CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 064150

Trade Name : RIFAMPIN CAPSULES USP 300MG

Generic Name: Rifampin Capsules USP 300mg

Sponsor : Eon Labs Manufacturing, Inc.

Approval Date: May 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 064150

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 064150

APPROVAL LETTER

AADA 64-150

MAY 28 1997

Eon Labs Manufacturing, Inc.
Attention: Mr Michael Lisjak
227-15 N. Conduit Avenue
Laurelton, NY 11413

Dear Sir:

This is in reference to your abbreviated antibiotic application dated April 12, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Rifampin Capsules USP, 300 mg.

Reference is also made to your amendments dated December 14, 1995, March 25 and May 2, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Rifampin Capsules USP, 300 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Rifadin® Capsules 300 mg of Hoechst Marion Roussel, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 5/28/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064150

FINAL PRINTED LABELING

NDC 0185-0799-42

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

240 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-42 8

NDC 0185-0799-05

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-05 3

NDC 0185-0799-10

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-10 7

Exp. Date:

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

NDC 0185-0799-08

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

8 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-08 4

Exp. Date:

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

NDC 0185-0799-30

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

30 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-30 5

Exp. Date:

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

NDC 0185-0799-60

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

60 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-60 2

Exp. Date:

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

NDC 0185-0799-01

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Capsules

Each capsule contains:
Rifampin, USP 300 mg

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-01 5

RIFAMPIN
CAPSULES, USP

0799

RIFAMPIN
CAPSULES, USP

MAY 28 199

DESCRIPTION

Rifampin is a semisynthetic antibiotic derivative of rifamycin SV. Rifampin is a red-brown crystalline powder very slightly soluble in water at neutral pH, freely soluble in chloroform, soluble in ethyl acetate and in methanol. Its molecular weight is 822.95 and its chemical formula is $C_{43}H_{58}N_4O_{12}$. The chemical name for rifampin is either:

3-[[(4-Methyl-1-piperazinyl)imino]-methyl]rifamycin

or

5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)-formimidoyl]-2,7(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-*b*]furan-1,11(2H)-dione 21-acetate.

Its structural formula is:

Each capsule, for oral administration, contains 300 mg of rifampin. In addition, each capsule contains the following inactive ingredients: colloidal silicon dioxide, corn starch, D&C Yellow No. 10 Aluminum Lake, docusate sodium, FD&C Blue No. 1, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40, FD&C Red No. 40 Aluminum Lake, gelatin, magnesium stearate, microcrystalline cellulose, silicon dioxide, sodium benzoate, sodium lauryl sulfate, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

Human Pharmacology:

Rifampin is readily absorbed from the gastrointestinal tract. Peak serum concentrations in healthy adults and pediatric populations vary widely from individual to individual. Following a single 600 mg oral dose of rifampin in healthy adults, the peak serum concentration averages 7 µg/mL but may vary from 4 to 32 µg/mL. Absorption of rifampin is reduced by about 30% when the drug is ingested with food.

Rifampin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampin is about 80% protein bound. Most of the unbound fraction is not ionized and, therefore, diffuses freely into tissues.

In healthy adults, the mean biological half-life of rifampin in serum averages 3.35 ± 0.66 hours after a 600 mg oral dose, with increases up to 5.08 ± 2.45 hours reported after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2 to 3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600 mg daily, and consequently, no dosage adjustment is required. Following a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively. Refer to the **WARNINGS** section for information regarding patients with hepatic insufficiency.

Rifampin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampin undergoes progressive deacetylation so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite is microbiologically active. Intestinal reabsorption is reduced by deacetylation, and elimination is facilitated. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

Pediatrics

In one study, pediatric patients 6 to 58 months old were given rifampin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7 ± 3.7 and 11.5 ± 5.1 µg/mL were obtained 1 hour after preprandial ingestion of the drug suspension and the applesauce mixture, respectively. After the administration of either preparation, the $t_{1/2}$ of rifampin averaged 2.9 hours. It should be noted that in other studi[illegible] formulations, at doses

no dosage adjustment is required. Following a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively. Refer to the WARNINGS section for information regarding patients with hepatic insufficiency.

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Microbiology

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. Rifampin at therapeutic levels has demonstrated bactericidal activity against both intracellular and extracellular *Mycobacterium tuberculosis* organisms.

Organisms resistant to rifampin are likely to be resistant to other rifamycins.

Rifampin has bactericidal activity against slow and intermittently growing *M tuberculosis* organisms. It also has significant activity against *Neisseria meningitidis* isolates (see INDICATIONS AND USAGE).

In the treatment of both tuberculosis and the meningococcal carrier state (see INDICATIONS AND USAGE), the small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. In addition, resistance to rifampin has been determined to occur as single-step mutations of the DNA-dependent RNA polymerase. Since resistance can emerge rapidly, appropriate susceptibility tests should be performed in the event of persistent positive cultures.

Rifampin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic Gram-Negative Microorganisms:
Neisseria meningitidis

"Other" Microorganisms:
Mycobacterium tuberculosis

The following in vitro data are available, but their clinical significance is unknown.

Rifampin exhibits in vitro activity against most strains of the following microorganisms; however, the safety and effectiveness of rifampin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (including Methicillin-Resistant *S. aureus*/MRSA)
Staphylococcus epidermidis

Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae

"Other" Microorganisms:
Mycobacterium leprae

β-lactamase production should have no effect on rifampin activity.

Susceptibility Tests

Prior to initiation of therapy, appropriate specimens should be collected for identification of the infecting organism and in vitro susceptibility tests.

In vitro testing for *Mycobacterium tuberculosis* isolates:

Two standardized in vitro susceptibility methods are available for testing rifampin against *M tuberculosis* organisms. The agar proportion method (CDC or NCCLS[1] M24-P) utilizes Middlebrook 7H10 medium impregnated with rifampin at a final concentration of 1.0 µg/mL to determine drug resistance. After three weeks of incubation MIC_{99} values are calculated by comparing the quantity of organisms growing in the medium containing drug to the control cultures. Mycobacterial growth in the presence of drug, of at least 1% of the growth in the control culture, indicates resistance.

The radiometric broth method employs the BACTEC 460 machine to compare the growth index from untreated control cultures to cultures grown in the presence of 2.0 µg/mL of rifampin. Strict adherence to the manufacturer's instructions for sample processing and data interpretation is required for this assay.

Susceptibility test results obtained by the two different methods can only be compared if the appropriate rifampin concentration is used for each test method as indicated above. Both procedures require the use of *M tuberculosis* H37Rv ATCC 27294 as a control organism.

The clinical relevance of in vitro susceptibility test results for mycobacterial species other than *M tuberculosis* using either the radiometric or the proportion method has not been determined.

In vitro testing for *Neisseria meningitidis* isolates:

Dilution Techniques: Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[2,4] (broth, agar, or microdilution) or equivalent with rifampin powder. The MIC values obtained should be interpreted according to the following criteria for *Neisseria meningitidis*:

MIC (µg/mL)	Interpretation

In vitro testing for *Mycobacterium tuberculosis* isolates:

Two standardized in vitro susceptibility methods are available for testing rifampin against *M tuberculosis* organisms. The agar proportion method (CDC or NCCLS[1] M24-P) utilizes Middlebrook 7H10 medium impregnated with rifampin at a final concentration of 1.0 µg/mL to determine drug resistance. After three weeks of incubation MIC_{99} values are calculated by comparing the quantity of organisms growing in the medium containing drug to the control cultures. Mycobacterial growth in the presence of drug, of at least 1% of the growth in the control culture, indicates resistance.

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In vitro testing for *Neisseria meningitidis* isolates:

Dilution Techniques: Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[2,4] (broth, agar, or microdilution) or equivalent with rifampin powder. The MIC values obtained should be interpreted according to the following criteria for *Neisseria meningitidis*:

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

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

Measurement of MIC or minimum bactericidal concentrations (MBC) and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The use of these microorganisms does not imply clinical efficacy (see INDICATIONS AND USAGE); they are used to control the technical aspects of the laboratory procedures. Standard rifampin powder should give the following MIC values:

Microorganism		MIC (µg/mL)
Staphylococcus aureus	ATCC 29213	0.008-0.06
Enterococcus faecalis	ATCC 29212	1-4
Escherichia coli	ATCC 25922	8-32
Pseudomonas aeruginosa	ATCC 27853	32-64
Haemophilus influenzae	ATCC 49247	0.25-1

Diffusion Techniques: Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3,4] that has been recommended for use with disks to test the susceptibility of microorganisms to rifampin uses the 5 µg rifampin disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for rifampin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 µg rifampin disk should be interpreted according to the following criteria for *Neisseria meningitidis*:

Zone Diameter (mm)	Interpretation
≥20	(S) Susceptible
17-19	(I) Intermediate
≤16	(R) Resistant

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

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms. The use of these microorganisms does not imply clinical efficacy (see INDI-
CATIONS AND USAGE).

Organism	Minimal Inhibitory Concentration (MIC) (µg/ml)
N. meningitidis	0.008-0.08
S. aureus	1-4
E. coli	8-32
H. influenzae	32-64
S. pneumoniae	0.25-1

Diffusion Techniques: Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[14] that has been recommended for use with disks to test the susceptibility of microorganisms to rifampin uses the 5 µg rifampin disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for rifampin.

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≥20	(S) Susceptible
17-19	(I) Intermediate
≤16	(R) Resistant

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

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms. The use of these microorganisms does not imply clinical efficacy (see INDICATIONS AND USAGE); they are used to control the technical aspects of the laboratory procedures. The 5 µg rifampin disk should provide the following zone diameters in these quality control strains:

Microorganism	ATCC	Zone Diameter (mm)
S. aureus	ATCC 25923	26-34
E. coli	ATCC 25922	8-10
H. influenzae	ATCC 49247	22-30

INDICATIONS AND USAGE

In the treatment of both tuberculosis and the meningococcal carrier state, the small number of resistant cells present within large populations of susceptible cells can rapidly become the predominant type. Bacteriologic cultures should be obtained before the start of therapy to confirm the susceptibility of the organism to rifampin and they should be repeated throughout therapy to monitor the response to treatment. Since resistance can emerge rapidly, susceptibility tests should be performed in the event of persistent positive cultures during the course of treatment. If test results show resistance to rifampin and the patient is not responding to therapy, the drug regimen should be modified.

Tuberculosis

Rifampin is indicated in the treatment of all forms of tuberculosis.

A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide (eg, RIFATER®) is recommended in the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin, and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs, may be considered.

Following the initial phase, treatment should be continued with rifampin and isoniazid (eg, RIFAMATE®) for at least 4 months. Treatment should be continued for longer if the patient is still sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive.

Meningococcal Carriers

Rifampin is indicated for the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. **Rifampin is not indicated for the treatment of meningococcal infection because of the possibility of the rapid emergence of resistant organisms.** (See WARNINGS.)

Rifampin should not be used indiscriminately, and therefore, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed for establishment of the carrier state and the correct treatment. So that the usefulness of rifampin in the treatment of asymptomatic meningococcal carriers is preserved, the drug should be used only when the risk of meningococcal disease is high.

CONTRAINDICATIONS

Rifampin is contraindicated in patients with a history of hypersensitivity to any of the rifamycins. (See WARNINGS.)

WARNINGS

Rifampin has been shown to produce liver dysfunction. Fatalities associated with jaundice have occurred in patients with liver disease and in patients taking rifampin with other hepatotoxic agents. Patients with impaired liver function should be given rifampin only in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially SGPT/ALT and SGOT/AST should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of hepatocellular damage occur, rifampin should be withdrawn.

...rhinomycin

(Rifampin is contraindica...
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In some cases, hyperbilirubinemia resulting from competition between rifampin and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels, and considering them in conjunction with the patient's clinical condition.

Rifampin has enzyme-inducing properties, including induction of delta amino levulinic acid synthetase. Isolated reports have associated porphyria exacerbation with rifampin administration.

The possibility of rapid emergence of resistant meningococci restricts the use of RIFAMPIN to short-term treatment of the asymptomatic carrier state. **RIFAMPIN is not to be used for the treatment of meningococcal disease.**

PRECAUTIONS

General

For the treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin greater than 600 mg given once or twice weekly have resulted in a higher incidence of adverse reactions, including the "flu syndrome" (fever, chills and malaise), hematopoietic reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia), cutaneous, gastrointestinal, and hepatic reactions, shortness of breath, shock, anaphylaxis, and renal failure. Recent studies indicate that regimens using twice-weekly doses of rifampin 600 mg plus isoniazid 15 mg/kg are much better tolerated. Intermittent therapy may be used if the patient cannot (or will not) self-administer drugs on a daily basis. Patients on intermittent therapy should be closely monitored for compliance and cautioned against intentional or accidental interruption of prescribed therapy, because of the increased risk of serious adverse reactions.

Rifampin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones, and vitamin D. Rifampin and isoniazid have been reported to alter vitamin D metabolism. In some cases, reduced levels of circulating 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D have been accompanied by reduced serum calcium and phosphate, and elevated parathyroid hormone.

Information for Patients

The patient should be told that rifampin may produce a reddish coloration of the urine, sweat, sputum, and tears, and the patient should be forewarned of this. Soft contact lenses may be permanently stained.

The patient should be advised that the reliability of oral or other systemic hormonal contraceptives may be affected; consideration should be given to using alternative contraceptive measures.

Patients should be instructed to take rifampin either 1 hour before or 2 hours after a meal with a full glass of water.

Patients should be instructed to notify their physicians promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, and pain or swelling of the joints.

Compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed.

Laboratory Tests

A complete blood count (CBC) and liver function tests should be obtained prior to instituting therapy and periodically throughout the course of therapy. Because of a possible transient rise in transaminase and bilirubin values, blood for baseline clinical chemistries should be obtained before rifampin dosing.

Drug Interactions

Enzyme Induction: Rifampin is known to induce certain cytochrome P-450 enzymes. Administration of rifampin with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of coadministered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampin.

Rifampin has been reported to accelerate the metabolism of the following drugs: anticonvulsants (eg, phenytoin), antiarrhythmics (eg, disopyramide, mexiletine, quinidine, tocainide), oral anticoagulants, antifungals (eg, fluconazole, itraconazole, ketoconazole), barbiturates, beta-blockers, calcium channel blockers (eg, diltiazem, nifedipine, verapamil), chloramphenicol, corticosteroids, cyclosporine, cardiac glycoside preparations, clofibrate, oral or other systemic hormonal contraceptives, dapsone, diazepam, doxycycline, fluoroquinolones (eg, ciprofloxacin), haloperidol, oral hypoglycemic agents (sulfonylureas), levothyroxine, methadone, narcotic analgesics, nortriptyline, progestins, tacrolimus, theophylline and zidovudine. It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampin.

Patients using oral or other systemic hormonal contraceptives should be advised to change to nonhormonal methods of birth control during rifampin therapy.

Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. In patients receiving anticoagulants and rifampin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Diabetes may become more difficult to control.

Concurrent use of ketoconazole and rifampin has resulted in decreased serum concentrations of both drugs. Concurrent use of rifampin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.

Other Interactions: Concomitant antacid administration may reduce the absorption of rifampin. Daily doses of rifampin should be given at least 1 hour before the ingestion of antacids.

Probenecid and cotrimoxazole have been reported to increase the blood level of rifampin.

When rifampin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampin and halothane should be avoided. Patients receiving both rifampin and isoniazid should be monitored close for hepatotoxicity.

Plasma concentrations of sulfapyridine may be reduced following the concomitant administration of sulfasalazine and rifampin. This finding may be the result of alteration in the colonic bacteria responsible for the reduction of sulfasalazine to sulfapyridine and mesalamine.

Drug/Laboratory Interactions

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}. Thus, alternate assay methods should be considered. Transient abnormalities in liver function tests (eg, elevation in serum bilirubin, alkaline phosphatase, and serum transaminases) and reduced biliary excretion of contrast media used for visualization of the gallbladder have also been observed. Therefore, these tests should be performed before the morning dose of rifampin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility. A few cases of accelerated growth of lung carcinoma have been reported in man, but a causal relationship with the drug has not been established. An increase in the incidence of hepatomas in female mice (of a strain known to be particularly susceptible to the spontaneous development of hepatomas) was observed when rifampin was administered in doses 2 to 10 times the average daily human dose for 60 weeks, followed by an observation period of 46 weeks. No evidence of carcinogenicity was found in male mice of the same strain, mice of a different strain, or rats under similar experimental conditions.

Rifampin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes in vitro, and humans. Antitumor activity in vitro has also been shown with rifampin.

There was no evidence of mutagenicity in bacteria, *Drosophila melanogaster*, or mice. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampin. Increased frequency of chromosomal aberrations was observed in vitro in lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide and combinations of streptomycin, rifampin, isoniazid, and pyrazinamide.

Pregnancy–Teratogenic Effects

Category C: Rifampin has been shown to be teratogenic in rodents given oral doses of rifampin 15 to 25 times the human dose. Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of RIFAMPIN, alone or in combination with other antituberculosis drugs, on the human fetus is not known. Neonates of rifampin-treated mothers should be carefully observed for any evidence of adverse effects. Isolated cases of fetal malformations

least 1 hour before the morning dose of rifampin.

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Pregnancy–Non-Teratogenic Effects

When administered during the last few weeks of pregnancy, rifampin can cause post-natal hemorrhages in the mother and infant for which treatment with vitamin K may be indicated.

Nursing Mothers

Because of the potential for tumorigenicity shown for rifampin in animal studies, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

See CLINICAL PHARMACOLOGY–Pediatrics; see also DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Gastrointestinal

Heartburn, epigastric distress, anorexia, nausea, vomiting, jaundice, flatulence, cramps, and diarrhea have been noted in some patients. Although *Clostridium difficile* has been shown in vitro to be sensitive to rifampin, pseudomembranous colitis has been reported with the use of rifampin (and other broad spectrum antibiotics). Therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Rarely, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported.

Hematologic

Thrombocytopenia has occurred primarily with high dose intermittent therapy, but has also been noted after resumption of interrupted treatment. It rarely occurs during well supervised daily therapy. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampin administration has been continued or resumed after the appearance of purpura.

Rare reports of disseminated intravascular coagulation have been observed.

Transient leukopenia, hemolytic anemia, and decreased hemoglobin have been observed.

Central Nervous System

Headache, fever, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, behavioral changes, muscular weakness, pains in extremities, and generalized numbness have been observed.

Rare reports of myopathy have also been observed.

Ocular

Visual disturbances have been observed.

Endocrine

Menstrual disturbances have been observed.

Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Renal

Elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, acute tubular necrosis, renal insufficiency, and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when rifampin is discontinued and appropriate therapy instituted.

Dermatologic

Cutaneous reactions are mild and self-limiting and do not appear to be hypersensitivity reactions. Typically, they consist of flushing and itching with or without a rash. More serious cutaneous reactions which may be due to hypersensitivity occur but are uncommon.

Hypersensitivity Reactions

Occasionally, pruritus, urticaria, rash, pemphigoid reaction, erythema multi-

observed.

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Hypersensitivity Reactions

Occasionally, pruritus, urticaria, rash, pemphigoid reaction, erythema multiforme including Stevens-Johnson Syndrome, toxic epidermal necrolysis, vasculitis, eosinophilia, sore mouth, sore tongue, and conjunctivitis have been observed.

Anaphylaxis has been reported rarely.

Miscellaneous

Edema of the face and extremities has been reported. Other reactions reported to have occurred with intermittent dosage regimens include "flu syndrome" (such as episodes of fever, chills, headache, dizziness, and bone pain), shortness of breath, wheezing, decrease in blood pressure and shock. The "flu syndrome" may also appear if rifampin is taken irregularly by the patient or if daily administration is resumed after a drug free interval.

OVERDOSAGE

Signs and Symptoms

Nausea, vomiting, and increasing lethargy will probably occur within a short time after ingestion; unconsciousness may occur when there is severe hepatic disease. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears, and feces will occur, and its intensity is proportional to the amount ingested.

Liver enlargement, possibly with tenderness, may develop within a few hours after severe overdosage; bilirubin levels may increase and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal. A direct effect upon the hematopoietic system, electrolyte levels or acid-base balance is unlikely.

Acute Toxicity

The LD_{50} of rifampin is approximately 885 mg/kg in the mouse, 1720 mg/kg in the rat, and 2120 mg/kg in the rabbit.

Nonfatal overdoses with as high as 12 g of rifampin have been reported. In one patient who swallowed 12 g of rifampin, vomiting occurred four times within 1 hour of ingestion. Gastric lavage with 20 liters of water was initiated 5 hours after ingestion. Twelve hours after ingestion of rifampin, a plasma concentration of 400 µg of rifampin/mL was measured by microbiological assay. The plasma concentration fell to 64 µg/mL on the following day, and to 0.1 µg/mL on the third day. Urinary rifampin concentration was 313 g/mL approximately 30 hours after ingestion of the drug; 625 µg/mL after 36 hours, and 78 µg/mL after 40 hours. By the fourth day following the dose, only 0.1 µg/mL rifampin was present in the urine. There was biochemical evidence of mild impairment of liver function. Liver function tests had returned to normal within 5 days, and the patient's recovery was described as uneventful.

One case of fatal overdose is known: a 26-year-old man died after self-administering 60 g of rifampin.

Treatment

Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis. Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting.

Active diuresis (with measured intake and output) will help promote excretion of the drug. Hemodialysis may be of value in some patients. In patients with previously adequate hepatic function, reversal of liver enlargement and of impaired hepatic excretory function probably will be noted within 72 hours, with a rapid return toward normal thereafter.

DOSAGE AND ADMINISTRATION

Rifampin can be administered by the oral route (see INDICATIONS AND USAGE).

See CLINICAL PHARMACOLOGY for dosing information in patients with renal failure.

Tuberculosis

Adults: 600 mg in a single daily administration.

Pediatric Patients: 10-20 mg/kg not to exceed 600 mg/day.

It is recommended that oral rifampin be administered once daily, either 1 hour before or 2 hours after a meal with a full glass of water.

Rifampin is indicated in the treatment of all forms of tuberculosis. A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide (eg, RIFATER®) is recommended in the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society and the Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered.

Following the initial phase, treatment should be continued with rifampin and isoniazid (eg, RIFAMATE®) for at least

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Following the initial phase, treatment should be continued with rifampin and isoniazid (eg, RIFAMATE® for at least 4 months. Treatment should be continued for longer if the patient is sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive.

Meningococcal Carriers

Adults: For adults, it is recommended that 600 mg rifampin be administered twice daily for two days.

Pediatric Patients: Pediatric patients 1 month of age or older: 10 mg/kg (not to exceed 600 mg per dose) every 12 hours for two days.

Pediatric patients under 1 month of age: 5 mg/kg every 12 hours for two days.

Preparation of Extemporaneous Oral Suspension

For pediatric and adult patients in whom capsule swallowing is difficult or where lower doses are needed, a liquid suspension may be prepared as follows:

Rifampin 1% w/v suspension (10 mg/mL) can be compounded using one of four syrups - Simple Syrup (Syrup NF), Simple Syrup (Humco Laboratories), Syrpalta Syrup (Emerson Laboratories), or Raspberry Syrup (Humco Laboratories).

1. Empty contents of four rifampin 300 mg capsules or eight rifampin 150 mg capsules onto a piece of weighing paper.
2. If necessary, gently crush the capsule contents with a spatula to produce a fine powder.
3. Transfer rifampin powder blend to a 4-ounce amber glass prescription bottle.
4. Rinse the paper and spatula with 20 mL of one of the above-mentioned syrups and add the rinse to the bottle. Shake vigorously.
5. Add 100 mL of syrup to the bottle and shake vigorously.

This compounding procedure results in a 1% w/v suspension containing 10 mg rifampin/mL. Stability studies indicate that the suspension is stable when stored at room temperature (25±3°C) or in a refrigerator (2-8°C) for four weeks. This extemporaneously prepared suspension must be shaken well prior to administration.

HOW SUPPLIED

Rifampin Capsules USP 300 mg are supplied as red capsules, imprinted E 799 and are available in bottles of 30, 60, 100 and 500.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place.** Avoid excessive heat.

Caution: Federal law prohibits dispensing without prescription.

References:

1. National Committee for Clinical Laboratory Standards. Antimycobacterial Susceptibility Testing; Proposed Standard. NCCLS Document M24-P, Vol. 10, No. 10. NNCLS, Villanova, PA. 1990.
2. 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.
3. 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.
4. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Fifth Informational Supplement. NCCLS Document M100-S5, Vol. 14, No.16. NCCLS, Villanova, PA. December 1994.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Iss. 04/97
MF0799ISS0497

NCCLS, Villanova, PA, [illegible]
1994.

Manufactured by:
Eon Labs Manufacturing, Inc
Laurelton, NY 11413

Iss. 04/97
MF0799ISS0497

10

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064150

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NO.** 4

2. **AADA#** 64-150

3. **NAME AND ADDRESS OF APPLICANT**
Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413

4. **LEGAL BASIS FOR AADA SUBMISSION**
21 CFR §455.170a - The application is based on the reference drug **Rifadin®** manufactured by Merrell Dow Pharmaceuticals Inc. (NDA 50-420).

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Rifampin Capsules USP

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

9. **AMENDMENTS AND OTHER DATES**
Firm:
Original Submission: 4/12/95
Amendment(bio): 12/14/95
Amendment (chemistry): 1/12/96
Amendment: 5/15/96
Amendment: 7/23/96

FDA:
Acceptance to File: 5/10/95
Bio Deficiency Letter: 10/31/95
Chemistry Deficiency Letter: 11/2/95
Chemistry Deficiency Letter: 3/19/96
Chemistry Deficiency Letter: 7/17/96

10. **PHARMACOLOGICAL CATEGORY**
Antibacterial

11. **HOW DISPENSED**
Rx

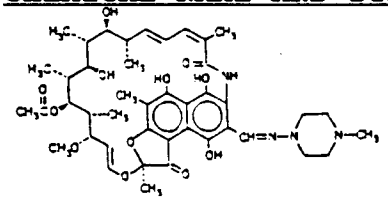
12. **RELATED IND/NDA/DMFs**

(b)4 - Confidential Business

13. **DOSAGE FORM**
Capsules

14. **STRENGTH**
300 mg

15. **CHEMICAL NAME AND STRUCTURE**



(1) Rifamycin, 3-[[(4-methyl-1-piperazinyl)imino]methyl]-;
(2) 5,6,9,17,19,21-Hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[*N*-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-*b*]furan-1,-11(2*H*)-dione 21-acetate.

$C_{43}H_{58}N_4O_{12}$.
Molecular Weight: 822.95

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**
All CMC issues have been resolved. Approval may be granted as soon as the FPL is submitted and found acceptable, and the bulk application is approved.

18. **CONCLUSIONS/RECOMMENDATIONS**
Approvable (bulk approval & FPL)

19. **REVIEWER** /S/ **DATE COMPLETED**
Susan Rosencrance 8/13/96

ADDENDUM TO CHEMISTRY REVIEW #4

DATE: May 13, 1997

FROM: Susan Rosencrance

SUBJECT: Eon's Rifampin Capsules USP, 300 mg

TO: AADA 64-150

SUMMARY:
Chemistry has been acceptable since Chemistry Review #4 (completed 8/13/96). Approval could not be granted, however, until the bulk application [redacted] was approved and concerns with the labeling were resolved. Both of these pending issues have now been resolved and approval may be granted. For details conerning chemistry (release/stability specifications, etc.) see Chemistry Review #4.

REMARKS AND CONCLUSIONS:
Recommend approval

cc: AADA 64-150
Division File
Field Copy

Endorsements:
HFD-643/SRosencrance/5/13/97
HFD-643/JHarrison/5/13/97
X:\NEW\FIRMSAM\EON\LTRS&REV\64150.apr
F/T by pah/5/15/97

[redacted](b)4 - [redacted]
Confidential
[redacted]Business[redacted]

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064150

BIOEQUIVALENCE REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AADA 64-150

JUN 26 1996

Eon Labs Manufacturing Inc.
Attention: Yau-Kit Lam
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Mr. Lam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Rifampin Capsules, 300 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 1 (basket) at 50 rpm. The test drug product should meet the following specifications:

   Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP - 5 1997

Rifampin
150 mg Capsule
NDA #64-150
Reviewer: J. Lee
64150DW.697

Eon Labs
Laurelton, NY
Submission date:
June 11, 1997

Review of Dissolution Data and a Request for Waiver

The sponsor has submitted a supplement to their approved application (app. 28 May 97) to include a new 150 mg strength in addition to the approved 300 mg capsule. An acceptable bio-study was conducted on the 300 mg capsule (S. Pradhan).

In support of the waiver request the company has submitted a formulation comparison between the approved 300 mg capsule and the proposed 150 mg capsule as well as comparative dissolution data between the 150 mg capsule vs Rifadin® 150 mg capsule (Merrell Dow Pharmaceuticals).

Comment:

1. The dissolution testing, using the current USP method (p. 2976) is acceptable.

Recommendation:

1. The dissolution testing conducted by Eon Labs, using the current USP method, on its rifampin 150 mg capsule, batch #960401, is acceptable.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37°C using USP XXIII apparatus I (100) at rpm. The test product should meet the following specification:

   Not less than (b)4 of the labeled amount of the drug in the capsule is dissolved in 45 minutes.

3. The Division of Bioequivalence agrees that the information submitted by the sponsor demonstrates that rifampin 150 mg capsule falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Eon's rifampin 150 mg capsule is deemed bioequivalent to Rifadin® 150 mg capsule manufactured by Merrell Dow Pharmaceuticals.

/S/ 9/19/97
J. Lee
Division of Bioequivalence

USP XXIII Apparatus __I__ Basket __x__ Paddle _____ rpm __100__

Medium: __0.1N HCl__ Volume: __900__ ml

Number of Tabs/Caps Tested: __12__

Reference Drug: __Rifadin® 150 mg capsule__

Assay Methodology: __UV absorbance @ 475 nm__

Results

Time (min)	Test Product Lot # 960401 Mean % Dissolved	Range	(CV)	Reference Product Lot # 4988AF Mean % Dissolved	Range	(CV)
15	97.1	(b)4 - Confidentia Business	(2.1)	89.8	(b)4 - Confidentia Business	(5.4)
30	97.3		(3.4)	96.5		(1.3)
45	97.9		(2.9)	97.1		(1.3)
60	98.7		(2.6)	97.7		(1.4)
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
	Lot #_____			Lot #_____		
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )
____	_____	_____	( )	_____	_____	( )

AADA 64-150 Rifampin Capsules, USP, 300 mg
Supplemental Application - Rifampin Capsules, USP, 150 mg

COMPOSITION COMPARISON BETWEEN RIFAMPIN CAPSULES, USP, 300 MG AND RIFAMPIN CAPSULES, USP, 150 MG

	Amount per capsule in mg		% W/W	
Component	**Rifampin Capsules, USP, 300 mg**	**Rifampin Capsules, USP, 150 mg**	**Rifampin Capsules, USP, 300 mg**	**Rifampin Capsules, USP, 150 mg**
Rifampin, USP	300.0	150.0	68.6	62.5
Microcrystalline cellulose, NF	(b)4 - Confidential Business			
Corn Starch, NF				
Colloidal Silicon Dioxide, NF				
Docusate Sodium (b)4 odium Benzoate (b)4				
Talc, USP				
Magnesium Stearate, NF				
Net Capsule Fill Weight	360.0	180.0	82.4	75.0
#2 Gelatin Capsule, Medium Orange Opaque Cap, Medium Orange Opaque body, Imprinted "E 801" in Black	77.0 (± 6 mg)	60.0 (± 5 mg)	17.6	25.0
Total Filled Capsule Weight	437.0	240.0	100.0	100.0

Note: The amount of active and inactive ingredients of Rifampin Capsules, USP, 300 mg and 150 mg strengths are proportional, the amount of each ingredient for Rifampin Capsules, USP 150 mg represents half the amount of each corresponding ingredient for Rifampin capsules, USP, 300 mg. It should be noted, that the weight of the capsule shells for the 150 mg strength is not half the weight of the capsules shells for the 300 mg strength . 60 mg versus 77 mg respectively, consequently the %w/w composition is not proportional.

JUN 14 1996

Rifampin
300 mg Capsules
AADA # 64-150
Reviewer: Sikta Pradhan, Ph.D.
WP #64150ASD.D95

Eon Labs Manufacturing, Inc.
Laurelton, NY
Submission Date:
December 14, 1995

REVIEW OF AN AMENDMENT TO A BIOEQUIVALENCE STUDY

Introduction

Rifampin is a semisynthetic derivative of rifamycin B, an antibiotic produced by certain strains of Streptomyces mediterranei. Rifampin is used in the treatment of both tuberculosis and the meningococcal carrier state. It inhibits DNA-dependent RNA polymerase activity in susceptible cells. It interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme.

Rifampin is currently available as Rifadin^{R}, 150 mg and 300 mg capsules manufactured by Marion Merrell Dow. The usual daily dosage of rifampin is 600 mg to 1200 mg depending on the indication. The drug is usually administered 30 minutes to 1 hour before or 2 hours after food to ensure maximum absorption.

The firm had previously conducted a bioequivalence study on its test product. The objective of the study was to compare the relative bioavailability of Rifampin 300 mg capsules, manufactured by Eon Labs., Inc. with that of Rifadin^{R} 300 mg capsules, manufactured by Marion Merrell Dow, in healthy, male volunteers dosed under fasting condition.

This amendment contains the firm's responses to the reviewer's comments made on the submission dated April 12, 1995.

Agency's Comments:

1. (b)4 - Confidential Business

2.

(b)4 - Confidential Business

provided.

5. The firm should inform the Agency the Lot size of the test product used in the in vitro dissolution testing and in vivo bioequivalence study.

6. There were a number of blood collections that deviated from the target times due to late arrival of some subjects. The firm was requested to provide the reason for late arrival of each subject.

7. The firm was also requested to submit all statistical analyses conducted on the test and reference samples collected at each sampling time.

Firm's Responses:

The firm has responded the Agency's comments in this amendment and provided the following analytical information.

1.

2. (b)4 - Confidential Business

3.

4. [redacted]

(b)4 - Confidential Business

5. The Lot size of the test product used in the in vitro dissolution testing and in vivo bioequivalence study was [redacted](b)4 -[redacted]sules.

6. The firm has indicated that the reasons for the late arrival of subjects for scheduled blood draws were not recorded at the time. However, adjustments for these time deviations were made to the data set.

7. The firm has submitted the requested statistical analyses conducted on the test and reference samples collected at each sampling time. Statistical data were acceptable. There was no significant difference in plasma rifampin and 25-desacetyl rifampin levels produced by the test and reference products at any time except at 0.5 hour sampling time. At 0.5 hour, the plasma rifampin levels of the test and reference products was significantly different but the difference in 25-desacetyl rifampin levels was non-significant.

Approval Comments:

1. The firm's responses to the Agency's comments are acceptable, and therefore, the in vivo bioequivalence study under fasting condition on 300 mg Rifampin Capsules (lot # 941101) is acceptable.

2. The drug is usually administered 30 minutes to 1 hour before or 2 hours after food to ensure maximum absorption, and therefore, no in vivo bioequivalence study under fed condition on the test product is required.

3. The firm has conducted an acceptable in vitro dissolution testing on 300 mg Rifampin Capsules (lot # 941101).

4. An inspection of the study facilities and an audit of data have been requested through the Division of Scientific Investigations (HFD-340).

Recommendations:

1. The in vivo bioequivalence study conducted by Eon Labs Manufacturing Inc. on its 300 mg Rifampin Capsules of lot #941101, versus the reference product, Rifadin^{R} 300 mg Capsules manufactured by Marion Merrell Dow Inc. has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that the test product, Rifampin Capsules is bioequivalent to the reference product, Rifadin^{R}, 300 mg capsule manufactured by Marion Merrell Dow Inc.

2. The in vitro dissolution testing conducted by Eon Labs Manufacturing, Inc. on its Rifampin 300 mg Capsules of lot #941101 is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37^{0}C using USP XXIII apparatus I (basket) at 50 rpm. The test drug product should meet the following specifications:

   Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

/S/

Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---- /S/ 6/14/96

/S/

Concur: ----- Date: 6/14/96

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 64-150 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Pradhan), Drug File, Division File.

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AADA 64-150

Eon Labs Manufacturing Inc.
Attention: Yau-Kit Lam
227-15 North Conduit Avenue
Laurelton, NY 11413

JUL 16 1996

Dear Mr. Lam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Rifampin Capsules, 300 mg. This correspondence which supersedes our previous correspondence dated June 26, 1996, modifies the dissolution specification as provided in USP 23, supplement 3; page 2976.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 1 (basket) at 100 rpm. The test drug product should meet the following specifications:
>
> > Not less tha(b)4f the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

(b)4 - Confidential Business

Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 1 2 1995

Rifampin 300 mg Capsules
300 mg Capsules
ANDA # 64-150
Reviewer: Sikta Pradhan, Ph.D.
WP #64150SD.495

Eon Labs Manufacturing, Inc.
Laurelton, NY
Submission Date:
April 12, 1995

REVIEW OF A BIOEQUIVALENCE STUDY

Introduction

Rifampin is a semisynthetic derivative of rifamycin B, an antibiotic produced by certain strains of Streptomyces mediterranei. Rifampin is used in the treatment of both tuberculosis and the meningococcal carrier state. It inhibits DNA-dependent RNA polymerase activity in susceptible cells. It interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme.

Rifampin is readily absorbed from the gastrointestinal tract. The peak plasma drug concentration occurs within 2 to 4 hours after oral administration. The plasma half-life of rifampin following a 600 mg oral dose in healthy adult subject is about 3 hours. More than 80% of the drug is bound to plasma proteins. Rifampin is widely distributed into most body tissues and fluids. Absorption of rifampin is delayed and reduced when it is given with food. The drug is rapidly eliminated in the bile and undergoes progressive enterohepatic circulation and deacetylation to the primary metabolite, 25-desacetyl-rifampin. This metabolite is microbiologically active. About 30% or less of the dose is excreted as rifampin or metabolites.

The drug is currently available as Rifadin^{R}, 150 mg and 300 mg capsules manufactured by Marion Merrell Dow. The usual daily dosage of rifampin is 600 mg to 1200 mg depending on the indication.

Objective:

The objective of the study is to compare the relative bioavailability of Rifampin 300 mg capsules, manufactured by Eon Labs., Inc. with that of Rifadin^{R} 300 mg capsules, manufactured by Marion Merrell Dow, in healthy, male volunteers dosed under fasting condition.

In-Vivo Study

The study was conducted under the direction of (b)4 - Confidential Business

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Manager, [redacted].

(b)4 - Confidential Business

Study Dates:

Date of Samples Collection: November 26, 1994 (Period I)
December 03, 1994 (Period II)

Study Design

A randomized 2-way crossover, single dose bioequivalence study on the test product, Rifampin, 300 mg capsule (Eon Labs) and reference product, Rifadin^{R} 300 mg capsule (Marion Merrell Dow) was conducted in healthy adult male volunteers according to the protocol #930852.

Subject: Thirty-six (36) volunteers and two (2) alternates between 20-45 years of age and within ± 15% of their ideal body weight according to Metropolitan life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Test (hematology, blood chemistry, urinalysis, etc.) The subjects were restricted from all medications for one week prior to the first drug administration until after the study was completed. The volunteers were not allowed to consume alcohol- or xanthine-containing beverages and food for 24 hours prior to the initiation of the study until after the completion of the study. The subjects were randomly divided into two dosing groups of equal numbers.

Treatments:

A. 300 mg x 2 Rifampin capsules (Eon Labs.), Lot #941101, Potency 100.1%, Lot size: Not reported.

B. 300 mg x 2 Rifadin^{R} capsules (Marion Merrell Dow), Lot #3405CM, Potency 98.5%, Exp. Date: 4/95.

Dose Administration:

A single dose of 600 mg (test or reference) was administered with 240 mL of water. A mouth check was performed to assure ingestion.

Drug Washout Period: 7 days

Meal and Food Restrictions:

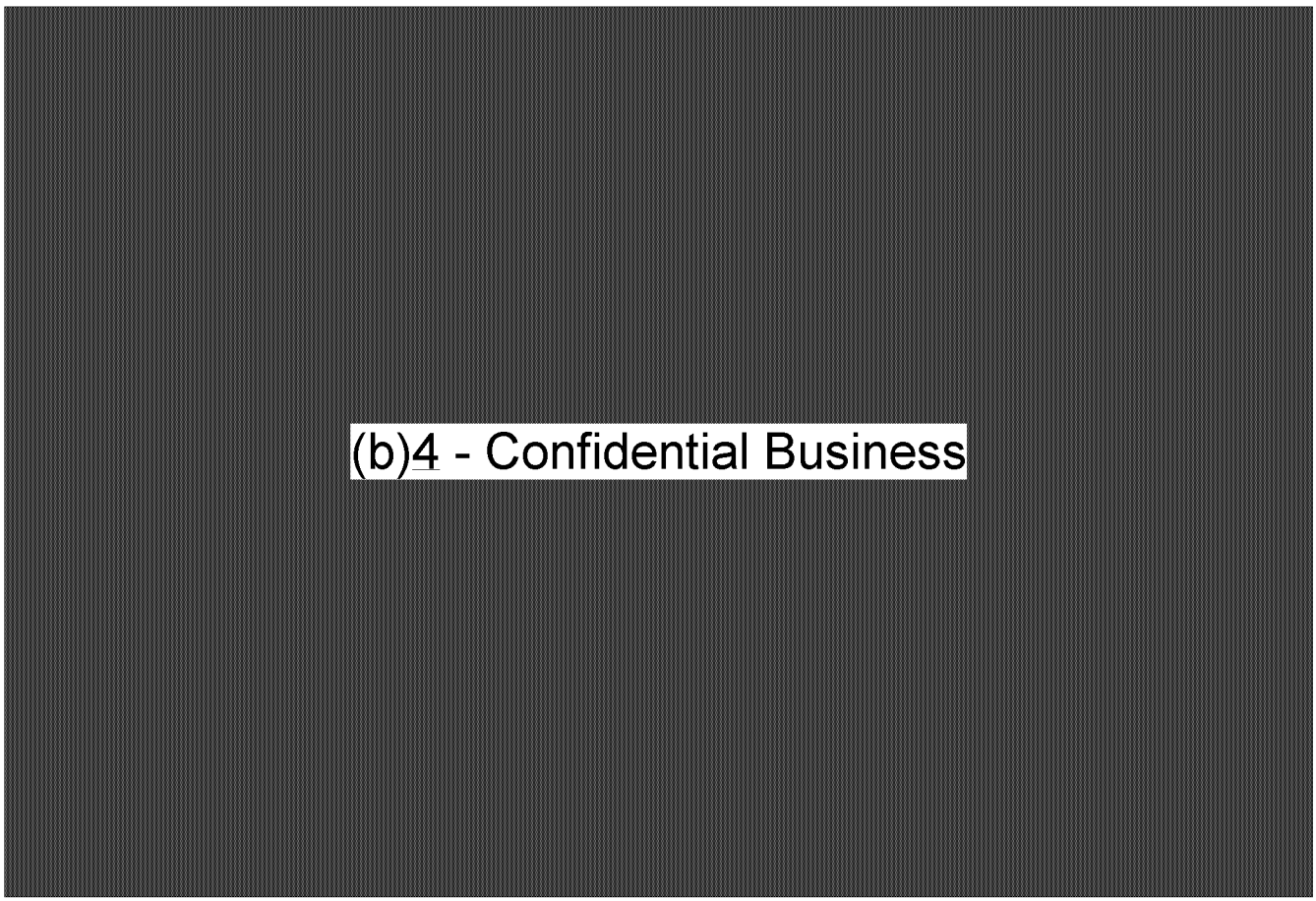
All volunteers fasted for 10 hours prior to and 4 hours after drug administration. No fluids were allowed from 2 hour before dosing

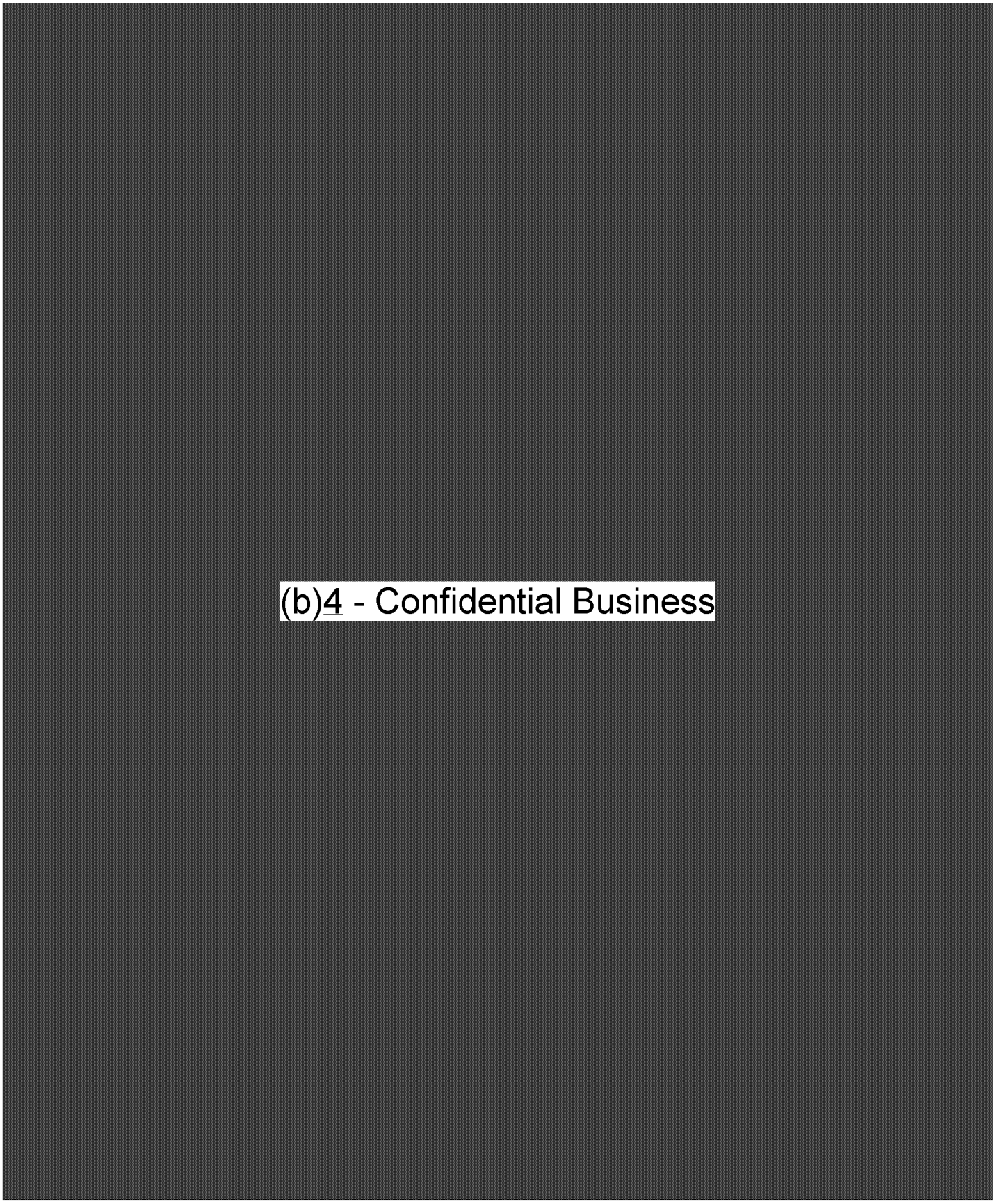
until 4 hours after each dose. Water was given ad lib after 4 hours of dosing. Standard meal was served after 4 hours of dosing. No caffeine-containing food or beverages were served during the first 24 hours. All subjects were confined from 10 hours pre-dose to 24 hours post-dose.

Blood Samples Collection

Ten (5x2) mL blood samples were collected in vacutainers containing EDTA at 0 (pre-dose), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose. Due to the sensitivity of rifampin to ultraviolet (UV) light, blood samples were collected and processed under UV filtered light bulbs to minimize their UV exposure. The collected blood samples were cooled in an ice bath and centrifuged under refrigeration as soon as possible. For pre-dose samples, 2 mL of plasma was transferred to tubes containing 20 µL of L-ascorbic acid (50 mg/mL), and for all post-dose samples, 1 mL of plasma was transferred to tubes containing 10 µL L-ascorbic acid (50 mg/mL), and were mixed thoroughly by vortexing. All plasma samples were stored at -80^0 C until analyzed.

Assay Methodology

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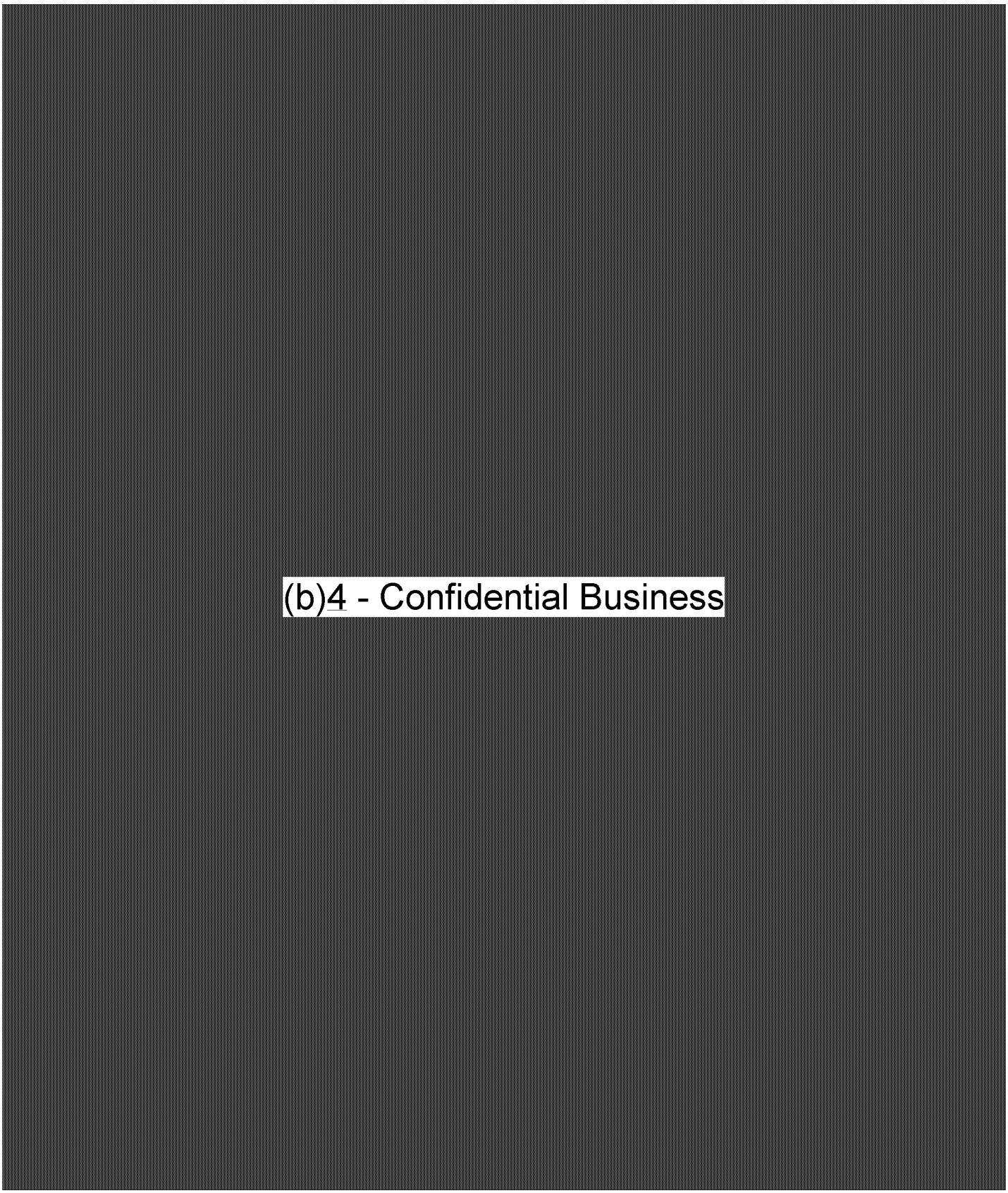
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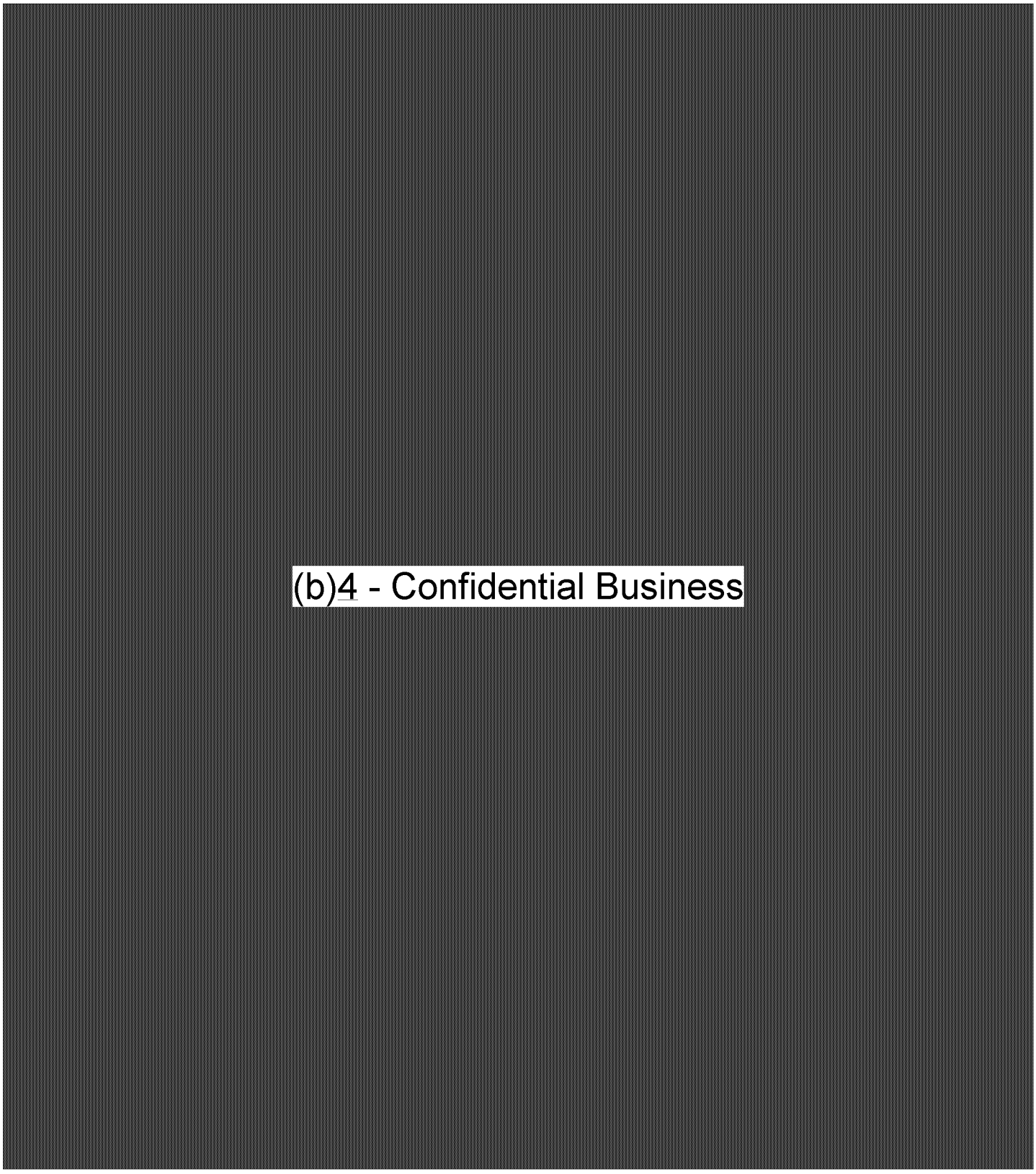
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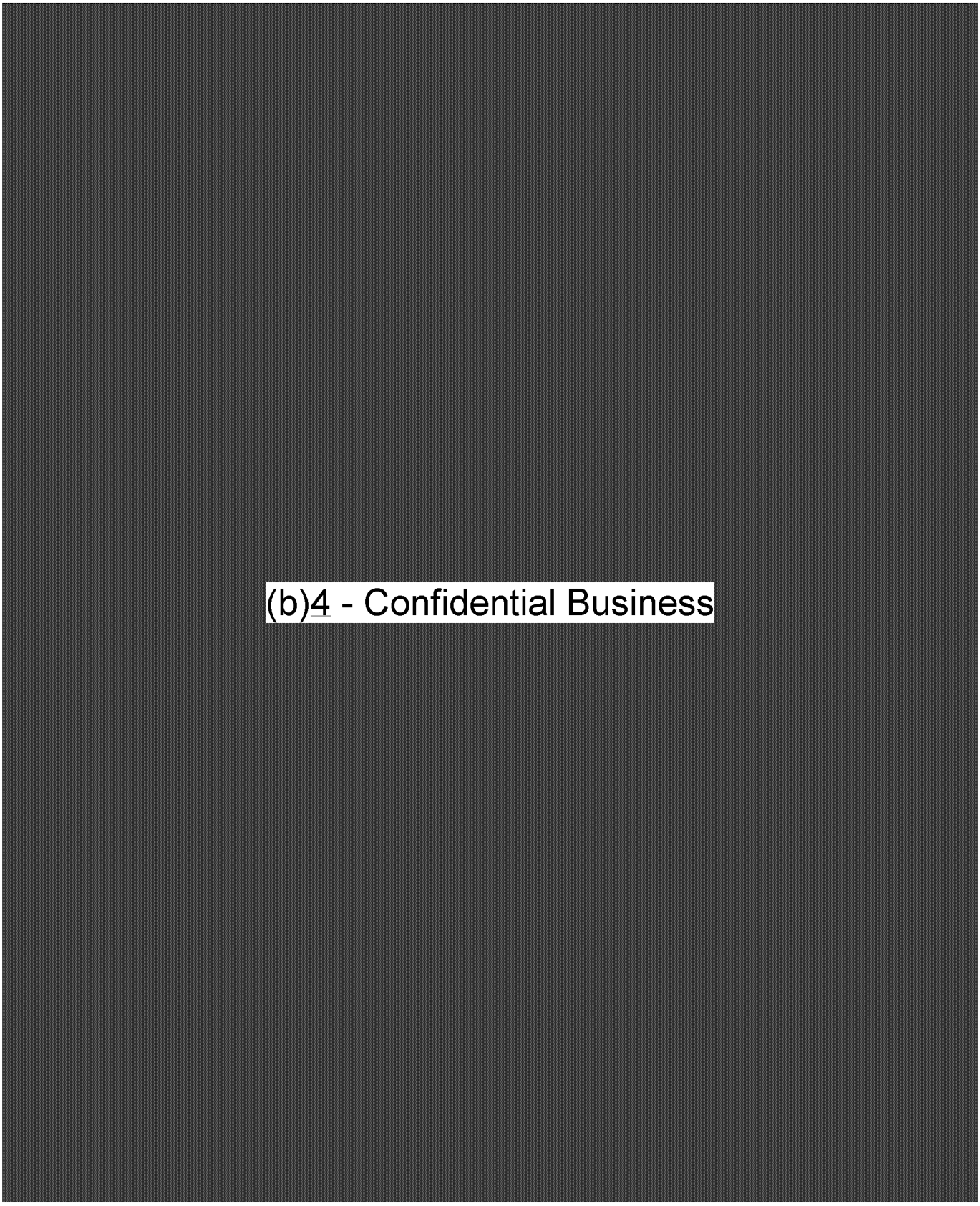
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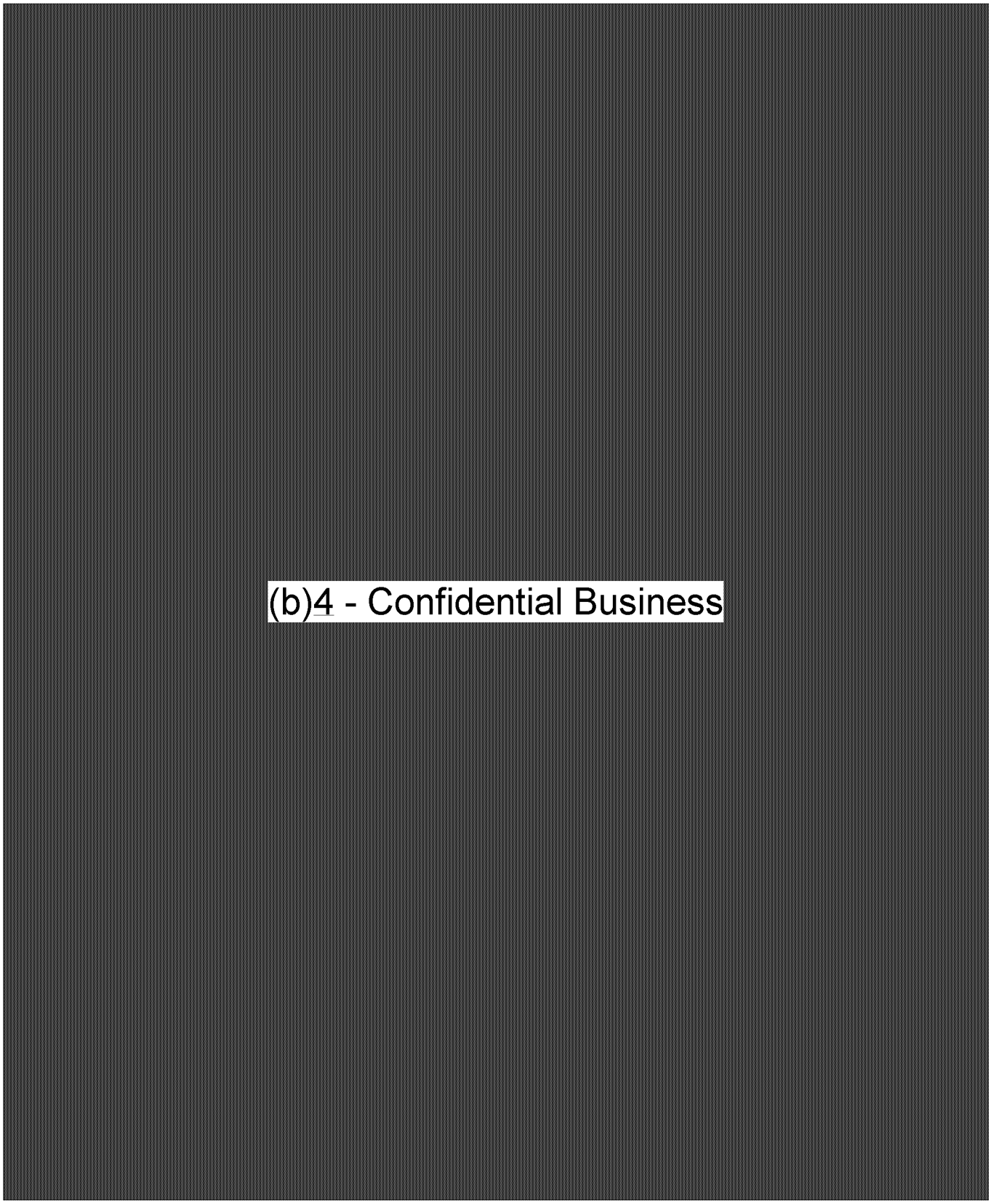
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Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) were calculated from plasma data of 36 subjects by the linear trapezoidal method. The elimination parameters for each subject in each dosing group were derived. Tmax, the time of the maximum measured plasma concentration and Cmax, the maximum measured plasma concentration were also reported. The mean pharmacokinetic parameters are presented in Table 3 and Table 4, respectively.

Statistical Analyses

Analysis of variance (ANOVA) was performed at an alpha=0.05 using the GLM procedure of SAS on the untransformed and log-transformed (only for AUC0-t, AUCinf and Cmax) pharmacokinetic data. The ANOVA model included sequence, subjects nested within sequence, period and drug formulation as factors. The significance of the sequence effect was tested using the subjects nested within sequence as the error term. The 90% confidence intervals for the differences between formulations were calculated for AUC0-t, AUC0-inf and Cmax by using two one-sided t-test.

Results:

Mean plasma rifampin and 25-desacetyl rifampin levels of 36 subjects are presented in Table 1 and Table 2, respectively.

Table 1
Mean Plasma Rifampin Levels (µg/mL)

Time (hour)	Test (A) 2X300mg Tab (Eon) Lot # 941101(Subj=36)	Reference (B) 2X300mg Rifadine^{R} Tab (M.M.Dow) Lot # 3405CM (Subj=36)	A v s B Diff **Signf.
0	0	0	
0.50	2.49 (117*)	1.31 (148)	
1.0	8.77 (49)	8.70 (37)	
1.5	9.32 (36)	9.80 (31)	
2.0	8.95 (32)	9.15 (25)	
2.5	8.51 (24)	8.66 (23)	
3.0	7.90 (23)	7.92 (25)	
4.0	6.76 (22)	6.71 (24)	
6.0	4.29 (25)	4.19 (24)	
8.0	3.08 (35)	2.97 (31)	
10.0	1.89 (44)	1.80 (40)	
12.0	1.16 (59)	1.09 (52)	
16.0	0.35 (114)	0.30 (108)	
24.0	0.01 (600)	0.02 (353)	

* Coefficient of Variation
** Statistical Data Not Provided

Table 2
Mean Plasma 25-Desacetyl Rifampin Levels (μg/mL)

Time (hour)	Test (A) 2X300mg Tab (Eon) Lot # 941101(Subj=36)	Reference (B) 2X300mg Rifadine^{R} Tab (M.M.Dow) Lot # 3405CM (Subj=36)	A v s B Diff **Signf.
0	0	0	
0.50	0.04 (204*)	0.01 (359)	
1.0	0.44 (60)	0.41 (58)	
1.5	0.74 (47)	0.77 (47)	
2.0	0.90 (41)	0.93 (39)	
2.5	0.98 (34)	1.02 (36)	
3.0	1.04 (31)	1.08 (38)	
4.0	1.12 (28)	1.15 (36)	
6.0	0.91 (30)	0.91 (37)	
8.0	0.74 (36)	0.74 (46)	
10.0	0.43 (44)	0.42 (56)	
12.0	0.26 (56)	0.25 (70)	
16.0	0.08 (116)	0.07 (140)	
24.0	0.00 (00)	0.004(600)	

* Coefficient of Variation
** Statistical Data Not Provided

Table 3
Mean Pharmacokinetic Parameters for Rifampin in Plasma

Parameters (*Arithmetic Means)	Test(A) (Subj=36)	Ref.(B) (Subj=36)	A/B (%)	Intrasubject variability (%)
AUC_{0-T} (μg.hr/mL)	57.63 (30**)	56.65 (27)	103	10.8
AUC_{0-inf} (μg.hr/mL)	59.91 (30)	58.52 (27)	104	9.8
C_{MAX} (μg/mL)	10.78 (24)	10.72 (23)	102	13.6
T_{max} (hour)	1.557(46)	1.486(32)		
t1/2 (hour)	2.91 (19)	2.84 (18)		
KE (1/hour)	0.2458 (17)	0.2513 (16)		

Parameters (Using LSM)	Test(A)	Ref.(B)	A/B (%)	90% C.I.
$LnAUC_{0-T}$ (μg.hr/mL)	4.011980	4.003321	101	**97; 105**
Geometric mean	55.26	54.78		
$LnAUC_{0-inf}$ (μg.hr/mL)	4.052288	4.037062	101	**98; 105**
Geometric mean	57.53	56.66		
LnC_{MAX} (μg/mL)	2.346180	2.348892	100	**94; 105**
Geometric mean	10.45	10.4		

* In this case, arithmetic means and least squares means are same.
** Coefficient of Variation

Table 4
Mean Pharmacokinetic Parameters for 25-Desacetyl Rifampin in Plasma

Parameters (Using Arithmetic Means)	Test(A) (Subj=36)	Ref.(B) (Subj=36)	A/B (%)	Intrasubject Variability (%)
AUC_{0-T} (μg.hr/mL)	8.93 (33**)	9.10 (45)	98	14.3
AUC_{0-inf} (μg.hr/mL)	9.61 (32)	9.73 (42)	99	13.1
C_{MAX} (μg/mL)	1.15 (28)	1.17 (36)	98	11.5
T_{max} (hour)	3.58 (23)	3.69 (20)		
t1/2 (hour)	2.92 (17)	2.86 (25)		
KE (1/hour)	0.2438 (17)	0.2558 (22)		

Parameters (Using LS Means)	Test(A)	Ref.(B)	A/B (%)	90% C.I.
$LnAUC_{0-T}$ (μg.hr/mL)	2.129931	2.112140	101	**97; 105**
Geometric mean	8.41	8.27		
$LnAUC_{0-inf}$ (μg.hr/mL)	2.209838	2.189779	101	**98; 105**
Geometric mean	9.11	8.93		
LnC_{MAX} (μg/mL)	0.091861	0.089399	100	**94; 105**
Geometric mean	1.10	1.10		

* Coefficient of Variation

For Parent Product

Both test and reference drugs produced peak concentration of rifampin between 1 to 2 hours after their administration. There were 2-4% differences between the test and reference products in AUC_{0-T}, AUC_{0-inf} and C_{MAX} values. The 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product remained within the acceptable range of 80 - 125%.

For Metabolite

Both test and reference drugs produced peak concentration of 25-desacetyl rifampin at about 4 hours after their administration. There was only 1% difference between the test and reference products in AUC_{0-T}, AUC_{0-inf} values. There was no difference in C_{MAX}. The 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product remained within the acceptable range of 80 - 125%.

In-Vitro Dissolution:

The firm has conducted an acceptable dissolution testing on Rifampin Capsules. The dissolution testing data are presented in Table 5 below:

Drug (Generic Name): Rifampin Capsules Firm: Eon Manufacture Lab.
Dose Strength: 300 mg
ANDA # 64-150 Submission Date: April 12, 1995

Table -5 In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket X Paddle __ RPM 50 No. Units Tested: 12

Medium: 0.1N HCl Volume: 900 ml

Reference Drug: Rifadin[R] (Marion Merrell Dow)

Assay Methodology: (b)4 -

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 941101 Strength (mg) 300 Mean % Dissolved	Range	(CV)	Reference Product Lot # 3405CM Strength (mg) 300 Mean % Dissolved	Range	(CV)
15	48.4	(b)4 -	(10.7)	19.2	(b)4 -	(41.2)
30	100.6	Confidentia	(4.4)	80.5	Confidentia	(8.0)
45	101.9	Business	(2.7)	99.0	Business	(4.3)
60	102.4		(2.6)	99.8		(4.0)

Formulations:

The composition of Rifampin Capsules, 300 mg (lot #941101) is presented below:

Ingredients	**Strengths (mg/ capsule)**
Rifampin, USP	300.0
Microcrystalline Cellulose, NF	[redacted]
Corn Starch, NF	
Colloidal Silicon Dioxide, NF	
Docusate Sodium [redacted] / Sodium Benzoate [redacted]	(b)4 -
Talc, USP	onfident
Magnesium Stearate,NF	Busines
(net Capsule Fill Weight)	
#1 Gelatin Capsule, [redacted] orange opaque cap & body, imprinted "E 799" in black ink	[redacted]
Total Capsule Weight	**437.0**

[redacted]

(b)4 - Confidential Business

Comments:

1. The comparative in vitro dissolution testing conducted on the test and reference products is acceptable. However, the in vivo bioequivalence study conducted on the test and the reference products has been found to be incomplete.

2. [redacted]

3.

4. (b)4 - Confidential Business

5.

6. [redacted] (b)4 - Confidential Business [redacted] to be

7. The firm should inform the Agency the Lot size of the test product used in the in vitro dissolution testing and in vivo bioequivalence study.

8. There were a number of blood collections that deviated from the target times due to late arrival of some subjects. The firm should be requested to provide the reason for late arrival of each subject.

9. The firm should be requested to submit all statistical analyses conducted on the test and reference samples collected at each sampling time.

Recommendation:

The in vivo bioequivalence study conducted by Eon Labs Manufacturing Inc. on its 300 mg Rifampin Capsules of Lot #941101, versus the reference product, Rifadin^{R} 300 mg Capsules manufactured by Marion Merrell Dow Inc. has been found to be incomplete by the Division of Bioequivalence for the reasons stated in Comments #1 - 9 above.

[redacted] /S/

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

[redacted] /S/

[redacted] /S/

Concu[redacted] Date:----------

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 64-150 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Pradhan), Drug File, Division File.

SP/09-25-95/X:\wpfile\Pradhan\64150SD.495

TABLE C1

SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

Subject	Product Code Period 1	Product Code Period 2	Age (yrs)	Height (cm)	Weight (kg)	Frame	Race	Sex
1	B	A	25	166	70.1	Medium	Caucasian	Male
2	B	A	25	166	66.4	Small	Caucasian	Male
3	A	B	24	175	73.0	Medium	Caucasian	Male
4	B	A	39	181	66.5	Medium	Caucasian	Male
5	B	A	29	168	62.6	Medium	Caucasian	Male
6	A	B	37	166	74.7	Medium	Caucasian	Male
7	A	B	45	168	78.3	Medium	Caucasian	Male
8	A	B	33	172	63.2	Medium	Caucasian	Male
9	B	A	38	163	66.5	Medium	Caucasian	Male
10	A	B	42	177	75.9	Large	Caucasian	Male
11	B	A	25	176	69.6	Large	Caucasian	Male
12	B	A	28	164	66.8	Medium	Caucasian	Male
13	A	B	42	170	76.4	Medium	Caucasian	Male
14	A	B	22	170	76.0	Medium	Caucasian	Male
15	A	B	25	170	64.4	Medium	Caucasian	Male
16	B	A	22	168	67.3	Medium	Caucasian	Male
17	B	A	22	169	72.2	Medium	Caucasian	Male
18	A	B	37	186	74.1	Medium	Caucasian	Male
19	B	A	26	163	61.0	Small	Caucasian	Male
20	B	A	26	188	75.2	Medium	Caucasian	Male
21	A	B	26	170	61.6	Medium	Caucasian	Male
22	A	B	21	182	81.4	Medium	Caucasian	Male
23	B	A	28	176	61.2	Small	Caucasian	Male
24	B	A	20	176	61.0	Medium	Caucasian	Male
25	B	A	30	178	74.6	Medium	Caucasian	Male
26	A	B	26	187	83.3	Medium	Caucasian	Male
27	A	B	23	178	81.2	Medium	Caucasian	Male
28	A	B	24	164	63.5	Small	Caucasian	Male
29	A	B	23	172	71.6	Medium	Caucasian	Male
30	B	A	45	170	65.9	Medium	Caucasian	Male
31	B	A	21	177	61.9	Small	Caucasian	Male
32	A	B	30	185	79.2	Medium	Caucasian	Male
33	A	B	37	185	87.9	Medium	Caucasian	Male
34	A	B	24	187	83.8	Small	Black	Male
35	B	A	22	176	75.2	Medium	Caucasian	Male
36	B	A	24	187	72.1	Medium	Caucasian	Male
37	A	B	31	171	79.0	Medium	Caucasian	Male
38	B	A	41	164	61.9	Medium	Caucasian	Male
Mean			29.2	174.0	71.22			
± SD			7.47	7.77	7.453			
N			38	38	38			
CV%			25.6	4.5	10.5			

A = Eon 2 x 300 mg rifampin capsules
B = MMD (Rifadin) 2 x 300 mg rifampin capsules

Subject ages are calculated as of Period 1 dosing.

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TABLE C2

DEVIATIONS FROM THE BLOOD SAMPLING SCHEDULE

Product Code	Subject	Period	Sampling Time (Hours post-dose)	Deviation Day	Hrs	Min	Comment
A	1	2	3	0	0	8	Late
A	17	2	12	0	0	24	Late
A	24	2	1	0	0	3	Late
B	2	1	16	0	0	39	Late
B	10	2	10	0	0	32	Late
B	16	1	12	0	0	24	Late
B	16	1	16	0	0	27	Late
B	23	1	10	0	0	17	Late
B	32	2	8	0	0	8	Late
B	33	2	12	0	0	10	Late
B	34	2	16	0	0	7	Late

A = Eon 2 x 300 mg rifampin capsules
B = MMD (Rifadin) 2 x 300 mg rifampin capsules

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Figure 2

Project No. 930852

Mean Plasma Rifampicin Concentrations

(Linear Plot)

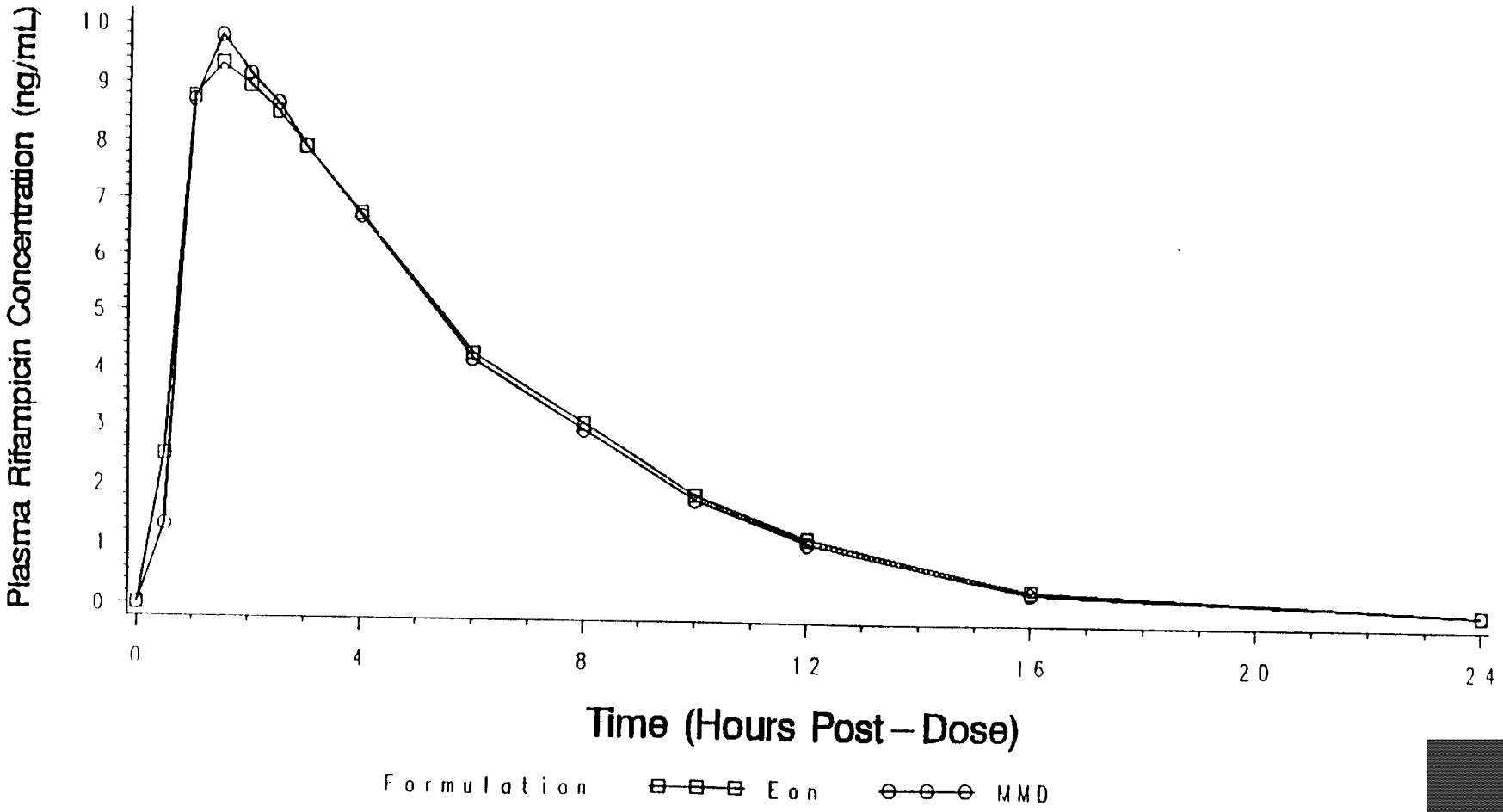

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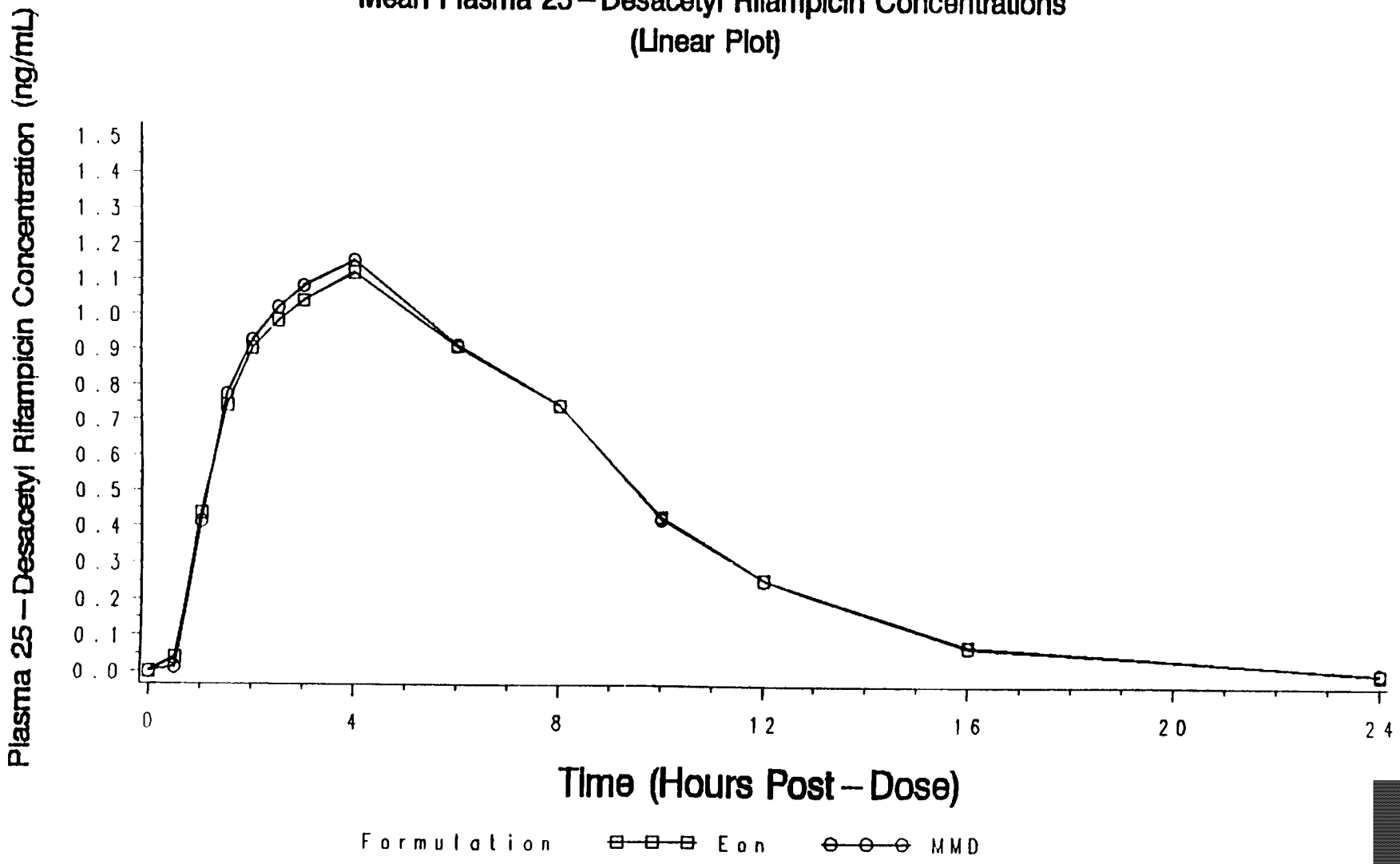
Figure 4

Project No. 930852

Mean Plasma 25 – Desacetyl Rifampicin Concentrations

(Linear Plot)



3 017

Table D4
Project Number :930852
Plasma Rifampicin
Pharmacokinetic Parameters by Formulation
Formulation: MMD (B)

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC/AUCinf (%)	Cmax/AUCinf (1/h)	Cmax (ng/mL)	tmax (h)
1	1						
2	1						
3	2						
4	1						
5	1						
6	2						
7	2						
8	2						
9	1						
10	2						
11	1						
12	1						
13	2						
14	2						
15	2						
16	1						
17	1						
18	2						
19	1						
20	1						
21	2						
22	2						
23	1						
24	1						

16-02-1995

Table D4
Project Number :930852
Plasma Rifampicin
Pharmacokinetic Parameters by Formulation
Formulation: MMD (B)

17:03

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC/AUCinf (%)	Cmax/AUCinf (1/h)	Cmax (ng/mL)	tmax (h)
25	1	72.7	74.0	[redacted]	[redacted]	[redacted]	[redacted]
26	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
31	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	1	[redacted]	[redacted]	[redacted]	[redacted]	8.25	1.00
Arithmetic Mean		56.65	58.52	96.70	0.1870	10.722	1.486
± SD		15.475	15.780	1.768	0.02927	2.4681	0.4704
CV%		27.3	27.0	1.8	15.7	23.0	31.6
n		36	36	36	36	36	36

(b)4 - Confidential Business

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16-02-1995

Table D5
Project Number :930852
Plasma Rifampicin
Ratio Analysis - AUC 0-t (ng·h/mL)

16:30

Subject	(A)	(B)	(A/B)%
1	51.6		
2		53.9	
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			

(b)4 - Confidential Business

Eon (A) vs MMD (B)

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16-02-1995

Table D5
Project Number :930852
Plasma Rifampicin
Ratio Analysis - AUC 0-t (ng·h/mL)

16:30

Subject	(A)	(B)	(A/B)%
27	57.0	[redacted]	
28			
29			
30			
31			
32			
33			
34			
35			
36			
Arithmetic Mean	57.63	56.65	103.13
± SD	17.412	15.475	21.687
CV%	30.2	27.3	21.0
n	36	36	36

Eon (A) vs MMD (B)

PhAST RTAB 2.2-005

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16-02-1995

Table D6
Project Number :930852
Plasma Rifampicin
Ratio Analysis - AUCinf (ng·h/mL)

16:30

Subject	(A)	(B)	(A/B)%
1	52.6		
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			97.2

(b)4 - Confidential Business

Eon (A) vs MMD (B)

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3 037

16-02-1995

Table D6
Project Number :930852
Plasma Rifampicin
Ratio Analysis - AUCinf (ng·h/mL)

16:30

Subject	(A)	(B)	(A/B)%
27	57.9		
28			
29			
30			
31			
32			
33			
34			
35			
36			
Arithmetic Mean	59.91	58.52	103.60
± SD	17.851	15.780	20.756
CV%	29.8	27.0	20.0
n	36	36	36

(b)4 - Confidential Business

Eon (A) vs MMD (B)

PhAST RTAB 2.2-005

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3 038

Table D7
Project Number :930852
Plasma Rifampicin
Ratio Analysis - Cmax (ng/mL)

Subject	(A)	(B)	(A/B)%
1	13.25		
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			

Eon (A) vs MMD (B)

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Table D7
Project Number :930852
Plasma Rifampicin
Ratio Analysis - Cmax (ng/mL)

Subject	(A)	(B)	(A/B)%
27	13.69	11.68	117.2
28			
29			
30			
31			
32			
33			
34			
35			
36			
Arithmetic Mean	10.781	10.722	102.05
± SD	2.5825	2.4681	22.392
CV%	24.0	23.0	21.9
n	36	36	36

Eon (A) vs MMD (B)

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