CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64164

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 64-155, 64-164, 64-165, 64-166 SPONSOR: Ranbaxy

DOSAGE FORM: Cefaclor Oral Suspension

STRENGTHS/(s): 375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, 125 mg/5 mL

TYPE OF STUDY: Single dose fasting and limited food study

STUDY SITE:

STUDY SUMMARY: Bioequivalence between the test and reference products was determined on the basis of pharmacokinetic data on cefaclor oral suspension. The firm has conducted single-dose fasting and limited food studies on test and reference products. The results of the studies indicate that Ranbaxy's 375 mg/mL suspension is bioequivalent to the reference product, Lilly's Ceclor® 375 mg/mL suspension. The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{inf}$, and LC_{max} are in the acceptable range of for single-dose study. Limited food study established the test/reference ratios for PK parameters within The inactive ingredients are within the IIG limits. The adverse reactions were minimal for each treatment. Waivers for biostudy for 250 mg/5 mL, 187 mg/5mL, 125 mg/5mL are granted.

DISSOLUTION: In vitro Dissolution is not required.

PRIMARY REVIEWER: S.P.Shrivastava, Ph.D. BRANCH: II

INITIAL: SVS DATE 9/30/97

BRANCH CHIEF: S. Nerurkar, Ph.D. BRANCH: II

INITIAL: DATE 9/30/1997

ACTING DIRECTOR

DIVISION OF BIOEQUIVALENCE: Rabindra Patnaik, Ph.D.

INITIAL: DATE 9/30/97

DIRECTOR

OFFICE OF GENERIC DRUGS: Douglas Sporn

INITIAL: DATE

~~OCT 9 1997~~ SEP 30 1997

ANDA # 64-155, 64-164, 64-165, 64-166
Cefaclor Oral Suspension
375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, 125 mg/5 mL
Reviewer: S. P. Shrivastava

Ranbaxy Labs. Ltd.
Raleigh, NC
Submission Date:
July 7, 1995
September 27, 1995

ADDENDUM TO REVIEW OF *IN VIVO* BIOEQUIVALENCE STUDIES

I. BACKGROUND

The firm has submitted *in vivo* bioequivalence data on fasting and limited food studies on its cefaclor 375 mg/5 mL, comparing it with Lilly's Ceclor[R] Oral Suspension, 375 mg/5 mL. It has also submitted composition data for its 375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, and 125 mg/5 mL strength cefaclor oral suspensions for review. However, no data on dissolution was submitted. The Division of Bioequivalence did not communicate to the firm the non-submission of dissolution testing data as a deficiency.

II. OBJECTIVE

This addendum is to clarify why the dissolution testing is not required for this product.

III. *IN VITRO* (DISSOLUTION) TESTING

In a meeting on May 2, 1995, with several members of Chemistry and Bioequivalence divisions (Moheb Makary, Rabindra Patnaik, Richard Adams, Larry Ouderkirk, and Surendra Shrivastava), dissolution of cefaclor suspension was discussed. Since the drug is soluble in water and in acidic media % in 10 minutes at 25 rpm in most cases), a decision was made that the firms need not carry out any dissolution testing for cefaclor suspensions (see Memo from Richard Adams to Cefaclor Oral Suspension file, dated May 4, 1995, Attachment-1). It was decided at that time, that only content uniformity test be required for these products for manufacturing controls and stability testing. On the basis of that decision, non-submission of dissolution testing was not considered a deficiency, and the firm was not informed to submit such data.

IV. RECOMMENDATION

The dissolution testing for Ranbaxy's cefaclor suspension, therefore, is not required at this time.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar /S/ Date 9/30/1997

Concur: /S/ Date: 9/30/97

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs

Attachment-1
SPS/sps/9-30-97/64155D.795

cc: ANDA #64-155 , 64-164, 64-165, 64-166 (Original, Duplicate), HFD-655 (SNerurkar, Shrivastava), Drug File, Division File.

Attachment-1

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: May 4, 1995

TO: Cefaclor Oral Suspension Grade Applications:

Lederle:	AADA 64-110	Zenith:	AADA 64-070
	64-114		64-085
	64-115		64-086
	64-115		64-087

FROM: Richard C. Adams, Branch 5, Division of Chemistry II, Office of Generic Drugs.

SUBJECT: Dissolution Testing Requirements for Cefaclor Oral Suspension Grades and Suspensions in General

1. Cefaclor Suspension Grade Applications

Our letters of approval for Cefaclor Oral Suspension Grade were issued simultaneously for Lederle and Zenith on 4/28/95. The letters contained a statement which indicated that the firms should incorporate the approved dissolution testing methodology in their quality control and stability programs. However, neither the Final Product Specifications nor Stability Specifications (for either firm), as approved for these applications, require dissolution testing. This situation results from the fact that there is no dissolution test listed in the USP monograph for this drug product and also because the recent Guidance on this subject, published by the Office of Generic Drugs Division of Bioequivalence in USP XXIII, Supp. 2, does not contain dissolution methodology for the suspension. The Guidance, issued April 23, 1993, although entitled "Cefaclor Capsules and Suspensions *in vivo* Bioequivalence and *in vitro* Dissolution Testing," only discusses *in vitro* dissolution testing for the capsules.

Late in the day on April 28 after Zenith had received a

copy of their approval letter, the firm called to find out if they would be required to conduct dissolution testing prior to release of their Cefeclor Suspension Grade products. We told them that was not the case for release and probably not for stability but that the official decision for this had to be made by Bioequivalence. But since we had signed off on the release specifications they could proceed with release and distribution; we would discuss this further and get back to them next week.

Toward that end on May 2, I had an informal discussion with several Bioequivalence principals (Drs' Shrivistava, Patniak, Ouderkirk, and Makary). They confirmed that they had intended to incorporate dissolution testing on some routine basis since it had been required in the initial waiver approval. On further discussion, however, it was agreed that based upon the solubility properties of this drug such testing was probably not necessary. The April 23, 1993 Guidance on Cefaclor was discussed and it was concluded that it may require revision.

2. Dissolution Testing of Suspensions: General

During the course of our discussion on Tuesday regarding cefaclor for oral suspension, it was noted that dissolution testing requirements would vary depending upon the properties of the active drug and the drug product. I discussed this subject further with Dr. Larry Ouderkirk on 5/5. He informed me that historically, *in vitro* testing methodology for suspension grade products has not been done; rather, suspensions were waived based upon other considerations similar to solution products. Some time ago this issue was apparently raised in the Division of Bioequivalence (Dr. S.Dighe) and it was felt that **some** sort of evaluation should be performed. Since that time, for waivers of *in vivo* studies, Bioequivalence has typically requested *in vitro* evidence of equivalence of different strength suspensions similar to that asked for solid oral dosage forms except for minor changes, *e.g.* slower paddle speed, *etc.* In short, the Division of Bioequivalence has typically required **some** sort of demonstration of *in vitro* equivalence in the original application. This approach has not resulted in translation of these technics to quality control or stability programs, at least in any general sense. USP monographs are silent on dissolution testing for suspensions as far as I can determine.

For drug substances such as cefaclor which have reasonable water solubility, especially in buffered systems above the pK_a of the carboxylic acid, (others are amoxicillin, cephalexin, ampicillin, cephradine, *et.al.*), the requisite assay procedure probably suffices as a "dissolution" test for the suspension and the need for *per se* dissolution testing for release and stability is obviated. However, even for these drug substances, particle size characteristics are probably important. For drug substances with poor water solubility (*e.g.*, nystatin, erythromycin ethylsuccinate) these conclusions may not apply.

CONCLUSIONS:

1. The Office of generic Drugs does not have a policy with regard to dissolution testing for suspension grade products, either to qualify them for waiver of *in vivo* testing requirements or for ongoing quality control/stability programs.

2. Products designated "For Oral Suspension" require a case-by-case evaluation in order to determine whether dissolution testing should be incorporated into the release and stability specifications for the product.

3. In view of the above statements, chemistry reviewers of these products should address the question of dissolution requirements with appropriate Bioequivalence personnel early in the review process so that appropriate specifications may become incorporated in the release and stability specifications. If the decision is made that no dissolution specification are needed, appropriate controls of particle size specifications become more crucial.

C:\ADAMS\osgdiss.req

MAY 13 1996

ANDA # 64-155, 64-164, 64-165, 64-166
Cefaclor Oral Suspension
375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, 125 mg/5 mL
Reviewer: S. P. Shrivastava

Ranbaxy Labs. Ltd.
Raleigh, NC
Submission Date:
July 7, 1995
September 27, 1995

REVIEW OF *IN VIVO* BIOEQUIVALENCE STUDIES AND THREE WAIVER REQUESTS

I. OBJECTIVE

The firm has submitted *in vivo* bioequivalence data on fasting and limited food studies on its cefaclor 375 mg/5 mL comparing it with Lilly's Ceclor[R] Oral Suspension, 375 mg/5 mL. The firm has also submitted composition data for its 375 mg/5 mL, 250 mg/5 mL, 187 mg/5 mL, and 125 mg/5 mL strength cefaclor oral suspensions for review.

II. BACKGROUND

Cefaclor is a semisynthetic cephalosporin antibiotic which inhibits bacterial cell-wall synthesis in a manner similar to that of penicillin. Cefaclor is used in the treatment of otitis media, lower and upper respiratory infections, urinary tract infections and skin and skin structure infections.

Cefaclor is well absorbed after oral administration in fasting subjects. Total absorption is similar regardless whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed in fasting subjects and generally appears about 1 hour later.

Following administration of 250 mg, 500 mg, and 1 g doses in fasting subjects, average peak serum levels of approximately 7, 13, and 23 μg/mL, respectively, were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in urine within 8 hours, the major portion being excreted within the first 2 hours. The serum elimination half-life in subjects with normal renal function is 0.6 to 0.9 hour. In patients with complete absence of renal function, the plasma elimination half-life of the drug is 2.3 to 2.8 hours.

Currently, cefaclor is marketed by Eli Lilly under the name Ceclor[R], 250 mg and 500 mg capsules, and as a powder for reconstitution as suspension for oral administration, 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL and 375 mg/5 mL. The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia), doses may be doubled.

III. STUDY #1. TWO-WAY CROSSOVER BIOSTUDY ON 375 MG/5 ML CEFACLOR UNDER FASTING CONDITIONS

A. Protocol #940784

Signed and dated, Oct. 26, 1994; One Amendment dated Nov. 14, 1994.
Laboratory/Site (Clinical):
Analytical Lab.
Investigator(s):

IRB Approval: Signed and dated by F. Varin, Ph.D., 10/25/94.
Subjects: 26 Healthy males, including 24 for the study and 2 replacements. There were no dropouts.
Study Design: Single-dose, two-way crossover study under fasting conditions.
Restrictions: Volunteers were instructed not to take any drugs including OTC drugs, one weeks prior to the start of the study; abstain from consuming alcohol or caffeine and/xanthine containing products 24 hours prior to and during the study.
Inclusion/Exclusion Criteria: Volunteers were healthy males, 18-45 years, weighing at least 60 kgs and within the 15% of ideal weight. They selected on the basis of normal observations during general physical, clinical, hematological, HIV and urinary examinations. Volunteers with history of chronic illness, e.g. alcohol or drug addiction within year; GI, renal, hepatic or cardiovascular disease; pulmonary, endocrine, immunologic, dermatologic, neurologic or psychiatric disease; subjects with abnormal clinical values, or had a history of allergic response, donated excess blood, were excluded from the study.
Treatment:

Test Drug: A: Ranbaxy's Cefaclor, 375 mg/5 mL suspension, Lot # P00194; Lot size: 90 kg, Manuf. Date - 8/94, Exp. Date - 7/96
Other dosage levels: Same as 375 mg/5 mL suspension.
Reference Drug: B: Lilly's Ceclor[R] 375 mg/5 mL, Suspension, Lot # 8AA04A, Exp. Date 1/1/96.
Study Dates: 28/11/94 - 5/12/94. **Analysis Dates:** 12/16/94 - 1/18/95
Sample Storage Period: 51 Days

B. Assay Methodology and Validation

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Assy methodology

C. Results

1. Pharmacokinetic Parameters

- 26 subjects were used in the study. However, samples from only 24 subjects were analyzed and computed for PK parameters.
- Average pharmacokinetic parameters are given in Table 1 and Attachments 1-5.
- ANOVA analysis did not show any significant treatment, period or sequence effect on PK parameters.
- The test/reference ratios for all PK parameters (average) for the products were within 0.95-1.02 (Table 1).

- The 90% CIs for $LAUC_{0-t}$, $LAUC_{0-\infty}$, and LC_{max} are within the 80-125%.
- The regression coefficients for individual terminal phase of the plasma concentration-time curve were between indicating a good curve fit, and an appropriate K_{el} and $AUC_{0-\infty}$ estimation.
- Ratios of individual $AUC_{0-t}/AUC_{0-\infty}$ averaged over 0.95 for the test and reference products.
- Individual PK parameters for test and reference products are given in Attachments 4-5.

Table 1. Pharmacokinetic Parameters (%CV)

Parameter	Test	Reference	Ratio, T/R	90% CI
AUC_{0-T}, μg.Hr/mL	15.81 (15.0)	16.56 (13.3)	0.95	
ln AUC_{0-T}, μg.Hr/mL	15.65 (14.5)	16.42 (13.3)	0.95	90.6-100.4
AUC_{0-Inf}, μg.Hr/mL	16.04 (15.2)	16.63 (12.4)	0.96	
ln AUC_{0-Inf}, μg.Hr/mL	15.87 (14.7)	16.50 (12.4)	0.96	91.3-101.0
C_{max}, μg/mL	16.46 (20.8)	17.16 (23.4)	0.96	
ln C_{max}, μg/mL	16.10 (22.5)	16.67 (25.4)	0.97	88.6-105.2
T_{max}, Hr	0.49 (31.9)	0.50 (33.0)	0.98	
$T_{1/2}$, Hr	0.624 (11.1)	0.640 (14.8)	0.98	
K_{el}, Hr^{-1}	1.1234 (10.7)	1.1042 (13.7)	1.02	

2. Drug Levels in Plasma

- The plasma concentration data for all subjects are given in Table 2 and Attachment #3.
- The lower limit of quantitation, μg/mL was properly validated.
- The average test/reference ratios for plasma concentration during 0.25-4 hours varied between 0.89-1.01.

TABLE 2. Mean Plasma Concentration at Each Sampling Time Point (μg/mL) (n = 24)

TIME (HR)	TEST	CV (%)	REFERENCE	CV (%)	Ratio, T/R
Pre-dose	0.02	342	0.01	490	2.00
0.25	10.00	49	11.21	53	0.89
0.50	15.46	27	16.38	23	0.94
0.75	10.91	21	11.22	22	0.97
1.00	7.36	32	7.42	24	0.99
1.25	4.98	31	5.18	28	0.96
1.50	3.46	31	3.55	28	0.97
2.00	1.86	33	1.89	27	0.98
3.00	0.69	33	0.68	26	1.01
4.00	0.28	40	0.29	44	0.97
5.00	0.05	238	0.08	192	0.63
6.00	0.03	358	0.02	352	1.50
8.00	0.02	490	0.01	490	2.00
Ave. 0.25-4 Hours					0.97

3. **Adverse Reactions:** One case of sore throat unrelated to the test product administration was reported.

4. **Conclusion:** The fasting study is acceptable.

IV. Study #2. 3-Way Crossover BE Study Under Fed and Fasted Conditions

A. Protocol # 940786

The study site, investigators, subject selection criteria, drug products, blood sampling schedule, analytical assay, methods validation, etc. were same as in the fasting study. Certain protocol differences are indicated below.

Subjects: 18 Healthy male volunteers participated in the study, but two dropped out.

Study Design: Randomized, 3-Way crossover, 3-period, 3-sequence study.

Drug Regimen

A. Ranbaxy 375 mg/5 mL cefaclor suspension administered under fasting conditions.
B. Ranbaxy 375 mg/5 mL cefaclor suspension administered under fed conditions.
C. Lilly's Ceclor[R] 375 mg/5 mL cefaclor suspension administered under fed conditions.

Dose: Single Oral dose, 375 mg/5 mL, administered with 240 mL water.

Fasting/Food: Regimen A: Subjects will be required to fast overnight before dosing and 4 hours post-dosing.
Regimen B & C: Subject will be required to fast overnight until 30 minutes prior to their dosing time, when they will be given standard breakfast. Standard meals will be provided at 4 hours post-dosing to all subjects.

Water: Water will be allowed *ad. libitum* except 4 hours predosing, 2 hours post-dosing, and during dosing time.

Washout Period: 72 Hours between dosing.

B. Results

1. Pharmacokinetic Parameters

- The firm has included Subject, Period, Residue A, Residue B, and Treatment in the ANOVA model, but it has not included Sequence as a factor. Additionally, the meaning of RESIDA AND RESIDB is not clear.

- It appears that there is no residual effect on PK parameters. However, it needs confirmation.

- Average pharmacokinetic parameters are given in Table 3 and Attachments 6-9.

- The ratios of test/reference (food) for AUCs and C_{max} are within 0.8-1.2 as required (Tables 3). However, ANOVA reanalysis with Sequence in the

model, is not provided.

- ANOVA analysis showed significant period effect on AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}.

- Individual PK parameters are given in Attachments 6-8.

- The test/reference ratios for all PK parameters for the products ranged between 0.95-1.18 (Table 3). The individual ratios ranged between 0.81-1.22, 0.8-1.2 and 0.64-1.76, respectively, for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

- Food increases the C_{max} and AUCs of test product significantly.

Table 3. Pharmacokinetic Parameters (%CV)

Parameter	Test (Fast)	Test (Food)	Reference (Food)	Ratio, T/T Fast/Food	Ratio, T/R (Food)
AUC_{0-T}, μg.Hr/mL	15.10 (15.3)	13.14 (18.4)	12.60 (19.7)	1.15	1.04
AUC_{0-Inf}, μg.Hr/mL	15.41 (15.0)	13.48 (17.5)	13.00 (18.7)	1.14	1.04
C_{max}, μg/mL	15.48 (21.8)	6.78 (27.9)	6.65 (25.3)	2.28	1.02
T_{max}, Hr	0.48 (29.6)	0.92 (49.2)	0.78 (52.1)	0.52	1.18
$T_{1/2}$, Hr	0.70 (13.3)	0.78 (11.4)	0.82 (10.6)	0.90	0.95
K_{el}, Hr^{-1}	1.01 (13.0)	0.90 (11.2)	0.85 (11.5)	1.12	1.06
$LAUC_{0-t}$, μg.Hr/mL	2.701	2.561	2.523	1.15	1.04
$LAUC_{0-inf}$, μg.Hr/mL	2.721	2.589	2.555	1.14	1.03
LC_{max}, μg/mL	2.685	1.908	1.871	2.17	1.04

2. Drug Levels in Plasma

- The plasma concentration data for all subjects are given in Table 4 and Attachment #9.

- The lower limit of quantitation, μg/mL was properly validated.
- The average test/reference ratios for plasma concentration during 0.25-4 hours varied between 0.86-1.11.

TABLE 4. Mean Plasma Concentration at Each Sampling Time Point (μg/mL) (n = 16)

TIME (HR)	TEST (Food)	CV (%)	REFERENCE (Food)	CV (%)	Ratio, T/R (Food)
Pre-dose	0.00	----	0.00	----	----
0.25	2.85	97	3.33	66	0.86
0.50	5.39	42	5.95	39	0.91
0.75	5.79	25	5.79	27	1.00
1.00	5.45	29	5.06	20	1.08
1.25	5.03	28	4.55	19	1.11
1.50	4.92	25	4.48	23	1.10
2.00	3.59	31	3.29	25	1.09
3.00	1.72	34	1.59	34	1.08
4.00	0.67	47	0.64	40	1.05
5.00	0.22	78	0.20	86	1.10
6.00	0.02	273	0.02	273	1.00
8.00	0.00	----	0.00	----	----
Ave. 0.25-4 Hours					1.03

3. Adverse Reaction

Adverse reactions were not serious and no differences in the test and reference products could be detected (see Table below).

Adverse Events	No. of Subjects		
	Test (Fast)	Test (Fed)	Reference (Fed)
Headache	4	0	1
Loose stools	1	0	0
Scratch in inner ear	1	0	0

4. Conclusion: The study requires reanalysis of data using Sequence in the ANOVA model. Study is incomplete.

V. FORMULATION

Comparative formulations for test and reference products, and for three other strengths of test products are given in Table 5 below. The inactive ingredients in test products are within the IIG limits. The batch size was kg dosage units), and the intended production batch size is kg. This meets the biobatch size requirement of % or greater.

VI. *IN VITRO* RESULTS (DISSOLUTION)

Since cefaclor is soluble in aqueous, *in vitro* dissolution of cefaclor suspension is not required.

VII. COMMENT

1. In future, the firm should also submit data on a computer diskette in ASCII format containing two separate files as follows:

   A. SUBJ SEQ PER TRT AUCT AUCI C_{MAX}

   B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

   The fields should be delimited by one blank space, and missing values should be indicated by a period.

2. The reviewer discussed with Jim Henderson and others in the division about the residual (RES) effects and sequence (SEQ) analysis. Jim had similar issues with other drugs and had discussed with Don Schuirmann. According to Don, the test for residue, and the estimates and standard errors of treatment differences, obtained by the usual model with sequence (Y= SEQ SUBJ(SEQ) PER TRT RES) and sponsor's model without sequence (Y = SUBJ PER TRT RES) should be the same.

   The sponsor has cited - Littell, R.C., Freund, R.J., and Spector, P.C. SAS Systems for

Linear Models, 3rd Ed., SAS Institute, Cary, NC, 1991, in support of a contrast approach to the assessment of residual effects. According to Don Schuirmann, the two contrast variables may capture the sum of squares for residuals. In the two treatment, two period standard crossover study, SEQ is included in the model because the test for SEQ is the only test we have for unequal residual effects. For a higher order crossover study (e.g. for four period, four treatment, four sequence), we have a separate test for first order residual effects. The interpretation of the SEQ test is not so clear in this case. Standard practice in CDER has been to base an assessment of residual effects on the RES test, and ignore the SEQ test for these higher order designs. Since we are going to ignore the SEQ, there is no reason to partition SUBJ into SEQ and SUBJ(SEQ). Therefore, according to Don Schuirmann, the model used by the sponsor is acceptable (Attachment 10).

VIII. RECOMMENDATIONS

1. The bioequivalence study conducted under fasting conditions by Ranbaxy Laboratories on its cefaclor oral suspension, 375 mg/5 mL, Lot # P00194, comparing it to Lilly's Ceclor^R, 375 mg/5 mL, Lot # 8AA04A, has been found acceptable by the Division of Bioequivalence.

2. The limited food study conducted by Ranbaxy Laboratories on its cefaclor suspension, 375 mg/5 mL, Lot #P00194, comparing it to Lilly's Ceclor^R, 375 mg/5 mL suspension, Lot #8AA04A, has been found acceptable by the Division of Bioequivalence. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability requirements for cefaclor oral suspension, 375 mg/5 mL, and the application is acceptable.

3. The formulations for the 250 mg/5 mL, 187 mg/5 mL, and 125 mg/5 mL strengths are proportionally similar to the 375 mg/5 mL strength of the test product, which underwent bioequivalence testing. The requests for waiver of *in vivo* bioequivalence study requirements are granted as per Section 320.22(d) of Bioavailability/Bioequivalence Regulations.

The firm should be informed of comment #1 and recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RNPatnaik /S/
FT INITIALED RNPatnaik _____ Date 5/7/96

Concur: /S/ Date: 5/13/96

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs

Attachments - 10

cc: ANDA #64-155 , 64-164, 64-165, 64-166 (Original, Duplicate) HFD-600 (DHare), HFD-630, HFD-655 (Patnaik, Shrivastava), Drug File, Div. File.