin Suspension

NDA 50-710

Safety Data

2666 patients received azithromycin

2098 patients received comparative agents

Most Frequently Occurring side effects

1. Diarrhea (2.6%)
2. Abdominal Pain (2.0%)
3. Vomiting (2.0%)

Incidence of Total Side Effects

Patients who received 30 mg/kg total dose	7%
Patients who received 60 mg/kg total dose	16%

Azithromycin Suspension

NDA 50-710

Therapeutic Advantage

Once-a-day dosage for only 5 days

Azithromycin Suspension

NDA 50-710

Potential Concerns

1. Different dosages are used in the two indications. A potential hazard for undertreatment of pharyngitis exists if the wrong dosage is used through misunderstanding.

2. The pharyngitis dosage does not have a loading dose, in contrast to all other indications, capsule or suspension. Lack of a loading dose for pharyngitis combined with the drug's long half-life implies that drug levels continuously rise during treatment and never reach a steady state. Could this pattern of drug level produce resistant organisms or other problems?

3. If pharyngitis treatment was ineffective for 10 mg/kg on the first treatment day followed by 5 mg/kg daily for 4 more days, is the optimal dose different from the dose requested?

ZITHROMAX (AZITHROMYCIN)

APPROVED NDAs

250 mg Capsules	**Acute Bacterial Exacerbations of COPD, Community-acquired Pneumonia, Pharyngitis/tonsillitis, Uncomplicated skin and skin structure infections**
Single Dose Packet 1 g	**Non-gonococcal urethritis and cervicitis due to *C. trachomatis***

APPROVABLE NDAs

Oral Suspension	**Acute otitis media and Pharyngitis/tonsillitis**
Tablets	(replacement for capsules; same indications)

PENDING SUPPLEMENTS

●Terfenadine/Theophylline Labeling	filed May 1993
●STD	filed December 1994
●PLE Reports/Labeling	filed February 1995

AZITHROMYCIN - ONGOING CLINICAL PROGRAMS

Anti-Infective Drugs Division

Pediatric Pneumonia

Intravenous Azithromycin for Hospitalized Pneumonia Patients

Oral Azithromycin in Atypical Pneumonia
(*Mycoplasma pneumoniae, Chlamydia pneumoniae)*

IV Azithromycin in Pneumonia due to *Legionella pneumophila*

Oral Azithromycin + omeprazole in Eradication
of *Helicobacter pylori*

Anti-Viral Drugs Division

MAC Prophylaxis

MAC Treatment

F.1. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SUMMARY

F.1.A Introduction

Azithromycin capsules were the subject of a previously-approved NDA (#50-670, approved Nov 1, 1991). This submission seeks to replace the commercial capsules with a new tablet formulation (FID #G00267AA). One study (#066-042-599) was conducted to establish the bioequivalence of this new tablet formulation to the currently available commercial 250 mg capsules. Another study (#066-055-54C) was performed to assess the effect of food upon the bioavailability of azithromycin delivered from this new tablet formulation.

Six additional studies (#066-041-503, #066-046-599, #066-050-29C, #066-057-54C, #066-206, AZM-NY-89-0) are presented in this submission to demonstrate that azithromycin bioavailability is not inherently affected by food and that the effect of food is formulation-dependent. Table F.1. summarizes the pharmacokinetics of azithromycin in the bioequivalence study and in the study to examine the affect of food on the bioavailability of the azithromycin tablets. Table F.2 summarizes azithromycin pharmacokinetics in the six other studies that demonstrate that the effect of food on the bioavailability of azithromycin is formulation-dependent.

The formulations used in these studies are described in Section 6 (Human Pharmacokinetics and Bioavailability Section) of this NDA.

In all six studies conducted by Pfizer Central Research in the United States (#066-042-599, #066-055-54C, #066-041-503, #066-046-599, #066-050-29C, #066-057-54C), concentrations of azithromycin in serum were determined with an HPLC assay with amperometric electrochemical detection, essentially as described in Shepard, et al (J. Chromatog, Biomed. Applic. 565:321-337, 1991). The method is described in detail in the assay reports appended to study reports in Section 6, HUMAN PHARMACOKINETICS AND BIOAVAILABILITY, of this NDA. Studies performed outside the USA by other Pfizer Divisions also utilized HPLC assays with electrochemical detection.

Summary Statements

As described in the following summaries, the results of studies of pharmacokinetics and bioavailability support the following statements:

1. The new tablet formulation of 250 mg azithromycin, FID #G00267AA, is bioequivalent to the present commercial capsule, when administered to volunteers in the fasted state.

2. The bioavailability of the new tablet formulation of azithromycin, FID #G00267AA, is not affected by coadministration with food.

3. The effect of food on the bioavailability of azithromycin is formulation-dependent.

F.1.B Description/Results of Studies

F.1.B.1 Bioequivalence Study

Clinical Study #066-042-599 was an open, randomized, two-way crossover study to examine the bioequivalence of azithromycin commercial capsules and the 250 mg tablets, which are the subject of this submission. Thirty-six fasted, healthy, male volunteers received two 250 mg commercial capsules (Lot #F311) and two 250 mg tablets (FID #G00267AA, Lot #ED-B-387-Z92). The doses were separated by two weeks. Blood samples were collected for times up to 120 hours post-dose for preparation of serum, which was frozen at -70°C until assay by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratios between treatments of C_{max} and of AUC.

The mean values of AUC_{0-72} were 4.26 µg•hr/ml for the tablets and 4.08 µg•hr/ml for the capsules. The geometric mean relative bioavailability was 105%. The 90% confidence limits on the tablet to capsule geometric mean ratio were 99% and 113%. The mean values of C_{max} were 0.512 µg/ml for the tablet and 0.482 µg/ml for the capsule. The 90% confidence limits of the tablet to capsule geometric mean ratio were 96% and 121%. The mean values of T_{max} were similar (2.2 hr for the tablets and 2.1 hr for the capsules). Both sets of confidence limits fell within the criteria for bioequivalence of 80 to 125%. Thus, the two formulations were bioequivalent.

F.1.B.2 Effect of Food on Bioavailability of the Tablet Formulation

Clinical Study #066-055-54C was an open, randomized, two-way crossover study to examine the effect of food on the bioavailability of azithromycin 250 mg tablets. Twelve healthy, male volunteers were administered two doses of two 250 mg tablets (FID G00267AA, Lot #ED-B-387-Z92), once following an overnight fast of at least 12 hours and once following a standard breakfast, containing at least 30 grams of fat (two eggs fried in one tablespoon butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk) ingested in the 20 minutes immediately prior to administration of drug. The treatments were separated by two weeks. Following the treatments, samples of blood were collected for up to 96 hours post-dose and serum was prepared and frozen until assay for azithromycin by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratio between treatments of C_{max} and of AUC.

The mean values of AUC_{0-48} were 2.49 µg•hr/ml following the overnight fast and 2.40 µg•hr/ml following the high-fat breakfast. The mean relative bioavailability was 97%. The 90% confidence limits of the geometric mean ratio of AUC_{fed}/AUC_{fasted} were 82% and 113%. The mean values of C_{max} were 0.336 µg/ml following the overnight fast and 0.412 µg/ml following the high-fat meal. The 90% confidence limits of the mean fed to fasted ratio were 88% and 146%. The mean values of T_{max} were similar (2.1 hr following the overnight fast and 2.3 hr following the high-fat breakfast). Thus, the extent of azithromycin bioavailability when administered as two 250 mg tablets was not decreased by administration immediately following a high-fat meal.

F.1.B.3 Effect of Food on Bioavailability of Other Formulations

Clinical Study #066-041-503 was an open, randomized, four-period, four-treatment crossover study to examine the relative bioavailability of azithromycin in solution and in commercial capsules when given with and without food. Twelve healthy male subjects received 500 mg azithromycin in solution, prepared from azithromycin for intravenous infusion (FID YY-91-092), and in two 250 mg commercial capsules (Lot #F311) following an overnight fast (10 - 12 hours) and following a standard breakfast, containing at least 30 grams of fat (two eggs fried in one tablespoon butter, two strips of bacon, two ounces of ham, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of milk) ingested in the 20 minutes immediately prior to administration of drug. The treatments were separated by an interval of two weeks. Serum was collected for up to 96 hours post-dose and frozen at about -70°C until assay for azithromycin by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratio between treatments of C_{max} and AUC.

The geometric mean ratio of AUC_{0-48}, comparing AUC following the high-fat meal with that following an overnight fast, was 90% for the solution and 80% for the capsule formulation. The 90% confidence limits on the geometric mean ratios of AUC_{fed}/AUC_{fasted} were 75% and 107% for the solution and 67% and 96% for the capsules. The geometric mean ratio of peak concentrations ($C_{maxfed}/C_{maxfasted}$) was 93% for the solution and 72% for the capsule formulation. The 90% confidence limits on the geometric mean ratios of $C_{maxfed}/C_{maxfasted}$ were 71% and 120% for the solution and 55% and 92% for the capsules. As expected, T_{max} was later following administration with food (2.3 vs 1.2 hr for the solution; 3.8 vs 2.2 hr for the capsules). Thus, the bioavailability of the capsule formulation was affected by coadministration of a high-fat breakfast.

Clinical Study #066-046-599 was an open, randomized, three-period, three treatment study to determine the absolute bioavailability of a research enteric-coated formulation of azithromycin and to examine the effect of food

on the bioavailability of this dosage form. Twelve healthy, male volunteers each received a single 1 hr intravenous infusion of 500 mg azithromycin in 500 ml of 0.9% normal saline (FID #YY-91-092), an oral dose of two capsules containing 500 mg enteric coated beads of azithromycin (FID #G00243AA) containing a total of 500 mg azithromycin following an overnight fast, and an oral dose of the enteric-coated beads immediately following ingestion of a standard high-fat breakfast containing at least 30 grams of fat (two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two pats of butter, eight ounces of whole-fat milk, and 6 oz of hash brown potatoes), consumed over a 20 minute period immediately prior to the doses. The treatments were separated by intervals of two weeks. Blood was collected for times up to 120 hours post-dose and serum was prepared and frozen at -70°C until assay for azithromycin by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratio between oral treatments of C_{max} and of AUC.

The mean values of AUC_{0-48} following oral administration of the enteric-coated beads were 3.30 µg•hr/ml in fasted subjects and 1.66 µg•hr/ml in the same subjects following the standard high-fat breakfast. The geometric mean relative bioavailability following the standard meal compared with that following the overnight fast was 46%, with 90% confidence limits of 36% and 58%. The absolute bioavailability of the enteric-coated beads administered in the fasted state was 39%. Mean values of C_{max} were 0.295 µg/ml following the overnight fast and 0.193 following the high-fat breakfast. The geometric mean ratio of C_{max} following the standard breakfast and the overnight fast was 54%, with 90% confidence limits of 36% and 83%. Thus, the standard high-fat breakfast substantially reduced the bioavailability of azithromycin in the enteric-coated beads.

Clinical Study #066-050-29C was an open, crossover study that examined the effect of meals of varying composition on the pharmacokinetics of azithromycin following single oral administration as a pediatric oral suspension (NDA #50-710, filed Nov. 1, 1993). Six healthy, adult male volunteers received 500 mg of azithromycin suspension (40 mg/ml, FID #G00007AA) under three conditions: (1) immediately following an overnight fast of 10-12 hours, or (2) following ingestion of a standard high-fat breakfast, or (3) following a light breakfast (one ounce of cereal and eight ounces of whole milk), each separated by a interval of 14 days. Six different treatment sequences were employed and each subject was randomly assigned to one of these sequences. Serum samples were collected from each subject at times from 0 (just prior to dosing) to 96 hours post-dose on each of the three treatment days. Serum concentrations of azithromycin were determined using an HPLC method with electrochemical detection. C_{max}, T_{max}, and AUC_{0-48} were determined. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits between treatments on the mean ratio of C_{max} and AUC.

The mean values of AUC_{0-48} were 2.19 µg•hr/ml, 2.22 µg•hr/ml, and 2.33 µg•hr/ml following the overnight fast, the high-fat breakfast, and the light breakfast, respectively. The geometric mean bioavailabilities, relative to the overnight fast, were 101% following the high-fat breakfast and 104% following the light breakfast. The 90% confidence limits on the geometric mean bioavailabilities were 79% and 128% following the high-fat breakfast and 82% and 133% following the light breakfast. The mean values of C_{max} were 0.312 µg/ml, 0.325 µg/ml, and 0.253 µg/ml following the overnight fast, the high-fat breakfast, and the light breakfast, respectively. The 90% confidence limits on the geometric mean ratio of fed to fasted values of C_{max} were 74% and 147% for the high-fat breakfast and 59% and 117% for the light breakfast. The mean values of T_{max} were 1.8 hr following the overnight fast and the high-fat breakfast and 2.5 hr following the light breakfast. Thus, there appears to be no clinically significant effect of food on the bioavailability of azithromycin suspension.

Clinical Study #066-057-54C was an open, randomized, three-period, three-treatment crossover study to determine the absolute bioavailability of the sachet formulation of azithromycin (Zithromax® Single Dose Packet (1 gm); NDA #50,693, response to Approvable Letter submitted Dec. 29, 1993) and to examine the affect of a high-fat breakfast on the bioavailability of the sachet formulation. Twelve healthy, male volunteers were given three doses of azithromycin, once following an overnight fast as a one hour intravenous infusion of 1000 mg in 1000 ml sterile water (FID #YY-91-092), once as the oral 1000 mg sachet (FID #G00047AA) with 240 ml of water following an overnight (10-12 hours) fast, and once as the 1000 mg sachet following a high-fat breakfast containing at least 30 grams of fat (two eggs fried in one tablespoon butter, two strips of bacon, six ounces of hash brown potatos, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of milk), ingested within 20 minutes prior to administration of drug. The treatments were separated by intervals of two weeks. Serum was collected for up to 120 hours post-dose and frozen at about -70°C until assay for azithromycin by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratio between oral treatments of C_{max} and of AUC.

Following oral administration of 1000 mg azithromycin sachet, the mean values of AUC_{0-72} were 6.49 µg•hr/ml in the fasted state and 7.37 µg•hr/ml following the high-fat meal. Comparison with AUC_{0-72} following the 1 hour infusion of 1000 mg (14.76 µg•hr/ml) indicated an absolute bioavailability of 44% in the fasted state and 49.9% following the high-fat meal. The geometric mean relative bioavailability comparing AUC following the high-fat meal and following the overnight fast was 112% with 90% confidence limits of 99% and 127%. Mean C_{max} was 1.052 µg/ml following the high-fat meal and 0.749 µg/ml following the overnight fast. The 90% confidence limits on the geometric mean ratio of C_{max} following the meal and overnight fast were 116% and 185%. Mean T_{max} was 2.04 hr following the meal and 1.46 hr

following an overnight fast. Thus, ingestion of a high-fat meal did not reduce the bioavailability of azithromycin when administered as a 1000 mg sachet.

Study #066-206 (conducted by Pfizer Central Research, Sandwich, UK) was previously discussed in the NDA for azithromycin capsules (NDA #50-670. Vol. 1.19, pp.6-1397 - 6-1506; Approved Nov. 1, 1991) and was the basis for the food effect labeling for azithromycin capsules. Descriptive paragraphs from that NDA are enclosed: This was an open label, randomized, two-way crossover study designed to examine the effect of food on the absorption of azithromycin. Following either a 12 hour fast or a breakfast meal (milk, bread, butter, fried eggs, bacon, coffee) estimated to contain 30 grams of fat, single oral doses of 500 mg azithromycin (2 x 250 mg research capsules; FID YY-85-005) were administered to 11 healthy male volunteers. The period between doses was 13 days. Plasma samples were withdrawn at intervals up to 24 hr, frozen at -20°C, and assayed for azithromycin by HPLC (lower limit of quantification 0.05 µg/ml). The effects of the treatment regimen on mean values of C_{max} and T_{max} were assessed with an ANOVA. 95% confidence limits on mean differences in C_{max} and T_{max} were calculated.

Following the dose in the fasting state, mean (n=10) AUC_{0-24} was 1.347 µg·hr/ml, with a C_{max} of 0.314 µg/ml at a T_{max} of 2.6 hr. Following a standard meal, the same dose produced a statistically significantly lower mean C_{max} (n=10) of 0.153 µg/ml ($p = 0.004$) at a T_{max} of 3.4 hr. Mean (n=5) AUC_{0-24} also appeared lower (0.776 µg·hr/ml), but formal comparisons were not possible because only 5 subjects in the non-fasting state had detectable plasma concentrations at sufficient time points to permit AUC calculations. Differences in T_{max} were not significant. Thus, bioavailability of this research capsule was greatly reduced by a high-fat concurrent meal.

Study AZM-NY-89-0 (conducted by Pfizer-Mack, Illertissen, Germany) was an open, randomized, two-way crossover study to examine the effect of a light breakfast on the bioavailability of azithromycin capsules, similar to the present commercial capsules. Twelve healthy, male volunteers each received two 1000 mg oral doses of azithromycin in four 250 mg capsules (FID #YY-89-051), once following an overnight (12 hr) fast and once following a light breakfast of two rolls with butter and jam and approximately 300 ml of coffee or tea with milk, ingested immediately prior to the doses. The treatments were separated by an interval of two weeks. Blood was collected for times up to 46.5 hours post-dose for preparation of serum, which was frozen until assay for azithromycin by HPLC with electrochemical detection and by bioassay. Urine samples were also collected for intervals up to 46.5 hours post-dose and assayed for azithromycin by HPLC-EC and bioassay. Since the results were similar for the two assays, only HPLC assay results are reported here. The lower limit of quantification of the HPLC assay was 0.010 µg/ml in serum and 0.060 µg/ml in urine. The data were analyzed with a two-way, repeat measures ANOVA. The 90%

confidence bounds on the differences in mean AUC, C_{max}, T_{max}, and urinary recovery between treatments were calculated.

Mean values of $AUC_{0-46.5}$ were 4.53 µg•hr/ml following the overnight fast and 3.37 µg•hr/ml following the light breakfast. The mean relative bioavailability was 74%. Mean C_{max} was 0.71 µg/ml following the overnight fast and 0.59 µg/ml following the light breakfast. The ratio of mean C_{max} values was 84%. Mean T_{max} was 2.3 hr following the fast and 3.1 hr following the light breakfast. The 90% confidence limits on the difference in AUCs (AUC_{fed} - AUC_{fasted}), expressed as a percentage of the observed mean following the overnight fast, were -46% and -3%. The corresponding limits on the difference in C_{max} were -38% and +5%. The mean recoveries of azithromycin in urine were 5.1% and 3.8% following the overnight fast and the light breakfast, respectively. Thus, the bioavailability of azithromycin in capsules was reduced by coadministration with a light breakfast.

F.1.C Summary and Conclusions

Study #066-042-599 examined the bioequivalence of the proposed 250 mg tablet formulation of azithromycin and the present commercial formulation. The geometric mean relative bioavailability was 105% with 90% confidence limits on the tablet to capsule AUC ratio of 99% and 113%. Thus, the proposed 250 mg tablet formulation was bioequivalent to the current commercial 250 mg capsule.

A further study (#066-055-54C) with 12 volunteers showed that administration of a standard breakfast, containing at least 30 grams of fat, did not affect the bioavailability of azithromycin from the proposed commercial 250 mg tablets. The geometric mean relative bioavailability, comparing the AUC following the standard meal with the AUC following an overnight fast, was 97% with 90% confidence limits on the fed to fasted ratio of 82% and 113%. Thus, the bioavailability of azithromycin administered as two 250 mg tablets was not decreased by administration immediately following a high-fat meal.

The effects of food on the bioavailability of azithromycin from several formulations were examined in six studies. Relative bioavailabilities ranged from less than or equal to 50% for two formulations (research capsule - Study #066-206; enteric-coated beads - Study #066-045-599) to values close to 100% for 500 mg in solution (Study #066-041-503), 500 mg from a powder for oral suspension (Study #066-050-29C) and a 1000 mg sachet (Study #066-057-54C). Examination of the effect of food on the bioavailability of the present commercial capsule showed a moderate effect, with a high-fat breakfast yielding a relative bioavailability of 82% in Study #066-041-503 and a light breakfast producing a relative bioavailability of 74% for a 1000 mg dose in Study AZM-NY-89-0. Thus, the effect of food on bioavailability is dependent upon the formulation.

These results demonstrate that the proposed 250 mg azithromycin tablets will produce serum concentrations in man equal to those produced by the present commercial capsules and that the tablets may be given without restrictions relative to the ingestion of meals.

F.1.D Dissolution

A dissolution rate test is employed to measure the *in vitro* dissolution rate of 250 mg tablets. The method uses USP Apparatus 2 (paddles) rotating at 100 rpm in 900 mL of pH 6.0 phosphate buffer held at 37°C±0.5°C. The pH 6.0 0.1M phosphate buffer was chosen to assure drug solubility exceeded sink conditions and to assure optimum stability of azithromycin in the dissolution medium. The drug has a solubility of approximately 39 mg/mL in the phosphate buffer at 37°C. Other media considered during the development of the dissolution rate included simulated gastric fluid and water. Simulated gastric fluid was not chosen as the dissolution medium because azithromycin is not sufficiently stable at this acidic pH for such a test. Water was not chosen because the aqueous solubility of azithromycin is only 1.1 mg/mL. Aliquots of the dissolution media are analyzed using an HPLC procedure. The specification has been set at Q= % in minutes.

This dissolution test is very similar to that used for the approved azithromycin capsules except that trypsin, which is included to aid dissolution of the gelatin capsule shell, is not added to the dissolution medium for the film-coated tablets. The dissolution specification is the same as that approved for azithromycin capsules in NDA-50-670.

Table F.1
Results of Clinical Pharmacology Studies:
Bioequivalence and Food Interaction Studies for Proposed Commercial Tablet

Protocol No. (Country)	Study Objective	Study Design	Number of Subjects enrolled/ completed	Treatment	Mean Parameters (%CV) Cmax (µg/ml)	Tmax (hr)	AUC[1] (µg·hr/ml)
066-042-599 (USA)	Bioequivalence of commercial capsule and proposed tablet	Two-way single dose crossover	36/36	2 x 250 mg commercial capsule	0.482 (40)	2.1 (38)	4.076^{0-72} (29)
			36/36	2 x 250 mg tablet	0.512 (41)	2.2 (41)	4.260^{0-72} (28)
066-055-640 (USA)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover	12/12	2 x 250 mg tablet, fasted	0.336 (24)	2.1 (33)	2.491^{0-48} (36)
			12/12	2 x 250 mg tablet, fed[a]	0.412 (47)	2.3 (35)	2.999^{0-48} (28)

[1] measured over the specified interval.
[a] High-fat breakfast containing at least 30 grams of fat.

Table F.2
Results of Clinical Pharmacology Studies: Effects of Food on Other Formulations

Protocol No. (Country)	Study Objective	Study Design	Number of Subjects enrolled/completed	Treatment	Mean Parameters (%CV) Cmax (μg/ml)	Tmax (hr)	AUC[t] (μg·hr/ml)
066-041-503 (USA)	Compare serum levels in fed and fasted subjects	Four-way single dose crossover	12/12	500 mg solution fasted.	0.517 (38)	1.2 (51)	3.20^{0-48} (22)
			12/12	500 mg solution fed.	0.502 (39)	2.3 (25)	2.94^{0-48} (26)
			12/11	2 x 250 mg commercial capsule, fasted.	0.357 (30)	2.2 (50)	2.57^{0-48} (32)
			12/12	2 x 250 mg commercial capsule, fed[a].	0.276 (54)	3.8 (31)	2.11^{0-48} (35)
066-048-599 (USA)	Absolute bioavail of enteric dose. Serum levels in fed and fasted subjects.	Three-way single dose crossover	12/12	1000 mg IV	3.22 (16)	0.9 (22)	8.60^{0-48} (16)
			12/12	500 mg enteric beads, fasted.	0.295 (29)	3.3 (45)	3.30^{0-48} (22)
			12/12	500 mg enteric beads, fed[a].	0.193 (76)	5.6 (32)	1.66^{0-48} (54)
066-050-29C (USA)	Compare serum levels in fed and fasted subjects.	Three-way single dose crossover	6/6	500 mg oral suspension, fasted.	0.312 (29)	1.8 (44)	2.194^{0-48} (26)
			6/6	500 mg oral suspension, fed[a].	0.325 (26)	1.8 (44)	2.216^{0-48} (27)
			6/6	500 mg oral suspension, fed[b].	0.253 (20)	2.5 (32)	2.325^{0-48} (30)
066-057-54C (USA)	Absolute bioavail of sachet. Serum levels in fed and fasted subjects.	Three-way single dose crossover	12/12	1000 mg IV, fasted			14.76^{0-72} (19)
			12/12	1000 mg oral sachet, fasted.	0.749 (57)	1.5 (47)	6.494^{0-72} (24)
			12/12	1000 mg oral sachet, fed[a].	1.052 (38)	2.0 (34)	7.372^{0-72} (29)

[t] measured over the specified interval.
[a] High-fat breakfast containing at least 30 grams of fat.
[b] Cereal and milk.
[c] Light breakfast of rolls with butter and jam and coffee or tea.

Table F.2 (Cont'd)
Results of Clinical Pharmacology Studies
Effects of Food on other Formulations

Protocol No. (Country)	Study Objective	Study Design	Number of Subjects enrolled/ completed	Treatment	Mean Parameters (%CV) Cmax (µg/ml)	Tmax (hr)	AUC[1] (µg·hr/ml)	Urinary Excretion[1] (% of Dose)
066-206 (Belgium)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover	11/10	2 x 250 mg capsule, fasted.	0.314 (39)	2.6 (50)	1.347^{0-24} (37)	
			11/10	2 x 250 mg capsule, fed[a].	0.153 (24)	3.4 (44)	0.776^{0-24} (39)	
AZM-NY-89-0 (Germany)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover.	12/12	4 x 250 mg capsule, fasted.	0.705 (21)	2.3 (33)	$4.532^{0-48.5}$ (32)	5.1^{0-72} (40)
			12/12	4 x 250 mg capsule, fed[c].	0.590 (52)	3.1 (44)	$3.979^{0-48.5}$ (42)	3.8^{0-72} (55)

[1] measured over the specified interval.
[a] High-fat breakfast containing at least 30 grams of fat.
[b] Cereal and milk.
[c] Light breakfast of rolls with butter and jam and coffee or tea.

H.1. CLINICAL PHARMACOLOGY

H.1.A Introduction

Azithromycin capsules were the subject of a previously-approved NDA (#50-670, approved Nov 1, 1991). This submission seeks to replace the commercial capsules with a new tablet formulation (FID #G00267AA). One study (#066-042-599) was conducted to establish the bioequivalence of this new tablet formulation to the currently available commercial 250 mg capsules. Another study (#066-055-54C) was performed to assess the effect of food upon the bioavailability of azithromycin delivered from this new tablet formulation.

Six additional studies (#066-041-503, #066-046-599, #066-050-29C, #066-057-54C, #066-206, AZM-NY-89-0) are presented in this submission to demonstrate that azithromycin bioavailability is not inherently affected by food and that the effect of food is formulation-dependent. Table H.1. summarizes the pharmacokinetics of azithromycin in the bioequivalence study and in the study to examine the affect of food on the bioavailability of the azithromycin tablets. Table H.2 summarizes azithromycin pharmacokinetics in the six other studies that demonstrate that the effect of food on the bioavailability of azithromycin is formulation-dependent.

The formulations used in these studies are described in Section 6 (Human Pharmacokinetics and Bioavailability Section) of this NDA.

In all six studies conducted by Pfizer Central Research in the United States (#066-042-599, #066-055-54C, #066-041-503, #066-046-599, #066-050-29C, #066-057-54C), concentrations of azithromycin in serum were determined with an HPLC assay with amperometric electrochemical detection, essentially as described in Shepard, et al (J. Chromatog, Biomed. Applic. 565:321-337, 1991). The method is described in detail in the assay reports appended to study reports in Section 6, HUMAN PHARMACOKINETICS AND BIOAVAILABILITY, of this NDA. Studies performed outside the USA by other Pfizer Divisions also utilized HPLC assays with electrochemical detection.

Summary Statements

As described in the following summaries, the results of studies of pharmacokinetics and bioavailability support the following statements:

1. The new tablet formulation of 250 mg azithromycin, FID #G00267AA, is bioequivalent to the present commercial capsule, when administered to volunteers in the fasted state.

2. The bioavailability of the new tablet formulation of azithromycin, FID #G00267AA, is not affected by coadministration with food.

3. The effect of food on the bioavailability of azithromycin is formulation-dependent.

H.1.B Description/Results of Studies

H.1.B.1 Bioequivalence Study

Clinical Study #066-042-599 was an open, randomized, two-way crossover study to examine the bioequivalence of azithromycin commercial capsules and the 250 mg tablets, which are the subject of this submission. Thirty-six fasted, healthy, male volunteers received two 250 mg commercial capsules (Lot #F311) and two 250 mg tablets (FID #G00267AA, Lot #ED-B-387-Z92). The doses were separated by two weeks. Blood samples were collected for times up to 120 hours post-dose for preparation of serum, which was frozen at -70°C until assay by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratios between treatments of C_{max} and of AUC.

The mean values of AUC_{0-72} were 4.26 µg•hr/ml for the tablets and 4.08 µg•hr/ml for the capsules. The geometric mean relative bioavailability was 105%. The 90% confidence limits on the tablet to capsule geometric mean ratio were 99% and 113%. The mean values of C_{max} were 0.512 µg/ml for the tablet and 0.482 µg/ml for the capsule. The 90% confidence limits of the tablet to capsule geometric mean ratio were 96% and 121%. The mean values of T_{max} were similar (2.2 hr for the tablets and 2.1 hr for the capsules). Both sets of confidence limits fell within the criteria for bioequivalence of 80 to 125%. Thus, the two formulations were bioequivalent.

H.1.B.2 Effect of Food on Bioavailability of the Tablet Formulation

Clinical Study #066-055-54C was an open, randomized, two-way crossover study to examine the effect of food on the bioavailability of azithromycin 250 mg tablets. Twelve healthy, male volunteers were administered two doses of two 250 mg tablets (FID G00267AA, Lot #ED-B-387-Z92), once following an overnight fast of at least 12 hours and once following a standard breakfast, containing at least 30 grams of fat (two eggs fried in one tablespoon butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk) ingested in the 20 minutes immediately prior to administration of drug. The treatments were separated by two weeks. Following the treatments, samples of blood were collected for up to 96 hours post-dose and serum was prepared and frozen until assay for azithromycin by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratio between treatments of C_{max} and of AUC.

The mean values of AUC_{0-48} were 2.49 µg•hr/ml following the overnight fast and 2.40 µg•hr/ml following the high-fat breakfast. The mean relative bioavailability was 97%. The 90% confidence limits of the geometric mean ratio of AUC_{fed}/AUC_{fasted} were 82% and 113%. The mean values of C_{max} were 0.336 µg/ml following the overnight fast and 0.412 µg/ml following the high-fat meal. The 90% confidence limits of the mean fed to fasted ratio were 88% and 146%. The mean values of T_{max} were similar (2.1 hr following the overnight fast and 2.3 hr following the high-fat breakfast). Thus, the extent of azithromycin bioavailability when administered as two 250 mg tablets was not decreased by administration immediately following a high-fat meal.

H.1.B.3 Effect of Food on Bioavailability of OTHER Formulations

Clinical Study #066-041-503 was an open, randomized, four-period, four-treatment crossover study to examine the relative bioavailability of azithromycin in solution and in commercial capsules when given with and without food. Twelve healthy male subjects received 500 mg azithromycin in solution, prepared from azithromycin for intravenous infusion (FID YY-91-092), and in two 250 mg commercial capsules (Lot #F311) following an overnight fast (10 - 12 hours) and following a standard breakfast, containing at least 30 grams of fat (two eggs fried in one tablespoon butter, two strips of bacon, two ounces of ham, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of milk) ingested in the 20 minutes immediately prior to administration of drug. The treatments were separated by an interval of two weeks. Serum was collected for up to 96 hours post-dose and frozen at about -70°C until assay for azithromycin by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratio between treatments of C_{max} and AUC.

The geometric mean ratio of AUC_{0-48}, comparing AUC following the high-fat meal with that following an overnight fast, was 90% for the solution and 80% for the capsule formulation. The 90% confidence limits on the geometric mean ratios of AUC_{fed}/AUC_{fasted} were 75% and 107% for the solution and 67% and 96% for the capsules. The geometric mean ratio of peak concentrations ($C_{max fed}/C_{max fasted}$) was 93% for the solution and 72% for the capsule formulation. The 90% confidence limits on the geometric mean ratios of $C_{max fed}/C_{max fasted}$ were 71% and 120% for the solution and 55% and 92% for the capsules. As expected, T_{max} was later following administration with food (2.3 vs 1.2 hr for the solution; 3.8 vs 2.2 hr for the capsules). Thus, the bioavailability of the capsule formulation was affected by coadministration of a high-fat breakfast.

Clinical Study #066-046-599 was an open, randomized, three-period, three treatment study to determine the absolute bioavailability of a research enteric-coated formulation of azithromycin and to examine the effect of food

on the bioavailability of this dosage form. Twelve healthy, male volunteers each received a single 1 hr intravenous infusion of 500 mg azithromycin in 500 ml of 0.9% normal saline (FID #YY-91-092), an oral dose of two capsules containing 500 mg enteric coated beads of azithromycin (FID #G00243AA) containing a total of 500 mg azithromycin following an overnight fast, and an oral dose of the enteric-coated beads immediately following ingestion of a standard high-fat breakfast containing at least 30 grams of fat (two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two pats of butter, eight ounces of whole-fat milk, and 6 oz of hash brown potatoes), consumed over a 20 minute period immediately prior to the doses. The treatments were separated by intervals of two weeks. Blood was collected for times up to 120 hours post-dose and serum was prepared and frozen at -70°C until assay for azithromycin by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratio between oral treatments of C_{max} and of AUC.

The mean values of AUC_{0-48} following oral administration of the enteric-coated beads were 3.30 µg•hr/ml in fasted subjects and 1.66 µg•hr/ml in the same subjects following the standard high-fat breakfast. The geometric mean relative bioavailability following the standard meal compared with that following the overnight fast was 46%, with 90% confidence limits of 36% and 58%. The absolute bioavailability of the enteric-coated beads administered in the fasted state was 39%. Mean values of C_{max} were 0.295 µg/ml following the overnight fast and 0.193 following the high-fat breakfast. The geometric mean ratio of C_{max} following the standard breakfast and the overnight fast was 54%, with 90% confidence limits of 36% and 83%. Thus, the standard high-fat breakfast substantially reduced the bioavailability of azithromycin in the enteric-coated beads.

Clinical Study #066-050-29C was an open, crossover study that examined the effect of meals of varying composition on the pharmacokinetics of azithromycin following single oral administration as a pediatric oral suspension (NDA #50-710, filed Nov. 1, 1993). Six healthy, adult male volunteers received 500 mg of azithromycin suspension (40 mg/ml, FID #G00007AA) under three conditions: (1) immediately following an overnight fast of 10-12 hours, or (2) following ingestion of a standard high-fat breakfast, or (3) following a light breakfast (one ounce of cereal and eight ounces of whole milk), each separated by a interval of 14 days. Six different treatment sequences were employed and each subject was randomly assigned to one of these sequences. Serum samples were collected from each subject at times from 0 (just prior to dosing) to 96 hours post-dose on each of the three treatment days. Serum concentrations of azithromycin were determined using an HPLC method with electrochemical detection. C_{max}, T_{max}, and AUC_{0-48} were determined. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits between treatments on the mean ratio of C_{max} and AUC.

The mean values of AUC_{0-48} were 2.19 µg•hr/ml, 2.22 µg•hr/ml, and 2.33 µg•hr/ml following the overnight fast, the high-fat breakfast, and the light breakfast, respectively. The geometric mean bioavailabilities, relative to the overnight fast, were 101% following the high-fat breakfast and 104% following the light breakfast. The 90% confidence limits on the geometric mean bioavailabilities were 79% and 128% following the high-fat breakfast and 82% and 133% following the light breakfast. The mean values of C_{max} were 0.312 µg/ml, 0.325 µg/ml, and 0.253 µg/ml following the overnight fast, the high-fat breakfast, and the light breakfast, respectively. The 90% confidence limits on the geometric mean ratio of fed to fasted values of C_{max} were 74% and 147% for the high-fat breakfast and 59% and 117% for the light breakfast. The mean values of T_{max} were 1.8 hr following the overnight fast and the high-fat breakfast and 2.5 hr following the light breakfast. Thus, there appears to be no clinically significant effect of food on the bioavailability of azithromycin suspension.

Clinical Study #068-057-54C was an open, randomized, three-period, three-treatment crossover study to determine the absolute bioavailability of the sachet formulation of azithromycin (Zithromax® Single Dose Packet (1 g); NDA #50,693, response to Approvable Letter submitted Dec. 29, 1993) and to examine the affect of a high-fat breakfast on the bioavailability of the sachet formulation. Twelve healthy, male volunteers were given three doses of azithromycin, once following an overnight fast as a one hour intravenous infusion of 1000 mg in 1000 ml sterile water (FID #YY-91-092), once as the oral 1000 mg sachet (FID #G00047AA) with 240 ml of water following an overnight (10-12 hours) fast, and once as the 1000 mg sachet following a high-fat breakfast containing at least 30 grams of fat (two eggs fried in one tablespoon butter, two strips of bacon, six ounces of hash brown potatos, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of milk), ingested within 20 minutes prior to administration of drug. The treatments were separated by intervals of two weeks. Serum was collected for up to 120 hours post-dose and frozen at about -70°C until assay for azithromycin by HPLC with electrochemical detection. The data were analyzed with a repeat measures ANOVA and by calculation of the 90% confidence limits on the geometric mean ratio between oral treatments of C_{max} and of AUC.

Following oral administration of 1000 mg azithromycin sachet, the mean values of AUC_{0-72} were 6.49 µg•hr/ml in the fasted state and 7.37 µg•hr/ml following the high-fat meal. Comparison with AUC_{0-72} following the 1 hour infusion of 1000 mg (14.76 µg•hr/ml) indicated an absolute bioavailability of 44% in the fasted state and 49.9% following the high-fat meal. The geometric mean relative bioavailability comparing AUC following the high-fat meal and following the overnight fast was 112% with 90% confidence limits of 99% and 127%. Mean C_{max} was 1.052 µg/ml following the high-fat meal and 0.749 µg/ml following the overnight fast. The 90% confidence limits on the geometric mean ratio of C_{max} following the meal and overnight fast were 116% and 185%. Mean T_{max} was 2.04 hr following the meal and 1.46 hr

confidence bounds on the differences in mean AUC, C_{max}, T_{max}, and urinary recovery between treatments were calculated.

Mean values of $AUC_{0-46.5}$ were 4.53 µg•hr/ml following the overnight fast and 3.37 µg•hr/ml following the light breakfast. The mean relative bioavailability was 74%. Mean C_{max} was 0.71 µg/ml following the overnight fast and 0.59 µg/ml following the light breakfast. The ratio of mean C_{max} values was 84%. Mean T_{max} was 2.3 hr following the fast and 3.1 hr following the light breakfast. The 90% confidence limits on the difference in AUCs (AUC_{fed} - AUC_{fasted}), expressed as a percentage of the observed mean following the overnight fast, were -48% and -3%. The corresponding limits on the difference in C_{max} were -38% and +5%. The mean recoveries of azithromycin in urine were 5.1% and 3.6% following the overnight fast and the light breakfast, respectively. Thus, the bioavailability of azithromycin in capsules was reduced by coadministration with a light breakfast.

H.1.C Summary and Conclusions

Study #066-042-599 examined the bioequivalence of the proposed 250 mg tablet formulation of azithromycin and the present commercial formulation. The geometric mean relative bioavailability was 105% with 90% confidence limits on the tablet to capsule AUC ratio of 99% and 113%. Thus, the proposed 250 mg tablet formulation was bioequivalent to the current commercial 250 mg capsule.

A further study (#066-055-54C) with 12 volunteers showed that administration of a standard breakfast, containing at least 30 grams of fat, did not affect the bioavailability of azithromycin from the proposed commercial 250 mg tablets. The geometric mean relative bioavailability, comparing the AUC following the standard meal with the AUC following an overnight fast, was 97% with 90% confidence limits on the fed to fasted ratio of 82% and 113%. Thus, the bioavailability of azithromycin administered as two 250 mg tablets was not decreased by administration immediately following a high-fat meal.

The effects of food on the bioavailability of azithromycin from several formulations were examined in six studies. Relative bioavailabilities ranged from less than or equal to 50% for two formulations (research capsule - Study #066-206; enteric-coated beads - Study #066-046-599) to values close to 100% for 500 mg in solution (Study #066-041-503), 500 mg from a powder for oral suspension (Study #066-050-29C) and a 1000 mg sachet (Study #066-057-54C). Examination of the effect of food on the bioavailability of the present commercial capsule showed a moderate effect, with a high-fat breakfast yielding a relative bioavailability of 82% in Study #066-041-503 and a light breakfast producing a relative bioavailability of 74% for a 1000 mg dose in Study AZM-NY-89-0. Thus, the effect of food on bioavailability is dependent upon the formulation.

following an overnight fast. Thus, ingestion of a high-fat meal did not reduce the bioavailability of azithromycin when administered as a 1000 mg sachet.

Study #066-206 (conducted by Pfizer Central Research, Sandwich, UK) was previously discussed in the NDA for azithromycin capsules (NDA #50-670. Vol. 1.19, pp.6-1397 - 6-1506; Approved Nov. 1, 1991) and was the basis for the food effect labeling for azithromycin capsules. Descriptive paragraphs from that NDA are enclosed: This was an open label, randomized, two-way crossover study designed to examine the effect of food on the absorption of azithromycin. Following either a 12 hour fast or a breakfast meal (milk, bread, butter, fried eggs, bacon, coffee) estimated to contain 30 grams of fat, single oral doses of 500 mg azithromycin (2 x 250 mg research capsules: FID YY-85-005) were administered to 11 healthy male volunteers. The period between doses was 18 days. Plasma samples were withdrawn at intervals up to 24 hr, frozen at -20°C, and assayed for azithromycin by HPLC (lower limit of quantification 0.05 µg/ml). The effects of the treatment regimen on mean values of C_{max} and T_{max} were assessed with an ANOVA. 95% confidence limits on mean differences in C_{max} and T_{max} were calculated.

Following the dose in the fasting state, mean (n=10) AUC_{0-24} was 1.347 µg·hr/ml, with a C_{max} of 0.314 µg/ml at a T_{max} of 2.6 hr. Following a standard meal, the same dose produced a statistically significantly lower mean C_{max} (n=10) of 0.153 µg/ml ($p = 0.004$) at a T_{max} of 3.4 hr. Mean (n=5) AUC_{0-24} also appeared lower (0.776 µg·hr/ml), but formal comparisons were not possible because only 5 subjects in the non-fasting state had detectable plasma concentrations at sufficient time points to permit AUC calculations. Differences in T_{max} were not significant. Thus, bioavailability of this research capsule was greatly reduced by a high-fat concurrent meal.

Study AZM-NY-89-0 (conducted by Pfizer-Mack, Illertissen, Germany) was an open, randomized, two-way crossover study to examine the effect of a light breakfast on the bioavailability of azithromycin capsules, similar to the present commercial capsules. Twelve healthy, male volunteers each received two 1000 mg oral doses of azithromycin in four 250 mg capsules (FID #YY-89-051), once following an overnight (12 hr) fast and once following a light breakfast of two rolls with butter and jam and approximately 300 ml of coffee or tea with milk, ingested immediately prior to the doses. The treatments were separated by an interval of two weeks. Blood was collected for times up to 46.5 hours post-dose for preparation of serum, which was frozen until assay for azithromycin by HPLC with electrochemical detection and by bioassay. Urine samples were also collected for intervals up to 46.5 hours post-dose and assayed for azithromycin by HPLC-EC and bioassay. Since the results were similar for the two assays, only HPLC assay results are reported here. The lower limit of quantification of the HPLC assay was 0.010 µg/ml in serum and 0.060 µg/ml in urine. The data were analyzed with a two-way, repeat measures ANOVA. The 90%

Table H.1
Results of Clinical Pharmacology Studies:
Bioequivalence and Food Interaction Studies for Proposed Commercial Tablet

Protocol No. (Country)	Study Objective	Study Design	Number of Subjects enrolled/ completed	Treatment	Mean Parameters (%CV) Cmax (µg/ml)	Tmax (hr)	AUC[1] (µg·hr/ml)
066-042-599 (USA)	Bioequivalence of commercial capsule and proposed tablet	Two-way single dose crossover	36/36	2 x 250 mg commercial capsule	0.482 (40)	2.1 (36)	4.076^{0-72} (29)
			36/36	2 x 250 mg tablet	0.512 (41)	2.2 (41)	4.260^{0-72} (28)
066-055-540 (USA)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover	12/12	2 x 250 mg tablet, fasted.	0.336 (24)	2.1 (33)	2.491^{0-48} (36)
			12/12	2 x 250 mg tablet, fed[a].	0.412 (47)	2.3 (35)	2.399^{0-48} (28)

[1] measured over the specified interval.
[a] High-fat breakfast containing at least 30 grams of fat.

These results demonstrate that the proposed 250 mg azithromycin tablets will produce serum concentrations in man equal to those produced by the present commercial capsules and that the tablets may be given without restrictions relative to the ingestion of meals.

R/066TAB/NDA SEC2H1/AB1 V2/1/94

Table H.2
Results of Clinical Pharmacology Studies:
Effects of Food on Other Formulations

Protocol No. (Country)	Study Objective	Study Design	Number of Subjects enrolled/ completed	Treatment	Mean Parameters (%CV) Cmax (µg/ml)	Tmax (hr)	AUC[t] (µg·hr/ml)
066-041-503 (USA)	Compare serum levels in fed and fasted subjects	Four-way single dose crossover	12/12	500 mg solution fasted.	0.517 (38)	1.2 (51)	3.20^{0-48} (22)
			12/12	500 mg solution fed.	0.502 (39)	2.3 (25)	2.94^{0-48} (25)
			12/11	2 x 250 mg commercial capsule, fasted.	0.357 (30)	2.2 (50)	2.57^{0-48} (32)
			12/12	2 x 250 mg commercial capsule, fed[a].	0.276 (54)	3.8 (31)	2.11^{0-48} (35)
066-046-599 (USA)	Absolute bioavail of enteric dose. Serum levels in fed and fasted subjects.	Three-way single dose crossover	12/12	1000 mg IV	3.22 (18)	0.9 (22)	8.80^{0-48} (18)
			12/12	500 mg enteric beads, fasted.	0.295 (29)	3.3 (45)	3.30^{0-48} (22)
			12/12	500 mg enteric beads, fed[a].	0.193 (76)	5.8 (32)	1.86^{0-48} (54)
066-050-29C (USA)	Compare serum levels in fed and fasted subjects.	Three-way single dose crossover	6/6	500 mg oral suspension, fasted.	0.312 (29)	1.8 (44)	2.194^{0-48} (25)
			6/6	500 mg oral suspension, fed[a].	0.325 (28)	1.8 (44)	2.216^{0-48} (27)
			6/6	500 mg oral suspension, fed[b].	0.253 (20)	2.6 (32)	2.325^{0-48} (30)
066-057-54C (USA)	Absolute bioavail of sachet. Serum levels in fed and fasted subjects.	Three-way single dose crossover	12/12	1000 mg IV, fasted.			14.76^{0-72} (19)
			12/12	1000 mg oral sachet, fasted.	0.749 (57)	1.5 (47)	6.494^{0-72} (24)
			12/12	1000 mg oral sachet, fed[c]	1.058 (38)	2.0 (34)	7.372^{0-72} (29)

t measured over the specified interval.
a High-fat breakfast containing at least 30 grams of fat.
b Cereal and milk.
c Light breakfast of rolls with butter and jam and coffee or tea.

Table H.2 (Cont'd)
Results of Clinical Pharmacology Studies
Effects of Food on other Formulations

Protocol No. (Country)	Study Objective	Study Design	Number of Subjects enrolled/completed	Treatment	Mean Parameters (%CV) Cmax (µg/ml)	Tmax (hr)	AUC† (µg·hr/ml)	Urinary Excretion† (% of Dose)
066-206 (Belgium)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover	11/10	2 x 250 mg capsule, fasted.	0.314 (39)	2.6 (50)	1.347^{0-24} (37)	
			11/10	2 x 250 mg capsule, fed[a].	0.153 (24)	3.4 (44)	0.778^{0-24} (39)	
AZM-NY-89-0 (Germany)	Compare serum levels in fed and fasted subjects.	Two-way single dose crossover.	12/12	4 x 250 mg capsule, fasted.	0.705 (21)	2.3 (33)	$4.532^{0-48.5}$ (32)	5.1^{0-72} (40)
			12/12	4 x 250 mg capsule, fed[c].	0.590 (52)	3.1 (44)	$3.373^{0-48.5}$ (42)	3.8^{0-72} (55)

† measured over the specified interval.
a High-fat breakfast containing at least 30 grams of fat.
b Cereal and milk.
c Light breakfast of rolls with butter and jam and coffee or tea.

Co. Corres.

ORIGINAL

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Pfizer

Robert B. Clark
Senior Associate Director

November 21, 1995

NDA ORIG AMENDMENT

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 50-711
ZITHROMAX® (azithromycin) Tablets

Dear Dr. Fanning:

Reference is made to our pending New Drug Application for ZITHROMAX® (azithromycin) Tablets, NDA 50-711. The Division of Anti-Infective Drug Products issued an approvable letter for this application on February 14, 1995.

The labeling for this application, containing the language noted in the February 14, 1995 approvable letter for NDA 50-711, is attached. Also included are the revisions made to the labeling following approval of NDA 50-710 for ZITHROMAX® (azithromycin for oral suspension) for Pediatric Use.

A highlighted version of the labeling is also attached.

If there are questions on the enclosed, please contact the undersigned [illegible] 3412. Please include this information in the subject file.

RECEIVED
NOV 22 1995
HFD-520
EVALUATION AND RESEARCH

Sincerely,

Robert B. Clark

cc: Ms. Frances LeSane, Project Manager (HFD-520)

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905 AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW.

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
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DESK COPY

BC

Robert B. Clark
Senior Associate Director

June 19, 1996

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 50-711
ZITHROMAX® (azithromycin) 250 mg Tablets

Dear Dr. Fanning:

Reference is made to our pending New Drug Application for ZITHROMAX® (azithromycin) 250 mg Tablets, NDA 50-711, submitted on February 15, 1994. The Division of Anti-Infective Drug Products (DAIDP) issued an approvable letter for this application on February 14, 1995. Draft versions of the labeling were submitted as amendments for review on November 21, 1995, March 25, 1996 and May 2, 1996. A second approvable letter for this application was issued by DAIDP on May 22, 1996.

Further reference is made to NDA 50-730 for ZITHROMAX® (azithromycin) 600 mg Tablets for the Prophylaxis of MAC Infection in HIV-Infected Patients. This NDA was approved by the Division of Antiviral Drug Products (HFD-530) on June 12, 1996. As you are aware, the 250 mg azithromycin tablets that are the subject of NDA 50-711 and the 600 mg azithromycin tablets share a common tablet blend. In addition, we refer to recent discussions between representatives of Pfizer, Dr. Eric Sheinin, Director, Office of New Drug Chemistry and other staff in both HFD-520 and HFD-530 regarding various chemistry, manufacturing, and controls issues for these two applications. During these discussions, all outstanding CMC issues were resolved.

Pfizer commits to the following two items as Phase IV commitments as noted in the May 22, 1996 approvable letter for NDA 50-711:

1) Biopharmaceutics - Please refer to our correspondence of May 2, 1996 in which we committed to perform additional dissolution testing on additional lots of azithromycin tablet formulation, report the results to the division and propose a suitable dissolution specification. We also note that an interim dissolution specification of Q % for 100 RPM at minutes has been agreed upon.

2) CMC - Attached please see Pfizer's June 11, 1996 (telefaxed to HFD-530 on June 4, 1996) response to the May 21, 1996 correspondence from the Division of Antiviral Drug Products on the azithromycin 600 mg tablet NDA which identified five chemistry, manufacturing, and controls issues. The attached Pfizer response was considered to be acceptable. As was previously agreed, the resolution of these five CMC issues will be incorporated into NDA 50-711 for the azithromycin 250 mg tablet to fulfill the division's request to revise the appropriate Chemistry, Manufacturing, and Control sections of this NDA.

We believe all issues regarding the New Drug Application for ZITHROMAX® (azithromycin) 250 mg Tablets have been resolved and as such the division is in a position to issue an approval letter for NDA 50-711. Please include this information in the subject file. If there are questions on the attached, please contact the undersigned at (212) 573-3412.

Sincerely,

Robert B. Clark

Enclosure

cc: Dr. Eric Sheinin, Director, Office of New Drug Chemistry
Ms. Frances LeSane, Project Manager (HFD-520)

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314)

Form approved : OMB No. 0910-0001. Expiration Date: December 31, 1995. See OMB Statement on Page 3

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT	DATE OF SUBMISSION
Pfizer Inc	6/19/96
ADDRESS *(Number, Street, City, State, and Zip Code)*	TELEPHONE NO. (Include Area Code)
235 East 42nd Street New York, New York 10017	(212) 573-2323
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* 50-711

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)	
azithromycin	Zithromax	
CODE NAME (If any)	CHEMICAL NAME	
	9-deoxo-9a-methyl-9a-homoerythromycin A (USAN)	
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
	Tablets	250 mg

PROPOSED INDICATIONS FOR USE

azalide antibiotic

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:

MF
IND

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

RIT

Central Research

June 11, 1996

Department of Clinical Research

David Feigal, M.D., Director
Division of Antiviral Drug Products
Center for Drug Evaluation and Research HFD #530
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #15B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Feigal:

RE: NDA 50-730 • **ZITHROMAX® - MAC PROPHYLAXIS**
RESPONSE TO FDA REQUEST FOR INFORMATION
CHEMISTRY, MANUFACTURING AND CONTROLS

Please note: These responses were previously submitted as a draft by facsimile on May 31, 1996.

Reference is made to Pfizer's pending NDA-50-730 for ZITHROMAX® - MAC Prophylaxis, submitted December 21, 1995. Reference is also made to a teleconference with the Division Chemistry Reviewers and Ms. Lisa Hubbard, Consumer Safety Officer, on May 28, 1996.

During this teleconference Pfizer informed the Division Chemistry Reviewers that although the NDA stability tablet lots contained lubricant levels of : %, newer commercial scale lots contained levels of : %. The Reviewers requested details of these newer lots that demonstrated acceptable dissolution characteristics (Enclosure #1). In addition, the Reviewers also requested further details regarding the rework procedure, including the conditions under which rework would be warranted, the level of testing to be used to qualify the product and the proposed expiration date to be used (Enclosure #2). Please note that both of these responses were previously submitted by facsimile. However, the references have not been submitted previously (Enclosure #1).

Per Division request, we are formally acknowledging that it is no longer applicable for any restrictions imposed on the pending azithromycin tablet NDAs to be extended to the other presently approved azithromycin NDAs.

Please include this information in our files for NDA-50-730.

Sincerely yours,

Linda Wypocki for:

Ronald I. Trust, Ph.D.
Associate Director I
Drug Regulatory Affairs - Liaison

lpw
Enclosures
Desk copies (1) Ms. L. Hubbard, CSO
Serial No. 537

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

DESK COPY

Robert B. Clark
Senior Associate Director

May 2, 1996

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 50-711
ZITHROMAX® (azithromycin) Tablets

Dear Dr. Fanning:

Reference is made to our pending New Drug Application for ZITHROMAX® (azithromycin) Tablets, NDA 50-711, submitted on February 15, 1994. The Division of Anti-Infective Drug Products issued an approvable letter for this application on February 14, 1995. Draft versions of the labeling were submitted as amendments for review on November 21, 1995 and March 25, 1996. Reference is also made to an April 26, 1996 memorandum from Ms. Frances LeSane, Project Manager in HFD-520 to the undersigned regarding this pending application. This memorandum requested a change in the text of the **CLINICAL PHARMACOLOGY** section of the labeling, as well as a phase IV commitment to perform additional dissolution tests for the azithromycin tablet dosage form.

Attached is draft labeling incorporating the change requested in the division's April 26, 1996 memorandum. We also commit to perform the requested dissolution tests on additional lots of the azithromycin tablet formulation, report the results to the division and propose a suitable dissolution specification. Please include this information in the subject file.

Sincerely,

Robert B. Clark

cc: Ms. Frances LeSane, Project Manager (HFD-520)

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

Central Research

NEW CORRESPONDENCE

February 8, 1995

Department of Clinical Research

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905 AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW. FURTHER DISSEMINATION MAY ONLY BE MADE WITH THE EXPRESS WRITTEN PERMISSION OF PFIZER INC.

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD
#520
Office of Drug Evaluation II
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Gavrilovich:

RE: NDA-50-711 - Zithromax® (azithromycin) Tablets

Reference is made to my conversation with Ms. Maureen Dillon-Parker on February 8, 1995, and the Division's request for a safety update to NDA 50-711. As discussed with Ms. Parker, please be advised that there is no additional safety information applicable for submission to our file for NDA 50-711.

NDA 50-711 was submitted to support a new formulation of azithromycin only, and contained no integrated summary of safety or clinical trial data to support new indications. Concerning relevant safety information for this product, reference is made to approved NDA 50-670 for azithromycin capsules and subsequent updates to that file.

If there are any questions regarding this submission, please feel free to contact me at (203)441-6899.

Sincerely yours,

Charles A. Ritrovato, Pharm.D.
Associate Director II
Regulatory Affairs - Liaison

Serial No. 6

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340.
Tel 860 441 4100

DRAFT

Pfizer

Central Research

May <>, 1996

Department of Clinical Research

David Feigal, M.D., Director
Division of Antiviral Drug Products
Center for Drug Evaluation and Research HFD #530
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #15B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Feigal:
RE: NDA 50-730 -

ZITHROMAX® - MAC PROPHYLAXIS
RESPONSE TO FDA REQUEST FOR INFORMATION
CHEMISTRY, MANUFACTURING AND CONTROLS

Reference is made to Pfizer's pending NDA #50-730 for ZITHROMAX® - MAC Prophylaxis, submitted December 21, 1995. Reference is also made to requests from Chandra Sahajwalla, Ph.D., Biopharmaceutics Reviewer, (received April 23, 1996), for consideration of modifications in the specification for dissolution testing of azithromycin 600 mg film-coated tablets, to Pfizer's response of April 29, and a telecon with Chemistry and Biopharmaceutics Reviewers from both the Anti-Viral and Anti-Infective Divisions.

Responses to the Reviewers' requests are enclosed.

Please include this information in our files for NDA-50-730.

Sincerely yours,

Ronald I. Trust

Ronald I. Trust, Ph.D.
Associate Director I
Drug Regulatory Affairs - Liaison

Enclosures
Desk copies (1): Ms. L. Hubbard, CSO
Serial No.

Regarding the Agency proposal of the interim dissolution rate specification of Q % at minutes at 100 rpm, we would like to present Pfizer's concerns in writing and further elaborate and explain each concern as you have requested. Additionally, as mentioned in our telecon, Pfizer would like to propose an alternative dissolution rate specification of Q % in minutes using the 100 rpm paddle speed.

FDA Comment 1:

Elaborate on Pfizer's lack of experience at the minute time point for the dissolution rate test.

Pfizer Response 1:

Our first concern was lack of substantial experience at minutes particularly on full scale commercial batches. We have not tested multiple production lots at full scale with such a specification in mind. It is true that data submitted in the application on clinical lots and limited 10% scale production batches would pass the interim specification at 15 minutes proposed by the Agency, but we have insufficient confidence that this would be reliably met with future full scale lots at the time of release or as the lots progress on stability. Although we have data at minutes, we do not have data at earlier time points than minutes and therefore cannot determine how close to the edge we might be to failing to meet the Agency's proposed interim specification. Whereas, if the Agency were to accept our proposal of Q % at minutes (100 rpm), we have data on either side of the minute time point (i.e., minutes, respectively) showing that Q % at minutes is not right on the edge of failure. This would give Pfizer sufficient comfort that we would not be failing batches due to a dissolution rate specification that had been set too restrictive (Q % at minutes). It should also provide the Agency a high level of confidence that this dosage form reliably releases the dose in a very short time frame minutes).

FDA Comment 2:

Provide clarification regarding the rationale for the slope argument for the minute time point of the dissolution rate test.

Pfizer Response 2:

This is very much related to the first concern described above.

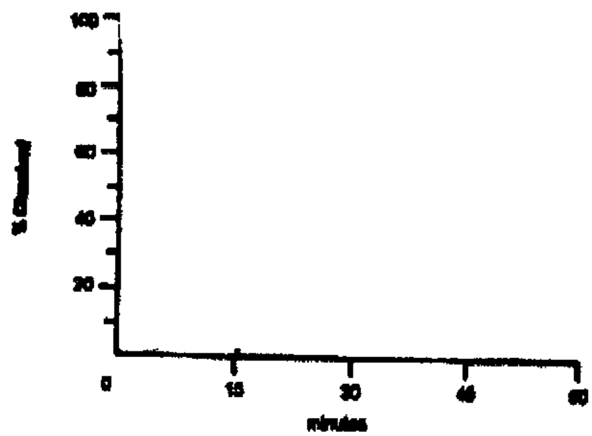
Although we agree with the Agency that the data submitted show dissolution results at minutes for the 600 mg tablet to be greater than 87%, it is unclear if these results are at the edge of a steep dissolution curve which plateaus at minutes (as represented by the figure on the following page by Case 1).

If this were the case (i. minutes is at the very edge of the curve), a very slight change in the dissolution profile, as demonstrated in Case 2, may result in a dissolution failure which is not representative of the 600 mg tablet's quality. This could be due to normal process variation or it could be due to analytical variation, etc. In any event, it would be difficult to scientifically defend that such a small shift had any reflection of drug product quality or clinical significance.

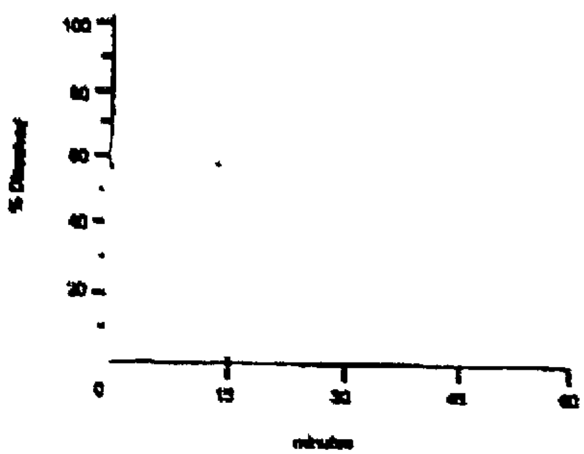
Based on the limited dissolution experience from material manufactured at our commercial facility and a lack of understanding of the dissolution profile prior to minutes a thirty minute specification would be more appropriate. The thirty minute time point is bracketed by data collected at minutes which provides a higher degree of confidence for establishing the specification.

ILLUSTRATIVE

CASE 1



CASE 2



FDA Comment 3:

Provide a Phase IV commitment for the dissolution testing of production batches of azithromycin 600 mg tablets at rates of 75 and 100 rpm.

Pfizer Response 3:

Pfizer will commit to generating additional data at 75 and 100 rpm on production batches (minimum of 3 lots). Pfizer will also commit to generate additional data on the 24 month test interval from the first 3 pivotal NDA stability batches included in the application. When data from these additional studies become available, Pfizer will commit to contacting the Agency to re-evaluate the establishment of an appropriate final dissolution rate specification. During the interim, Pfizer would propose to employ a dissolution rate specification of Q % in minutes at a paddle speed of 100 rpm.

FDA Comment 4:

Provide a time frame for providing the Agency with the additional data and establishment of a final dissolution rate specification.

Pfizer Response 4:

Pfizer would propose to meet this post-approval commitment in 3 stages and on the following timeline:

1.	Produce and provide release data at 75 and 100 rpm on 3 production batches	6 months post-approval
2.	Provide the 24 month stability data from the NDA lots as soon as they are available	1st lot June 1996 Last lot May 1997
3.	Meet with the Agency, review the above database and propose final dissolution rate specification	June 1997

ORIGINAL

AMENDMENT

BL

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3422 Fax 212 573 1563

Robert B. Clark
Senior Associate Director

May 2, 1996

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

RE: NDA 50-711
ZITHROMAX® (azithromycin) Tablets

Dear Dr. Fanning:

Reference is made to our pending New Drug Application for ZITHROMAX® (azithromycin) Tablets, NDA 50-711, submitted on February 15, 1994. The Division of Anti-Infective Drug Products issued an approvable letter for this application on February 14, 1995. Draft versions of the labeling were submitted as amendments for review on November 21, 1995 and March 25, 1996. Reference is also made to an April 26, 1996 memorandum from Ms. Frances LeSane, Project Manager in HFD-520 to the undersigned regarding this pending application. This memorandum requested a change in the text of the **CLINICAL PHARMACOLOGY** section of the labeling, as well as a phase IV commitment to perform additional dissolution tests for the azithromycin tablet dosage form.

Attached is draft labeling incorporating the change requested in the division's April 26, 1996 memorandum. We also commit to perform the requested dissolution tests on additional lots of the azithromycin tablet formulation, report the results to the division and propose a suitable dissolution specification. Please include this information in the subject file.

Sincerely,

Robert B. Clark

Robert B. Clark

cc: Ms. Frances LeSane, Project Manager (HFD-520)

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905 AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW.

ORIGINAL

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

RL

NDA ORIG AMENDMENT

Noted 3/29/96 Lesane F. LeSane

March 25, 1996

Robert B. Clark
Senior Associate Director

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO
CSO INITIALS: DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 2 6 1996
HFD

RE: NDA 50-711
ZITHROMAX® (azithromycin) Tablets

Dear Dr. Fanning:

Reference is made to our pending New Drug Application for ZITHROMAX® (azithromycin) Tablets, NDA 50-711. The Division of Anti-Infective Drug Products issued an approvable letter for this application on February 14, 1995.

On November 21, 1995 a draft version of labeling for this application was submitted. This labeling containing the language noted in the February 14, 1995 approvable letter for NDA 50-711 as well as the revisions made to the labeling following approval of NDA 50-710 for ZITHROMAX® (azithromycin for oral suspension) for Pediatric Use.

Further reference is made to a March 20, 1996 discussion between the undersigned and Ms. Frances LeSane of the division on the labeling for this pending application. At that time, minor revisions to the labeling were provided by Ms. LeSane. All of these changes have also been incorporated into the attached final draft labeling. A computer disk (virus-checked) containing the labeling formatted into a WordPerfect file is also enclosed. If there are questions on the enclosed, please contact the undersigned at (212) 573-3412. Please include this information in the subject file.

Sincerely,

Robert B. Clark

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905 AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW.

cc: Ms. Frances LeSane, Project Manager (HFD-520)

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

Pfizer

Central Research

BC

NDA ORIG AMENDMENT

Department of Clinical Research

February 9, 1995

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD
#520
Office of Drug Evaluation II
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Gavrilovich:

RE: NDA-50-710 - Zithromax® (azithromycin) for Pediatric Use

As discussed with Ms. Maureen Dillon-Parker on February 3, 1995, this letter confirms our intention to withdraw our facility in Barceloneta, Puerto Rico as a manufacturing site for the azithromycin pediatric POS drug product. Our facility in Brooklyn, New York will remain as the manufacturing site for this product, as indicated in the original NDA.

If there are any questions regarding this submission, please feel free to contact me at (203) 441-6899.

FEB 1 [illegible] 1995

Sincerely yours,

Charles A. Ritrovato, Pharm.D.
Associate Director II
Regulatory Affairs - Liaison

Serial No. S39

Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

Central Research

Department of Clinical Research

September 26, 1994

R1
NDA ORIG AMENDMENT

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation II
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Gavrilovich:

RE: NDA-50-711 - Zithromax® (azithromycin) Tablet

Response to FDA Request for Information

Reference is made to our teleconference of July 22, 1994 with the Division's Biopharmaceutics reviewers Mr. Frank Pelsor and Dr. He Sun concerning dissolution testing and results for azithromycin film-coated tablets. This submission contains information in response to each of the following items requested by Mr. Pelsor and Dr. Sun:

1. Dissolution rate profiles for the film-coated tablets and commercial capsules used in the pivotal bioequivalence study, including raw data (individual values), summary statistics (if applicable) and validation information on the analytical test method;
2. Additional copies of the NDA CMC sections pertaining to dissolution testing;
3. A dissolution rate profile for film-coated tablets using the current dissolution method; and
4. Dissolution data for all the film-coated tablet lots in the NDA and any production batches (including individual values for the single specification timepoint of minutes).

If there are any questions regarding this submission, please feel free to contact me at (203)441-6899.

Sincerely yours,

Charles A. Ritrovato, Pharm.D.
Associate Director II
Regulatory Affairs - Liaison

CENTER FOR DRUG
REC'D
SEP 27 1994
HFD-520
EVALUATION AND RESEARCH

mfb
Enclosure
Copy No. 1
Serial No. S5

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

Pfizer

Central Research

NEW CORRESPONDENCE

Department of Clinical Research

April 29, 1994

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation II
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Gavrilovich:

RE: NDA-50-711 - Zithromax®(azithromycin) Tablets

Reference is made to our original New Drug Application for azithromycin 250 mg tablets submitted to the Division on February 15, 1994. During a recent review of this Application, we realized that cross-reference had not been provided to several bioequivalence studies submitted to NDA 50-670 (azithromycin capsules) which the Division reviewers may find of interest during their review of NDA 50-711. Several of these studies were submitted with the original NDA for azithromycin capsules on April 11, 1990, and a more recent study, 066-031, "Phase I Bioequivalency Study Comparing Azithromycin (CP-62,933) proposed commercial 250 mg Capsules to the 500 mg Tablet," was submitted to NDA 50-670 on January 28, 1994. All of these studies employed different tablet formulations and/or strengths than that for which approval is requested in our pending NDA 50-711. The titles and location of these studies within NDA 50-670 are as follows:

Study Title	Date submitted to NDA-50-670
Study 066-017: Phase I Bioequivalency Study Comparing Azithromycin (CP-62,993) 250 mg Tablets to 250 mg Research Capsules	4-11-90 (Vol 1.46)
Study 066-023: Phase I Bioequivalency Study Comparing Azithromycin (CP-62,993) 250 mg Tablets to 250 mg Research Capsules	4-11-90 (Vol 1.48)
Study 066-024: Phase I Bioequivalency Study Comparing Azithromycin (CP-62,993) 200 mg Tablets to 250 mg Research Capsules	4-11-90 (Vol 1.48)

Study 066-025:
Phase I Bioequivalency Study Comparing Azithromycin (CP-62,993) Anhydrous 250 mg Capsules to Dihydrate 250 mg Capsules — 4-11-90 (Vol 1.30)

Study 066-031:
Phase I Bioequivalency Study Comparing Azithromycin (CP-62,933) proposed commercial 250 mg Capsules to the 500 mg Tablet — 1-28-94

The results of these studies are not felt to alter the conclusions drawn in NDA 50-711 concerning the bioequivalence of the proposed 250 mg azithromycin tablet and the current commercial 250 mg azithromycin capsule. We provide cross-reference to these reports for completeness of information.

If you have any questions concerning this submission, please feel free to contact me at (203) 441-6899.

Sincerely yours,

Charles A. Ritrovato, Pharm.D.
Associate Director II
Regulatory Affairs - Liaison

Copy No. 1
Serial No. S3
Desk Copy: Maureen Parker (CSO)

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

Pfizer

Central Research

February 15, 1994

Department of Clinical Research

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation II
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Gavrilovich:

RE: NDA-50-711 : Zithromax® (azithromycin) Tablets

Pursuant to Paragraph 507 of the Federal Food, Drug, and Cosmetic Act, and Paragraph 314.1 of the Code of Federal Regulations, Title 21, we are submitting a New Drug Application for Zithromax Tablets, a new dosage form of azithromycin intended to replace the current capsule formulation. Data contained in this NDA demonstrate that azithromycin tablets are bioequivalent to the currently marketed capsule formulation and unlike the capsule, can be taken without regard to meals. This Application also presents data from food effect studies with other azithromycin formulations to demonstrate that the effect of food on the bioavailability of azithromycin is a formulation dependent phenomena.

Azithromycin previously received marketing approval in the U.S. on November 1, 1991 (NDA-50-670) as a capsule dosage form for the treatment of respiratory tract, skin and skin structure infections, and chlamydia trachomatis genitourinary infections in patients 16 years of age and older. A majority of the technical information contained in NDA-50-670, including clinical efficacy and safety data, in vitro microbiology data, manufacturing and control data pertaining to azithromycin drug substance, and nonclinical pharmacology and toxicology data is incorporated into the current Application by cross-reference.

The current Application consists of 13 volumes. The volumes are numbered consecutively and are organized according to the itemized listing for the contents of an Application as provided in the NDA Overall Index. A complete archival copy of all 13 volumes (blue binders) and a review copy of 15 volumes have been provided. Two additional review copies of the Application Summary (Section 2, Volume 1) are provided for each of the technical reviewers.

The lead manufacturing site identified in this Application is located in Brooklyn, NY, and New York City is the site of Pfizer's corporate headquarters. As such, the Sponsor hereby certifies that a field copy of portions of this Application has been provided to the FDA district office in Brooklyn, NY, and that it is an exact copy of the Chemistry, Manufacturing and Controls section, FDA Form 356h and the Application Summary contained in the archival and review copies of this NDA.

The locations of the various sections of this NDA are listed in Attachment I of this letter.

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this application, to the best of its knowledge, Pfizer Inc. did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act.

Please be advised that the applicable user fee for this submission has been remitted in accordance with the Prescription Drug User Fee Act of 1992. We believe this Application to be complete for review by the Division and look forward to a response within 180 days of receipt.

Should you have any questions regarding the content or organization of this submission, please contact Dr. Charles A. Ritrovato at (203) 441-6899.

Sincerely yours,

Charles A. Ritrovato, Pharm.D.
Associate Director II
Regulatory Affairs - Liaison

Dilip J. Mehta, M.D., Ph.D.
Vice President
Department of Clinical Research

mgd
Enclosures
Copy No.
Serial No. 000