CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-077

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

ANDA 75-077

FEB 25 2000

L..Perrigo Company
Attention: Brian R. Schuster
117 Water Street
Allegan, MI 49010

Dear Sir:

This is in reference to your abbreviated new drug application dated February 10, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Acetaminophen Extended-release Tablets, 650 mg.

Reference is also made to your amendments dated July 14, September 23, and December 20, 1999; and January 21, and January 24, 2000.

As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, 19th Edition, the "Orange Book", the listed drug product (RLD) referenced in your application, Tylenol Extended-release Tablets (currently marketed as Tylenol Arthritis Extended Relief Caplets) of McNeil Consumer Products Company, is subject to periods of patent protection. These periods expire on July 27, 2007 (U.S. Patents 5,004,613 and 4,820,522) and November 6, 2007 (U.S. Patent 4,968,509). Your application contains patent certifications under 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on any of the listed patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately unless an action for patent infringement is brought by either the patent holder or holder of the new drug application (NDA) for the RLD before the expiration of forty-five (45) days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified the Agency that L. Perrigo Company (Perrigo) has complied with the requirements of Section 505 (j)(2)(B) of the Act and that no action for infringement of any of the listed patents was brought

against Perrigo within the statutory forty-five day period.

Furthermore, we have concluded that Perrigo was the first applicant to submit a substantially complete ANDA with a Paragraph IV Certification to the three listed patents. Therefore, you are eligible for 180-days of market exclusivity for this drug product. Such exclusivity will begin to run either from the date Perrigo begins commercial marketing of this drug product, or from the date of a decision of a court finding the patent(s) invalid or not infringed, whichever occurs earlier (Section 505(j)(5)(B)(iv). A court decision that can trigger the beginning of exclusivity is a decision of any court in a patent infringement action resulting from a Paragraph IV Certification in which the court finds that the patent(s) is invalid or not infringed. With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. If you have a question concerning the Agency's determination of the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710), or contact Mr. Donald Hare, Special Assistant to the Director, Office of Generic Drugs, at (301) 827-5845.

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 over-the-counter (OTC) labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acetaminophen Extended-release Tablets, 650 mg, to be bioequivalent to the listed drug (Tylenol Extended-release Tablets, 650 mg of McNeil Consumer Products Co.).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution test and tolerances are:

The dissolution testing should be conducted in 900 mL of

simulated gastric fluid w/o pepsin, pH 1.2, at 37°C, using USP Apparatus II(paddles) at 50 rpm. The test product should meet the following "interim" specifications:

Time	% Dissolved

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. A "Special Supplement - Changes Being Effected" (zero) should be submitted if there are no revisions to be proposed to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances a Prior Approval supplement should be submitted.

Under 505 (j) certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

Sincerely yours,

/S/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-077

FINAL PRINTED LABELING

FINAL PRINTED LABELING
ANDA 75-077
Apap Extended Release Tablets, 650mg
300 count
LABEL

Marge

Usual Dosage: Adults and Children 12 years of Age and Older: Take two caplets every 8 hours, not to exceed 6 caplets in any 24-hour period. TAKE TWO CAPLETS WITH WATER. SWALLOW EACH CAPLET WHOLE. DO NOT CRUSH, CHEW, OR DISSOLVE THE CAPLET. Not for use in children under 12 years of age.

Warnings: Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a physician. If pain or fever persists, or gets worse, if new symptoms occur, or if redness or swelling is present, consult a physician because these could be signs of a serious condition. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a physician or poison control center immediately. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms. Do not use with any other products containing acetaminophen.

Active Ingredients (Per Caplet): Acetaminophen 650 mg.

Inactive Ingredients: Carnauba Wax, Crospovidone, Hydroxypropyl Methylcellulose, Isononylphenylpolyoxethylene Glycol Ethers, Magnesium Stearate, Maltodextrin, Methacrylic Acid Copolymers, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Povidone, Talc, Titanium Dioxide.

Store at room temperature. Avoid excessive heat (40°C)

US Patent 5,773,031

MANUFACTURED BY
PERRIGO
ALLEGAN, MI 49010 U.S.A.

DO NOT USE IF PRINTED FOIL INNER SEAL IS BROKEN

ACETAMINOPHEN EXTENDED-RELEASE TABLETS, 650 mg

Pain Reliever/Fever Reducer

Extended Relief Caplets

APPROVED

Lasts Up To 8 Hours

300 **CAPLETS*** - 650 MG EACH
*Capsule-Shaped Tablet

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Uses: For the temporary relief of the minor pain of arthritis, and the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the pain of menstrual cramps and for the reduction of fever.

Extended Relief Caplets:
- Works for up to eight hours. Can get relief all day or night with fewer doses.

How ACETAMINOPHEN products are different:
- Contain no aspirin and are unlikely to cause the gastric irritation often associated with aspirin, naproxen sodium or ibuprofen.
- May be used by most persons with peptic ulcer, when taken as directed for recommended conditions.
- Are not likely to cause a reaction in those who are allergic to aspirin / naproxen sodium and ibuprofen.

PRODUCTION QUALITY SAMPLE NOT FOR RESALE

FEB 25 2000

0 00000 00000 0 L 544 87 FA F1

FINAL PRINTED LABELING
ANDA 75-077
Apap Extended Release Tablets, 650mg
24 count
LABEL

Maego

FINAL PRINTED LABELING
ANDA 75-077
Apap Extended Release Tablets, 650mg
CARTON

Margo

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-077

CHEMISTRY REVIEW(S)

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

2. ANDA **#75-077**

3. NAME AND ADDRESS OF APPLICANT
L. Perrigo Company
117 Water Street
Allegan, MI 49010

4. LEGAL BASIS FOR ANDA SUBMISSION
As the basis for submission, the company has submitted Tylenol® extended release tablets are an over-the-counter drug product in the same strength and dosage form.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Acetaminophen Extended Release

9. AMENDMENTS AND OTHER DATES:
2/10/97 - Original submission
4/8/97 - New correspondence
12/19/97 - FDA Deficiency letter
5/8/98 - Amendment Response
10/16/98 - FDA Deficiency letter
1/15/99 - Amendment Response
7/15/99 - FDA deficiency (Fax later turned to minor)
9/23/99 - Minor amendment Response
12/20/99 - Telephone amendment

Documentation of receipt and evidence of the date of "Notice of Non-infringement of patent"

10. PHARMACOLOGICAL CATEGORY
Analgesic, antipyretic

11. ℞ or OTC
OTC

12. RELATED IND/NDA/DMF(s)

NDA# 19872

DMF #

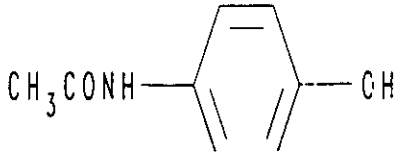
13. DOSAGE FORM
Extended-release Tablet

14. POTENCY
650 mg

15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP

$C_8H_9NO_2$; M.W. = 151.16



4'-Hydroxyacetanilide. CAS [103-90-2]

16. RECORDS AND REPORTS
NA

17. COMMENTS
Labeling is acceptable in review dated 10/8/99.

Bio was found acceptable on 11/4/99.

Methods Validation was performed on the new Impurities method #1503 by the Detroit DO (Shirley Ii). The DO had a few deficiencies which were relayed to the firm. The firm has since resolved all issues.

All Chemistry issues have been resolved.

EER is acceptable dated 5/24/99.

DMF's are satisfactory

18. CONCLUSIONS AND RECOMMENDATIONS

This application was reviewed in accordance with OGD PPG #29-90. At this time all chemistry is acceptable.

19. REVIEWER DATE COMPLETED

Karen Bernard, Ph.D. October 11, 1999

Page(s) 25

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemist Review #4

1/4/00

Chemistry comments to be provided to the applicant.

ANDA: 75-077 APPLICANT: L Perrigo Company

DRUG PRODUCT: Acetaminophen Extended-release Tablets, 650 mg

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

The District laboratory has concluded Method #1503 is not adequate for the determination of impurities for the following reasons:

1. The district analyst found the 4-Aminophenol to be

You should satisfactorily address each of the above comments.

Sincerely yours,

/S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 16

38. Chemistry comments to be provided to the applicant.

ANDA: 75-077 APPLICANT: **L Perrigo Company**

DRUG PRODUCT: Acetaminophen Extended-release Tablets, 650 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

B. In addition to responding to the deficiencies presented above please note and acknowledge the following comments in your response:

i. Your newly revised Impurities Testing procedure #1503 must be re-validated by the Detroit DO. Please submit samples and a copy of the new method to Ms. Shirley A. L. Ii, FDA District Office, 1560 E. Jefferson Detroit, MI 48207.

ii. Please be aware that since you do not intend to follow recommendations made by the Division of Bioequivalence, your proposal must be reviewed and this may require future communication with the Division of Bioequivalence concerning your application.

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 75-077 APPLICANT: L Perrigo Company

DRUG PRODUCT: Acetaminophen Extended-release Tablets, 650 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

When submitting LOA's, please submit recent letters with accurate page numbers and volume numbers in order to facilitate the review process. Please refer to CFR 314.420(b).

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-077

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75077 SPONSOR : Perrigo

DRUG AND DOSAGE FORM : Acetaminophen ER Caplet

STRENGTH(S) : 650 mg

TYPES OF STUDIES : Fasting . Non-fasting. and Multiple-dose studies submitted earlier

CLINICAL STUDY SITE(S) : Pharmakinetics

ANALYTICAL SITE(S) : Pharmakinetics

AMENDMENT
ORIGINAL SIGNED ON 1-15-1997.

STUDY SUMMARY : Bio-studies were acceptable.

DISSOLUTION : Acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results: O.K.
First Generic _x____	Inspection requested: (date)	
New facility _____	Inspection completed: (date) June 21, 1999	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep R. Dhariwal /S/ BRANCH : II

INITIAL __ DATE : 10/15/99

TEAM LEADER : S. Nerurkar /S/ BRANCH : II

INITIAL : DATE : 10/18/1999

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 11/4/99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-077 APPLICANT: L. Perrigo

DRUG PRODUCT: Acetaminophen Extended Release Tablets, 650 mg

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

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

> The dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2, at 37°C, using USP Apparatus II(paddles) at 50 rpm. The test product should meet the following interim specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-077 APPLICANT: L. Perrigo

DRUG PRODUCT: Acetaminophen Extended Release Tablets, 650 mg

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

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

> The dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2, at 37°C, using USP Apparatus II(paddles) at 50 rpm. The test product should meet the following interim specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Acetaminophen
Extended Release Tablets, 650 mg
Caplets (capsule shaped tablet)
ANDA #75-077
Reviewer: Kuldeep R. Dhariwal
File name: 75077SD.999

L. Perrigo Company
117 Water Street
Allegan, MI 49010
Submission Date:
September 23, 1999

Review of Amendment

Background:

Perrigo submitted ANDA #75077 on February 10, 1997 for first generic acetaminophen extended release tablets, 650 mg. The bioequivalence studies were reviewed by this reviewer and were found acceptable (file name: 75077SD.297). The dissolution testing conducted by the firm was found acceptable. The firm was informed that dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2 using USP apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

The firm submitted a major amendment on May 8, 1998 responding mainly to the Chemistry deficiencies. The firm also responded to the above dissolution specifications given by the Division of Bioequivalence.

The firm stated the following:

1. Based on dissolution testing performed on the bio-lots, our product meets these specifications but the reference listed drug does not.

2. At this time we have not manufactured a sufficient number of batches of the drug product to ascertain that these limits are appropriate in consideration of the unique controlled drug release mechanism used for the Perrigo product. We will evaluate the applicability of the recommended specifications following the manufacture and stability testing of an adequate number of batches following the approval of this application.

The firm was informed that these specifications are interim and it should not be a concern if the reference drug does not meet the specs.

In this amendment the firm is requesting to modify the specifications based on their 24 month R/T stability data. The firm proposes the following specifications:

Time min	Firm's new specifications	DBE proposed specifications

Comments:

1. Firm's proposed specifications are acceptable.

Recommendations:

1. The *in vivo* bioequivalence studies conducted under fasting, non-fasting, and multiple-dose steady-state conditions submitted earlier were found acceptable to the Division of Bioequivalence. These studies demonstrated that Perrigo's acetaminophen ER 650 mg caplet, lot #6N0778 is bioequivalent to the reference product Tylenol ER 650 mg caplet, lot #MPM492.
2. The dissolution testing conducted on acetaminophen ER 650 mg caplet is acceptable. 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 simulated gastric fluid w/o pepsin, pH 1.2 at 37°C using apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

3. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

/S/ Date 10/18/99

Concur: Date 11/4/99

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
/S/

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-077 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Acetaminophen Extended Release Tablets, 650 mg

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

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

> The dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2, at 37°C using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Acetaminophen
Extended Release Tablets, 650 mg
Caplets (capsule shaped tablet)
ANDA #75-077
Reviewer: Kuldeep R. Dhariwal
Filename: 75077SD.297

L. Perrigo Company
117 Water Street

Allegan, MI 49010
Submission Date:
February 10, 1997

Review of Fasting, Non-Fasting, and Multi-dose/ Steady-State Studies and Dissolution Data

The firm has submitted *in vivo* bioequivalence studies under fasting, non-fasting, and multi-dose/steady-state conditions and dissolution data comparing its acetaminophen extended release tablets, 650 mg with McNeil's Tylenol® tablets, 650 mg. The fasting study was done with two test formulations and a reference drug. The non-fasting and multi-dose/steady state studies were done with one of the test formulations used in the fasting study and a reference drug. The firm intends to market only the test formulation used in all three studies. The firm has also submitted the dissolution data on test and reference products.

Introduction:

Acetaminophen is an analgesic and antipyretic. The reference listed drug is Tylenol® Extended Relief (acetaminophen extended release) caplets from McNeil. Tylenol® Extended Relief uses a unique, patented bilayer caplet. The first layer dissolves quickly to provide prompt relief while the second layer is time released to provide up to 8 hours of relief. The usual dosage for adults and children 12 years of age and older is two caplets every 8 hours, not to exceed 6 caplets in any 24-hour period. It is an OTC product.

Bioavailability of Acetaminophen Extended Release Caplets, 650 mg under Fasting Conditions:

A. Objective:

To compare the bioavailability of two different formulations of acetaminophen extended release 650 mg caplets manufactured by Perrigo with the bioavailability of a marketed reference formulation Tylenol® 650 mg extended release caplets, manufactured by McNeil.

B. Study Sites and Investigators:

Clinical and Analytical Site:

Principal Investigator:
Project Director:
Protocol # 10971 "Bioavailability of Acetaminophen Extended Release Caplets, 650 mg" was approved by the Institutional Review Board for
Consent Form: A copy of volunteer informed consent form used in the study is given on page 87, vol. 1.1.
Study Dates: Period I April 16-17, 1996
Period II April 23-24, 1996
Period III April 30-May 1, 1996
Analysis Dates: May 6 to June 25, 1996

C. Study Design:

The study was designed as a randomized, single oral dose, three-treatment, three period, three sequence crossover study, with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 16 hours postdose each period. The subjects were assigned as follows:

Subject number	Period I	Period II	Period III
1,6,7,11,13,18,20, 24,27	C	A	B
2,5,9,10,15,16,21, 22,26	A	B	C
3,4,8,12,14,17,19, 23,25	B	C	A

Subject #5 did not return for period III.

A= Acetaminophen Extended Release Caplets, 1x650 mg; Perrigo Company; Lot 1 (#6N0778); Batch size: caplets; Manufacture Date: January 1996; Assay: 100.61%; Content Uniformity: 101.6%
B= Acetaminophen Extended Release Caplets, 1x650 mg; Perrigo Company; Lot 2 (#6N0780); Batch size: caplets; Manufacture Date: January 1996; Assay: 100.15%; Content Uniformity: 101.6%
C= Tylenol® Extended Release Caplets, 1x650 mg; McNeil; Lot #MPM492; Expiry Date: August 1997; Assay: 100.0%; Content Uniformity: 99.1%

The subjects fasted for no fewer than 10 hours prior to dosing and 4 hours after administration of study drug. Water was restricted within one hour of drug administration. The drug products were administered with 240 mL of water. The subjects were dosed at 2 minute intervals and were not allowed to be supine for 4 hours postdose. Identical meals were served during all phases. Blood pressure and pulse measurements were obtained predose, 4 and 16 hours postdose. Diagnostic blood and urine specimens were obtained from the subjects prior to discharge from the study at the end of period III.

D. Subject Selection:

Twenty-seven healthy subjects (9 females, 18 males) were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age
- no more than ±15% from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study
- must not have smoked within the last 6 months

Subjects were excluded from the study based on the following criteria:

- history of tuberculosis, epilepsy, diabetes, psychosis, glaucoma, asthma, serious cardiovascular, neurological, hepatic, renal, hematopoietic or gastrointestinal diseases or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to acetaminophen

- positive serum pregnancy test at screening or positive urine pregnancy test at check-in for each period

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications (excluding ibuprofen, OTC aspirin, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol consumption for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers at 0 (predose), 0.25, 0.50, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 16 hours. Immediately after the last sample was collected at each time point, the samples were centrifuged at 2500 rpm for 20 minutes at 10°C. The plasma was transferred to prelabeled tubes and stored at -20°C.

F. Analytical Methods:

A high performance liquid chromatographic method was used for the determination of acetaminophen in human plasma. USP reference standard acetaminophen was used to prepare plasma calibration standards and control samples. USP reference standard acetanilide was used as internal standard.

ACCEPTANCE CRITERIA: Calibration lines and duplicate control samples containing 75, 7.50, and 1.25 μg/mL acetaminophen were analyzed with each sample set. The final assay results of each sample set were accepted only if a minimum of 4 out of 6 control samples processed with each sample set were within 15% of the nominal concentration for the 75 and 7.50 μg/mL acetaminophen control samples and 20% of the nominal concentration for the 1.25 μg/mL acetaminophen control samples. Also, one control sample at each concentration must have been within the above specified

range.

G. Pharmacokinetics/Statistics:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last three to five concentrations versus time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences (α=0.05) between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Twenty-seven subjects entered the study. Subject #5 was withdrawn prior to period II dosing because of a rash on both forearms.

Adverse events:

Six subjects experienced adverse events like headache, nausea, and lightheadedness. None of them required any medications.

Deviations in the study:

1. Subject #25, period II, 15-minute samples was withdrawn 1 minute late.
2. Subject #13 took ibuprofen tablet approximately 6 days prior to period II dosing.

Reassays:

Of the 1404 samples assayed for this study, 53 samples were reassayed for following reasons:

20	due to chromatographic interference
32	due to concentration outside the range of the calibration line or to reexamine the effect of endogenous peak at the retention time of the drug
1	due to pharmacokinetic anomaly

2. Analytical:

SPECIFICITY: The plasma used to prepare calibration standards and control samples was screened chromatographically to confirm the absence of endogenous compounds that would interfere with the analysis of acetaminophen. Selectivity was also confirmed by assaying a predose plasma sample from each study phase for every subject with and without the addition of internal standard. No significant interferences were observed from endogenous components at the retention times of acetaminophen or internal standard in predose plasma samples.

LINEARITY: For most analytical runs, the coefficients of determination of the calibration lines were greater than 0.977 for acetaminophen. The weighting factor of [1/concentration^2] was used for least-squares linear regression analysis of all study data.

SENSITIVITY: The range of quantification for this assay was between 0.500 and 100 μg/mL for acetaminophen. The lower limit of quantification of the assay was 0.500 μg/mL for acetaminophen. Plasma sample values calculated to be less than 0.500 μg/mL were reported as zero.

ACCURACY AND PRECISION: The accuracy of the assay for acetaminophen was between 93.8% and 103% for all standards and control samples. The inter-run precision of the calibration standards was 1.64% to 4.23% for acetaminophen. The inter-run precision of the control samples was 4.70% to 5.71%.

STABILITY: Plasma samples spiked with known concentrations of acetaminophen were prepared on April 16, 1996. These stability samples were transferred from the clinic and stored with the study samples in the laboratory freezer at -20°C on May 6, 1996. The concentrations prepared were 75 and 1.25 μg/mL of acetaminophen. These stability samples were assayed in duplicate during the course of the sample analysis. The results demonstrate the stability of acetaminophen in plasma for 64 days which covers both the clinical and analytical portion of the study.

The firm has provided following pre-study method validation results:

Accuracy:
Intra-day 89.1% to 97.7%
Inter-day 93.2% to 105%

Precision:
Intra-day 0.995% to 4.98%
Inter-day 3.18% to 11.3%

Sensitivity: The limit of quantification was 0.500 μg/mL for acetaminophen. The intra-day %CV at this concentration ranged from 1.17% to 4.69%.

Standard curve range: 0.500 to 100 μg/mL

Specificity: Six lots of plasma were screened and did not show significant interfering peak for acetaminophen. Several common compounds including nicotine, naproxen, caffeine, ibuprofen and salicylic acid were tested in the chromatographic system. No interferences from these compounds were observed in a sample containing these compounds.

Recovery:

Acetaminophen	0.50 μg/mL	88.1%
	1.00 μg/mL	83.6%
	5.00 μg/mL	81.8%
	50.0 μg/mL	83.0%
Internal Standard	300 μg/mL	93.2%

Stability:

a) Room temperature: stable over 24 hours
   1.00 μg/mL 105%
   50.0 μg/mL 102%
b) Freeze-thaw: stable over 3 cycles. Concentrations (%) after exposing to 3 freeze-thaw cycles:
   1.00 μg/mL 103%
   50.0 μg/mL 96.9%
c) Autosampler: stable over 34 hours

Theoretical	Original	Reinjected after 34 hours
	Concentrations, μg/mL	
100	88.36	89.26
5.0	4.75	4.85
1.00	0.957	0.997
0.50	0.433	0.445

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of acetaminophen at each time point after test (lot 1 and lot 2) and reference products are shown in Table 2. The time courses of acetaminophen concentrations after the three products are plotted in Figure 1.

The pharmacokinetic parameters are summarized in Tables 3 and 4. The firm intends to market only test lot 1 (#6N0778). AUC_{0-t} and AUC_{0-inf} of test lot #1 were about 4% higher than the reference product. The C_{max} of test lot #1 was 7% lower than the reference product and occurred 31 minutes later. The elimination rate constant could not be estimated for subject #14 (Test Lot 1) because the concentrations did not decline continuously. Consequently, half-life and AUC_{0-inf} for this subject could not be calculated.

The individual test lot #1/reference ratio for AUC_{0-t} ranged from 0.80 to 1.54 (mean 1.04), AUC_{0-inf} ranged from 0.80 to 1.50 (mean 1.04) and for C_{max} ranged from 0.69 to 1.22 with a mean of 0.95 (Tables 5 and 6).

The AUC_{0-t}/AUC_{0-inf} ratios range from 0.87 to 0.95 for test lot #1 and 0.89 to 0.97 for reference product (Tables 7 and 8).

The 90% confidence intervals for AUC and C_{max} are within the acceptable limits of 80-125% (Table 4). Statistical analysis of the data show significant sequence effect for AUC_{0-t} (p=0.0774), $LAUC_{0-t}$ (p=0.0754), AUC_{0-inf} (p=0.0638), $LAUC_{0-inf}$ (p=0.0608). Significant treatment effect was observed for C_{max} (p=0.0033) and LC_{max} (p=0.0021).

Bioavailability of Acetaminophen ER Caplets, 650 mg: Non-Fasting Study

A. Objective: (1) To compare the acetaminophen plasma levels produced after administration of the test formulation, with those produced after administration of a marketed reference product, when both products are administered after a standard meal
(2) To compare the acetaminophen plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of the same test formulation, after an overnight fast

B. Study Sites and Investigators:

Clinical and Analytical Site: P
B

Principal Investigator:
Project Director:
Protocol #10972 "Bioavailability of Acetaminophen Extended Release Caplets, 650 mg: Effect of Food Study" was approved by the National Institutional Review Board of

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 88, vol. 1.4.
Study Dates: Period I July 29-31, 1996
Period II August 5-7, 1996
Period III August 12-14, 1996
Analysis Dates: August 29 to September 24, 1996

C. Study Design:

The protocol was designed as a randomized, single oral dose, three-treatment, three-period, six-sequence crossover bioavailability study with a one week wash-out between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at least 16 hours after drug administration. The subjects (who completed the study) were assigned as follows:

Subject number	Period I	Period II	Period III
1,11,15	B	A	C
2,12,17	C	A	B
3,10,13	A	C	B
4,8,14	B	C	A
5,7,16	A	B	C
6,9,18	C	B	A

A= Acetaminophen extended ~~relief~~ release caplets, 1x650 mg following a standard meal; Perrigo Company; Lot #6N0778
B= Tylenol® extended ~~relief~~ release caplets, 1x650 mg following a standard meal; McNeil; Lot #MPM492
C= Acetaminophen extended ~~relief~~ release caplets, 1x650 mg following an overnight fast; Perrigo Company; Lot #6N0778

Lot numbers of drug products administered in this study are the same as those used for the fasting study.

D. Subject Selection:

Eighteen non-smoking subjects (12 females, 6 males) were enrolled in the study with essentially same inclusion and exclusion criteria as used for fasting study.

E. Study Procedure:

Treatments A and B: Subjects were given a standard breakfast after a fast lasting at least 10 hours. The breakfast was served 35 minutes prior to dosing and subjects ate the entire meal

within 30 minutes. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, six fluid oz. of orange juice and eight fluid oz. of whole milk. The drug was administered with 240 mL of water.

Treatment C: Subjects were given the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers 0 (predose), 0.25, 0.50, 0.75, 1, 1.25, 1.50, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 hours. The samples were centrifuged at 2500 rpm, 10°C for 20 minutes. The plasma was separated and stored at -20°C. The samples were transferred to the analytical laboratory on August 15, 1996.

G. Analytical Methods, Pharmacokinetics/Statistics:

Same as for fasting study.

H. Results:

1. Clinical:

All enrolled eighteen subjects completed the study. Two subjects experienced headache and stomachache.

Deviations in the study:

1. There were four sampling deviations of 2, 3, 4, and 4 minutes. The difference in AUC values calculated using actual time versus scheduled time was minimal (0.12% or less) and therefore scheduled times were used for PK calculations.
2. There were three reports of interphase alcohol use (Subject #12 period III, subject #7 period II and III). However, all alcohol consumptions were more than 24 hours prior to dosing.
3. Subject #3,4,5 reported continued use of birth control pills during the study.

Reassays: Of 1026 samples assayed for this study, 28 samples were reassayed for following reasons:

18	pharmacokinetic anomaly
1	suspected or documented processing error
7	chromatographic interference
2	reassayed in error

2. Analytical:

LINEARITY: The coefficients of determination of the calibration lines were greater than 0.979 for acetaminophen.

SENSITIVITY: The range of the assay was 0.500 to 100 μg/mL for acetaminophen. The LOQ was 0.500 μg/mL.

ACCURACY AND PRECISION: The accuracy of the assay for acetaminophen was between 94.6 and 104% for all standards and control samples. The inter-run precision of the standards was 1.48 to 4.75%. The inter-run precision of the control samples was 6.77 to 7.03%.

STABILITY: Plasma samples spiked with 1.25 μg/mL and 75 μg/mL of acetaminophen were prepared on July 29, 1996 and were stored with study samples at -20°C. These stability samples were assayed during the course of study sample analysis. The results demonstrate the stability of acetaminophen in plasma for 57 days which covers both clinical and analytical portions of the study.

Pre-study Method Validation: same as for fasting study.

3. Pharmacokinetics/Statistics:

The concentration of acetaminophen measured at each time point after each product is summarized in Table 9. The time courses of acetaminophen concentration after the three treatments are plotted in Figure 2.

The elimination rate constant could not be reliably estimated for subjects #15 and 17 (test-fed) and for subjects #16 and 18 (reference-fed) because there wasn't a continuous decline in plasma levels at the terminal phase of elimination. Consequently, half-life and AUC_{0-inf} could not be calculated for these subjects.

Test formulation after a meal vs. reference formulation after a meal: There was no significant difference in AUC of the test and reference formulations. The C_{max} of the test formulation was 2% lower than that of the reference product and occurred 11 minutes earlier.

Test formulation after a meal vs. test formulation after a 10 hour fast: The arithmetic means for AUC were almost the same for test-fed and test-fast. The mean C_{max} was 9% higher and 100 minutes earlier in test-fast compared to the test-fed conditions.

The following are the ratios of the means of the pharmacokinetic parameters:

Test-fed/Ref-fed

Parameter	Ratio of Arithmetic means	Ratio of Geometric means
AUC_{0-t}	1.01	1.00
AUC_{0-inf}	0.99	0.99
C_{max}	0.98	0.97

Test-fed/Test-fast

AUC_{0-t}	0.99	1.00
AUC_{0-inf}	0.99	0.99
C_{max}	0.91	0.92

The means of ratios (test-fed/ref-fed) for AUC_{0-t}, AUC_{0-inf}, and C_{max} were 1.008, 1.026, and 0.980 respectively.

Bioavailability of Acetaminophen Caplets, 650 mg: Multidose/Steady-State Study

A. Objective:

To determine the relative bioavailability of test acetaminophen extended release 650 mg caplets to that of a reference formulation at steady-state.

B. Study Sites and Investigators:

Clinical and Analytical Site:
Principal Investigator:
Project Director: [1] Ph.D.
Protocol #10973 'Bioavailability of acetaminophen extended release caplets, 650 mg: Steady-state study' was approved by the Institutional Review Board for
Consent Form: A copy of the volunteer informed consent form used in the study is given on page 87, vol. 1.7.
Study Dates: Period I August 24-29, 1996
Period II September 7-12, 1996
Analysis Dates: September 26-October 10, 1996

C. Study Design:

The study was designed as a randomized, multiple-dose, two-treatment, two-period, two-sequence crossover study, with a one-week period between the last dosing of period I and the first dosing of period II. The subjects were housed in a dormitory facility from approximately 12 hours prior to the first dose until at least 104 hours after the last drug administration for each period. The subjects were assigned to two sequences at random as follows:

Sequence	Subject number	Period I	Period II
1	1,3,6,7,10,12,14,16,17,20, 22,23,25	A	B
2	2,4,5,9,11,13,15,18,19,21, 24,26,27	B	A

A= Acetaminophen extended relief caplets, 1x650 mg; Perrigo
B= Tylenol® extended release caplets, 1x650 mg; McNeil

Lot number of the drug products administered in this study were the same as used for fasting and food study.

The subjects fasted for 10 hours prior to and 4 hours after each morning dose. The other two daily doses were administered after at least a 2 hour fast, which was continued at least 2 hours after dosing. Water was allowed freely except within one hour before, and 2 hours after each dose. The drug products were administered with 240 mL of water. The subjects were dosed at 2 minute intervals and were not allowed to be supine for 4 hours postdose. One 650 mg caplet was administered at 0,8,16,24,32,40, 48,56,64,72,80,88, and 96 hours (every 8 hours, 13 doses) in each period. The steady-state interval was from 96 hours to 104 hours after the first dose, each period. Blood pressure and pulse measurements were obtained predose, 4 hours after the first dose, 4 and 8 hours after the last dose and at discharge from the facility. Diagnostic blood and urine specimens were obtained from the subjects prior to discharge from the study at the end of period II.

D. Subject Selection:

Twenty-six healthy, non-smoking subjects (19 male, 7 female) were enrolled in the study with essentially same inclusion exclusion criteria as used for fasting study.

E. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers at 0 (predose), 24,48,72,96,96.33,96.67,97,97.5,98, 99,100,101,102,103 and 104 hours. The samples were centrifuged at 10°C, 2500 rpm for 20 minutes. The plasma was transferred and stored at -20°C.

F. Analytical Methods:

Same as for fasting study.

G. Pharmacokinetics/Statistics:

The plasma concentrations were used to calculate AUC for the steady state interval (96-104 hours) by linear interpolation between consecutive plasma drug levels. AUC, C_{max}, T_{max}, and C_{min} were calculated over the 96-104 hour steady-state interval. Fluctuation in concentration during the steady-state interval was calculated as $(C_{max}-C_{min})/(AUC_{96-104})/8)x100$ (%). All parameters were analyzed by analysis of variance using type III sum of squares to determine statistically significant differences. The statistical analyses were performed using SAS version 6.11 and PROC GLM for the analysis of variance. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Twenty-six subjects were enrolled. Subject #19 withdrew during period II complaining of lower back pain which began following a motor vehicle accident. Thirteen subjects reported adverse events like headache, nausea, cough, fatigue, diarrhea. None of them required any medications.

Deviations in the study:

1. Subject #8 was withdrawn during period I dosing because he could not swallow the caplet. An alternate subject (#27) was dosed.
2. Subject #2, period I, 96 hour blood sample was drawn 3 minutes late.

Reassays:

Of the 800 samples assayed for this study, 13 samples were reassayed for following reasons:

6	pharmacokinetic anomaly
1	processing error
3	chromatographic interference
2	less than the adjusted LOQ
1	to confirm the presence of peak at the retention time of the drug

2. Analytical:

LINEARITY: The coefficients of determination of the calibration lines were greater than 0.978 for acetaminophen.

SENSITIVITY: The range of the assay was 0.500 to 100 μg/mL. The LOQ was 0.500 μg/mL.

ACCURACY AND PRECISION: The accuracy of the assay for acetaminophen was between 93.8 and 106% for all standards and control samples. The inter-run precision of the standards was 1.30 to 3.10%. The inter-run precision of the control samples was 3.43 to 7.21%.

STABILITY: Plasma samples spiked with 1.25 and 75 μg/mL of acetaminophen were prepared on August 23, 1996 and were stored with study samples at -20°C. These stability samples were assayed during the course of study sample analysis. The results demonstrates the stability of acetaminophen in plasma for 48 days which covers both clinical and analytical portions of the study.

Pre-study Method Validation: same as for fasting study.

3. Pharmacokinetics/Statistics:

The concentration of acetaminophen measured at each time point after each product is summarized in Table 11. The time courses of acetaminophen concentration after the two products are plotted for the 96-104 hour interval (figures 3 and 4). The mean predose concentrations at 48, 72, and 96 hours were 1.85, 1.85 and 1.78 μg/mL for the test formulation and 1.74, 1.80 and 1.59 μg/mL for the reference formulation, respectively. The percent fluctuation in acetaminophen concentration for the 96-104 hour interval was 137% for test and 146% for reference product.

The AUC_{96-104} hours of test product was 4% higher than that of the reference product. There was no difference in C_{max} of the two products, however it occurred 4 minutes later in test compared to reference product. The test product C_{min} was 12% higher than the reference product. The 90% confidence intervals for $LAUC_{96-104}$, LC_{max}, LC_{avg}, and LC_{min} are within 80-125%.

In Vitro Dissolution Testing:

The firm has submitted dissolution testing results on test and reference products. The testing was done using USP apparatus II (paddles) at two speeds (50 and 75 rpm) and four media: water, simulated gastric fluid (without enzyme) pH 1.3, sodium acetate buffer pH 4.3, and potassium phosphate buffer pH 7.5 (see attached).

Comments:

Fasting study:

1. Twenty-seven subjects entered the study. Subject #5 was withdrawn prior to period II dosing because of a rash on both forearms. Six subjects experienced adverse events like headache, nausea, and lightheadedness. None of them required any medications.

2. The fasting study was done with two test products (lot 1 and lot 2) and a reference product as a three treatment, three period, three sequence crossover study. The firm intends to market only test lot 1. The food and multi-dose studies were done with reference product and one test product (lot 1).

3. Fasting study was a three treatment, three period, three sequence crossover study. The reviewer discussed the issue of residual effect with Don Schuirmann. This drug has a short half-life (about 3 to 3½ hours) and there was an adequate wash-out period (7 days) between doses. The drug does not naturally occur in the body and none of the subjects had detectable drug levels at 0 hour in period II and period III. Therfore we should not be concerned about residual effects in this case.

4. AUC_{0-t} and AUC_{0-inf} of test lot 1 were about 4% higher than the reference product. The C_{max} of test lot 1 was 7% lower than the reference product and occurred 31 minutes later.

5. The 90% confidence intervals for AUC and C_{max} are within the acceptable limits of 80-125%. Statistical analysis of the data

show significant sequence effect for AUC_{0-t} (p=0.0774), $LAUC_{0-t}$ (p=0.0754), AUC_{0-inf} (p=0.0638), $LAUC_{0-inf}$ (p=0.0608). Significant treatment effect was observed for C_{max} (p=0.0033) and LC_{max} (p=0.0021).

6. Subject #10, 26, and 27 had their first plasma concentration as C_{max} (test drug lot 2); subject # 3, 17, and 26 had their first plasma concentration as C_{max} (reference drug). The reviewer repeated statistical analysis of the data after deleting subjects 3, 10, 17, 26, and 27. The 90% confidence intervals for pharmacokinetic parameters remained within 80-125% limit.

7. Most of the samples analyzed in this study had acetaminophen plasma concentrations below 11 μg/mL. The firm has used the standard curve of 0.500 to 100 μg/mL and these QC sample concentrations: low 1.25 μg/mL, medium 7.5 μg/mL, and high 75 μg/mL.

8. There was a good agreement between reviewer's calculations and those provided by the firm.

9. The study demonstrates that test product is bioequivalent to the reference product.

Food study:

1. All enrolled eighteen subjects completed the study. Two subjects experienced headache and stomachache.

2. There was no difference in AUC_{0-t} and AUC_{0-inf} of the test and reference formulations administered after a meal. The C_{max} of the test formulation was 2% lower than that of the reference product and occurred 11 minutes earlier.

3. The arithmetic means for AUC were almost the same for test-fed and test-fast. The mean C_{max} was 9% higher and 100 minutes earlier in test-fast compared to the test-fed conditions.

4. Ratio of means as well as mean of ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test fed and reference fed are within acceptable limits.

5. The food study is acceptable.

Multiple-dose Study:

1. Twenty-six subjects were enrolled. Subject #19 withdrew during period II complaining of lower back pain which began following a motor vehicle accident. Thirteen subjects reported adverse events like headache, nausea, cough, fatigue, diarrhea. None of them required any medications.

2. The AUC_{96-104} of test product was 4% higher than that of the reference product. There was no difference in C_{max} of the two products, however it occurred 4 minutes later in test compared to reference product. The test product C_{min} was 12% higher than the reference product. The 90% confidence intervals for $LAUC_{96-104}$, LC_{max}, LC_{avg}, and LC_{min} are within 80-125%.

3. The firm has used 104 hr (last time point) sample values as C_{min}. The reviewer used the lowest value during 96-104 hours period as C_{min}.

4. Statistical analysis of the data was repeated by the reviewer. In general, there was a good agreement between the reviewer's and firm's calculations.

5. The reviewer checked the attainment of steady state in individual subjects by PROC REG programme using the plasma concentrations at 48, 72, and 96 hours. Following subjects showed slopes significantly different from zero (p values <0.05):

Subject	Period	p value
1	1	0.0000
2	1	0.0000
4	1	0.0000
6	2	0.0003
10	1	0.0380
12	2	0.0011
15	2	0.0001
18	1	0.0190
19	1	0.0000

Following 90% confidence intervals were obtained after omitting above subjects from statistical analysis:

$LAUC_{96-104}$	99.07-110.63%
LC_{max}	91.94-108.54%
LC_{min}	97.67-112.26%

The ratio of test/reference mean C_{min} was 1.17.

Dissolution: **NOT TO BE RELEASED UNDER FOI**

There is no USP or FDA method available for acetaminophen ER caplets. The firm has done dissolution testing using four media and two paddle speeds. It is evident from these results that the dissolution of acetaminophen ER caplets is pH independent. {Note: The pKa of acetaminophen is in the range of 9.0 to 10.0 which is outside the range of physiological pH's and therefore changes in the solubility of the drug due to shifts in pH is not expected}.

The caplets are not scored and therefore the dissolution testing on half caplets is not required.

The firm proposes following specifications:

Time (min)	Mean (% of claim)

Method: USP apparatus II (paddles) at **75 rpm in 900 mL water**

The innovator's specifications are:

Time (min)	Mean (% of claim)

Method: USP apparatus II (paddles) **at 50 rpm in 900 mL simulated gastric fluid w/o pepsin, pH 1.2**

The dissolution rate of the test product is slower than the reference product. The test product does not meet the innovator's tolerance limits using innovator's dissolution conditions. If the medium and conditions used by innovator are followed then the tolerances will have to be different for the test product. On the other hand if one adheres to the tolerances of the reference product, then the medium and conditions have to be different for test product. The firm would be recommended to use USP apparatus II (paddles) at 50 rpm and 900 mL simulated gastric fluid w/o pepsin, pH 1.2 as medium to keep the same method as innovator and following tolerances will be recommended for their test product:

Time (min)	Mean (% of claim)

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Perrigo on its acetaminophen ER 650 mg caplets, lot #6N0778, comparing it to the reference product Tylenol® ER 650 mg caplets, lot #MPM492 manufactured by McNeil has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Perrigo's acetaminophen ER 650 mg caplets are bioequivalent to the reference product Tylenol® ER 650 mg caplet manufactured by McNeil.

2. The *in vivo* bioequivalence study conducted under fed conditions by Perrigo on its acetaminophen ER 650 mg caplets, lot #6N0778, comparing it to the reference product Tylenol® ER 650 mg caplets, lot #MPM492 manufactured by McNeil has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Perrigo's acetaminophen ER 650 mg caplets is similar to the reference product Tylenol® ER 650 mg caplet manufactured by McNeil.

3. The *in vivo* multiple-dose steady-state bioequivalence study conducted by Perrigo on its acetaminophen ER 650 mg caplets, lot #6N0778, comparing it to the reference product Tylenol® ER 650 mg caplets, lot #MPM492 manufactured by McNeil has been found acceptable to the Division of Bioequivalence. The study demonstrates that Perrigo's acetaminophen ER 650 mg caplets are bioequivalent to the reference product Tylenol® ER 650 mg caplets manufactured by McNeil.

4. The dissolution testing conducted on acetaminophen ER 650 mg caplets is acceptable. 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 simulated gastric fluid w/o pepsin, pH 1.2 at 37°C using apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

5. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

/S/ 6/26/97
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 6/26/1997

Concur: /S/ Date 11/20/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

Draft: 062097; Final: 062697

Table 1

Quantitative Composition of Acetaminophen 650 mg ER Caplets

Ingredient	mg/unit dose
Acetaminophen,	650
Carnauba Wax,	
Crospovidone,	
Hydroxypropyl Methylcellulose,	
Isononylphenylpolyoxethylene Glycol Ethers@	
Magnesium Stearate,	
Maltodextrin,	
Methacrylic Acid Copolymers@	
Microcrystalline Cellulose,	
Polyethylene Glycol,	
Polysorbate 80,	
Povidone,	
Talc,	
Titanium Dioxide,	
Water, Purified,	
Total Weight	[illegible]

* Individual values for these two ingredients are not available as it is proprietary information of the The value stated is the sum of the individual values.

** Removed during processing

@ These two components constitute

TABLE 2

MEAN PLASMA ACETAMINOPHEN LEVELS FOR TEST AND REFERENCE PRODUCTS IN FASTING STUDY (n=26)
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	2.06	1.91	1.60	1.53	2.60	2.57	1.29
0.5	5.67	2.28	4.87	2.34	6.22	2.41	1.16
0.75	6.13	2.04	5.46	1.86	6.36	1.92	1.12
1	6.03	1.97	5.56	1.85	6.26	1.96	1.08
1.25	6.05	1.90	5.57	1.79	6.07	1.71	1.09
1.5	6.02	1.81	5.40	1.76	5.95	1.80	1.11
2	5.81	1.78	5.14	1.52	5.58	1.78	1.13
2.5	5.49	1.72	5.01	1.45	5.26	1.66	1.10
3	5.09	1.63	4.72	1.39	4.88	1.55	1.08
3.5	4.58	1.48	4.31	1.13	4.57	1.37	1.06
4	4.19	1.35	3.96	1.09	4.14	1.31	1.06
5	3.31	1.19	3.23	1.04	3.18	1.05	1.02
6	2.57	0.98	2.57	0.87	2.41	0.84	1.00
8	1.53	0.69	1.60	0.67	1.46	0.65	0.95
10	0.93	0.56	1.05	0.49	0.86	0.50	0.89
12	0.63	0.45	0.72	0.38	0.49	0.42	0.89
16	0.18	0.36	0.16	0.28	0.11	0.23	1.12

(CONTINUED)

UNIT: PLASMA LEVEL=μg/mL TIME=HRS
MEAN PLASMA ACETAMINOPHEN LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.25	0.79	0.61
0.5	0.91	0.78
0.75	0.96	0.86
1	0.96	0.89
1.25	1.00	0.92
1.5	1.01	0.91
2	1.04	0.92
2.5	1.04	0.95
3	1.04	0.97
3.5	1.00	0.94
4	1.01	0.96
5	1.04	1.01
6	1.07	1.07
8	1.05	1.10
10	1.08	1.21
12	1.31	1.47
16	1.70	1.52

Mean 1= Test Lot 1 (#6N0778)
Mean 2= Test Lot 2 (#6N0780)
Mean 3= Reference

RMEAN 12= ratio Test Lot 1/Test Lot 2
RMEAN 13= ratio Test Lot 1/Reference
RMEAN 23= ratio Test Lot 2/Reference

TABLE 3

ARITHMETIC MEANS AND RATIOS IN FASTING STUDY

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	38.61	13.31	37.64	10.64	37.40	10.91	1.03
AUCT	35.86	12.64	34.26	10.42	34.62	10.76	1.05
CMAX	6.76	1.82	6.39	1.74	7.24	2.03	1.06
KE	0.23	0.06	0.22	0.06	0.25	0.06	1.07
LAUCI	36.72	0.32	36.23	0.28	36.01	0.28	1.01
LAUCT	34.02	0.32	32.82	0.30	33.19	0.29	1.04
LCMAX	6.55	0.25	6.18	0.26	7.00	0.26	1.06
THALF	3.16	0.82	3.41	0.80	2.94	0.66	0.93
TMAX	1.23	0.82	1.08	0.74	0.71	0.33	1.14

(CONTINUED)

UNIT: AUC=μg/mLxhr CMAX=μg/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

PARAMETER	RMEAN13	RMEAN23
AUCI	1.03	1.01
AUCT	1.04	0.99
CMAX	0.93	0.88
KE	0.93	0.87
LAUCI	1.02	1.01
LAUCT	1.03	0.99
LCMAX	0.94	0.88
THALF	1.08	1.16
TMAX	1.73	1.51

MEAN 1= Test Lot 1 (#6N0778)
MEAN 2= Test Lot 2 (#6N0780)
MEAN 3= Reference

RMEAN 12= ratio Test Lot 1/Test Lot 2
RMEAN 13= ratio Test Lot 1/Reference
RMEAN 23= ratio Test Lot 2/Reference

TABLE 4

LSMEANS AND RATIOS IN FASTING STUDY

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	38.51	37.43	37.18	1.03	1.04	1.01
AUCT	35.63	34.07	34.42	1.05	1.04	0.99
CMAX	6.75	6.38	7.22	1.06	0.93	0.88
LAUCI	36.68	36.02	35.79	1.02	1.02	1.01
LAUCT	33.81	32.64	32.99	1.04	1.02	0.99
LCMAX	6.54	6.18	6.98	1.06	0.94	0.88

UNIT: AUC=μg/mLxh CMAX=μg/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSM1	LSM2	LSM3	LOWCI12	UPPCI12	LOWCI13	UPPCI13
AUCI	38.51	37.43	37.18	98.26	107.49	98.92	108.22
AUCT	35.63	34.07	34.42	99.69	109.48	98.69	108.38
CMAX	6.75	6.38	7.22	99.56	111.93	87.95	98.88
LAUCI	36.68	36.02	35.79	97.47	106.38	98.10	107.06
LAUCT	33.81	32.64	32.99	98.93	108.50	97.85	107.32
LCMAX	6.54	6.18	6.98	100.19	111.83	88.63	98.92

(CONTINUED)

UNIT: AUC=μg/mL CMAX=μg/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LOWCI23	UPPCI23
AUCI	96.03	105.32
AUCT	94.15	103.84
CMAX	82.88	93.81
LAUCI	96.34	105.14
LAUCT	94.45	103.59
LCMAX	83.73	93.46

LSM1= Test Lot 1
LSM2= Test Lot 2
LSM3= Reference

RLSM12= ratio Test Lot 1/Test Lot 2
RLSM13= ratio Test Lot 1/Reference
RLSM23= ratio Test Lot 2/Reference

CI 12= Confidence Interval Test Lot 1-Test Lot 2
CI 13= Confidence Interval Test Lot 1-Reference
CI 23= Confidence Interval Test Lot 2-Reference

TABLE 5

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS IN FASTING STUDY

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12	RAUCT13	RAUCI13	RCMAX13
1	1	3									
2	2	1									
3	3	2									
4	4	2									
5	6	3									
6	7	3									
7	8	2									
8	9	1									
9	10	1									
10	11	3									
11	12	2									
12	13	3									
13	14	2									
14	15	1									
15	16	1									
16	17	2									
17	18	3									
18	19	2									
19	20	3									
20	21	1									
21	22	1									
22	23	2									
23	24	3									
24	25	2									
25	26	1									
26	27	3									

OBS	RTMAX13	RKE13	RTHALF13	RAUCT23	RAUCI23	RCMAX23	RTMAX23	RKE23	RTHALF23
1									
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	8.00	0.79	1.26	1.20	1.15	1.15	1.00	0.82	1.21

12= ratio Test Lot 1/Test Lot 2
13= ratio Test Lot 1/Reference
23= ratio Test Lot 2/Reference

TABLE 6

STATISTICS ON THE TEST/REFERENCE RATIOS IN FASTING STUDY

Variable	N	Mean of ratios	Std Dev	Minimum	Maximum
RAUCT12	26	1.04	0.10	0.90	1.22
RAUCI12	25	1.02	0.10	0.87	1.23
RCMAX12	26	1.07	0.17	0.81	1.57
RTMAX12	26	1.70	1.79	0.20	8.00
RKE12	25	1.11	0.25	0.54	1.80
RTHALF12	25	0.95	0.25	0.56	1.85
RAUCT13	26	1.04	0.16	0.80	1.54
RAUCI13	25	1.04	0.15	0.80	1.50
RCMAX13	26	0.95	0.15	0.69	1.22
RTMAX13	26	2.07	1.71	0.40	8.00
RKE13	25	0.95	0.20	0.52	1.43
RTHALF13	25	1.10	0.25	0.70	1.92
RAUCT23	26	1.00	0.19	0.79	1.64
RAUCI23	26	1.02	0.17	0.80	1.60
RCMAX23	26	0.90	0.16	0.65	1.31
RTMAX23	26	1.76	1.34	0.17	6.00
RKE23	26	0.88	0.16	0.50	1.18
RTHALF23	26	1.18	0.26	0.85	1.98

TABLE 7

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS
IN FASTING STUDY

OBS	SUB	TRT	AUCRATIO
1	1		
2	2		
3	3		
4	4		
5	6		
6	7		
7	8		
8	9		
9	10		
10	11		
11	12		
12	13		
13	14		
14	15		
15	16		
16	17		
17	18		
18	19		
19	20		
20	21		
21	22		
22	23		
23	24		
24	25		
25	26		
26	27		
27	1		
28	2		
29	3		
30	4		
31	6		
32	7		
33	8		
34	9		
35	10		
36	11		
37	12		
38	13		
39	14		
40	15		
41	16		
42	17		
43	18		
44	19		
45	20		
46	21		
47	22		
48	23		
49	24		
50	25		
51	26		
52	27		

TRT 1= Test Lot 1
TRT 2= Test Lot 2

Continued

TABLE 8

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS
IN FASTING STUDY

OBS	SUB	TRT	AUCRATIO
53	1		
54	2		
55	3		
56	4		
57	6		
58	7		
59	8		
60	9		
61	10		
62	11		
63	12		
64	13		
65	14		
66	15		
67	16		
68	17		
69	18		
70	19		
71	20		
72	21		
73	22		
74	23		
75	24		
76	25		
77	26		
78	27	3	0.8.

STATISTICS ON AUCT/AUCI RATIOS

	N	Mean	Std Dev	Minimum	Maximum
TRT 1 (Test Lot 1)	25	0.92	0.02	0.87	0.95

	N	Mean	Std Dev	Minimum	Maximum
TRT 2 (Test Lot 2)	26	0.91	0.03	0.86	0.96

	N	Mean	Std Dev	Minimum	Maximum
TRT 3 (Reference)	26	0.92	0.02	0.89	0.97

TABLE 9

MEAN PLASMA ACETAMINOPHEN LEVELS FOR TEST AND REFERENCE PRODUCTS IN NONFASTING STUDY (n=18)
ARITHMETIC MEANS AND RATIOS

TIME (HR)	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	2.33	1.53	0.18	0.59	0.00	0.00	13.03
0.5	5.82	2.35	1.11	1.86	0.53	0.69	5.23
0.75	6.16	1.93	2.03	2.16	1.96	1.94	3.04
1	6.12	1.60	3.02	2.14	3.52	2.34	2.03
1.25	6.34	1.68	4.14	2.09	4.32	2.37	1.53
1.5	6.19	1.61	4.83	2.01	5.02	2.15	1.28
2	5.72	1.32	5.66	1.65	5.51	1.90	1.01
2.5	5.42	1.31	5.96	1.63	5.77	1.66	0.91
3	4.80	1.28	5.79	1.31	5.77	1.83	0.83
3.5	4.32	1.19	5.46	1.57	5.43	1.35	0.79
4	3.76	1.14	4.83	1.52	4.98	1.44	0.78
4.5	3.34	1.24	4.07	1.12	4.18	1.20	0.82
5	2.90	0.90	3.53	1.00	3.65	1.09	0.82
6	2.24	1.00	2.59	0.76	2.74	1.26	0.87
8	1.27	0.59	1.49	0.50	1.44	0.84	0.85
10	0.71	0.55	0.89	0.39	0.79	0.49	0.80
12	0.29	0.40	0.37	0.41	0.36	0.43	0.78
16	0.03	0.13	0.13	0.31	0.08	0.23	0.24

(CONTINUED)

UNIT: PLASMA LEVEL=μg/mL TIME=HRS

TIME HR	RMEAN13	RMEAN23
0	.	.
0.25	.	.
0.5	11.05	2.11
0.75	3.15	1.04
1	1.74	0.86
1.25	1.47	0.96
1.5	1.23	0.96
2	1.04	1.03
2.5	0.94	1.03
3	0.83	1.00
3.5	0.79	1.00
4	0.76	0.97
4.5	0.80	0.97
5	0.79	0.97
6	0.82	0.94
8	0.88	1.04
10	0.90	1.12
12	0.80	1.03
16	0.39	1.66

MEAN 1= Test-fast
MEAN 2= Test-fed
MEAN 3= Ref-fed

RMEAN 12= ratio Test-fast/Test-fed
RMEAN 13= ratio Test-fast/Ref-fed
RMEAN 23= ratio Test-fed/Ref-fed

TABLE 10

ARITHMETIC MEANS AND RATIOS IN NONFASTING STUDY

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	34.89	10.65	34.42	10.16	34.76	9.53	1.01
AUCT	32.25	10.41	32.12	9.39	31.83	8.30	1.00
CMAX	7.02	2.02	6.41	1.71	6.57	1.69	1.09
KE	0.28	0.07	0.27	0.05	0.31	0.08	1.02
LAUCI	33.58	0.28	33.18	0.27	33.59	0.27	1.01
LAUCT	30.94	0.29	30.97	0.27	30.86	0.25	1.00
LCMAX	6.76	0.27	6.21	0.26	6.40	0.23	1.09
THALF	2.65	0.59	2.65	0.54	2.43	0.75	1.00
TMAX	0.90	0.43	2.58	0.65	2.76	1.31	0.35

(CONTINUED)

UNIT: AUC=μg/mLxhr CMAX=ug/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.00	0.99
AUCT	1.01	1.01
CMAX	1.07	0.98
KE	0.90	0.89
LAUCI	1.00	0.99
LAUCT	1.00	1.00
LCMAX	1.06	0.97
THALF	1.09	1.09
TMAX	0.33	0.93

MEAN 1= Test-fast
MEAN 2= Test-fed
MEAN 3= Ref-fed

RMEAN 12= Test-fast/Test-fed
RMEAN 13= Test-fast/Ref-fed
RMEAN 23= Test-fed/Ref-fed

TABLE 11

MEAN PLASMA ACETAMINOPHEN LEVELS (μg/mL) FOR TEST AND REFERENCE PRODUCTS IN MULTIDOSE STUDY (n=25): ARITHMETIC MEANS AND RATIOS

TIME (HR)	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.0	0.0	0.0	0.0	0.0
24	2.02	0.79	1.95	0.60	1.04
48	1.85	0.75	1.74	0.65	1.06
72	1.85	0.75	1.80	0.69	1.03
96	1.78	0.64	1.59	0.73	1.12
96.33	4.60	1.90	4.98	2.55	0.92
96.67	6.08	1.76	6.05	1.83	1.00
97	6.09	1.59	5.84	1.45	1.04
97.5	5.83	1.50	5.61	1.41	1.04
98	5.55	1.64	5.24	1.40	1.06
99	4.72	1.42	4.44	1.33	1.06
100	3.75	1.11	3.57	1.08	1.05
101	3.01	0.99	2.85	0.83	1.06
102	2.39	0.82	2.24	0.64	1.07
103	1.88	0.70	1.78	0.56	1.06
104	1.46	0.56	1.40	0.50	1.04

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	29.95	8.71	28.70	7.72	1.04
CAVG	3.74	1.09	3.59	0.97	1.04
CMAX	6.47	1.65	6.47	1.78	1.00
CMIN	1.46	0.55	1.30	0.57	1.12
FLUC1	1.37	0.25	1.46	0.27	0.94
LAUCT	28.81	0.28	27.74	0.27	1.04
LCAVG	3.60	0.28	3.47	0.27	1.04
LCMAX	6.28	0.25	6.24	0.27	1.00
LCMIN	1.36	0.37	1.27	0.34	1.07
LFLUC1	1.35	0.16	1.43	0.19	0.95
LTMAX	00.91	0.00	00.84	0.00	1.08
TMAX	00.91	0.46	00.84	0.46	1.08

UNIT: AUC=μg/mLxh CMAX=μg/mL TMAX=hr

LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCT	29.87	28.67	99.35	109.05
CAVG	3.73	3.58	99.35	109.05
CMAX	6.46	6.47	93.08	106.46
CMIN	1.45	1.29	98.70	125.10
FLUC1	1.37	1.46	86.48	101.89
LAUCT	28.73	27.71	99.33	108.18
LCAVG	3.59	3.46	99.33	108.18
LCMAX	6.26	6.24	94.06	106.85
LCMIN	1.35	1.29	98.30	111.39
LFLUC1	1.35	1.43	87.69	101.91
LTMAX	00.91	00.84		
TMAX	00.91	00.84		

Mean 1= Test; Mean 2= Reference
Rmean 12= ratio Test/Reference
CI 12= Confidence Interval Test-Reference

TABLE 12

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS IN MULTIDOSE STUDY

OBS	SUB	SEQ	RAUCT12	RCMIN12	RCMAX12	RCAVG12	RFLUC112	RTMAX12
1	1	1						
2	2	2						
3	3	1						
4	4	2						
5	5	2						
6	6	1						
7	7	1						
8	9	2						
9	10	1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
10	11	2						
11	12	1						
12	13	2						
13	14	1						
14	15	2						
15	16	1						
16	17	1						
17	18	2						
18	20	1						
19	21	2						
20	22	1						
21	23	1						
22	24	2						
23	25	1						
24	26	2						
25	27	2						

UNIT: AUC=μg/mLxh CMAX=μg/mLxh TMAX=HR
STATISTICS ON THE TEST/REFERENCE RATIOS

Variable	N	Mean of ratios	Std Dev	Minimum	Maximum
RAUCT12	25	1.05	0.14	0.76	1.36
RCMIN12	24	1.06	0.19	0.85	1.53
RCMAX12	25	1.02	0.20	0.65	1.43
RCAVG12	25	1.05	0.14	0.76	1.36
RFLUC112	25	0.97	0.21	0.63	1.53
RTMAX12	25	1.33	0.91	0.33	3.03

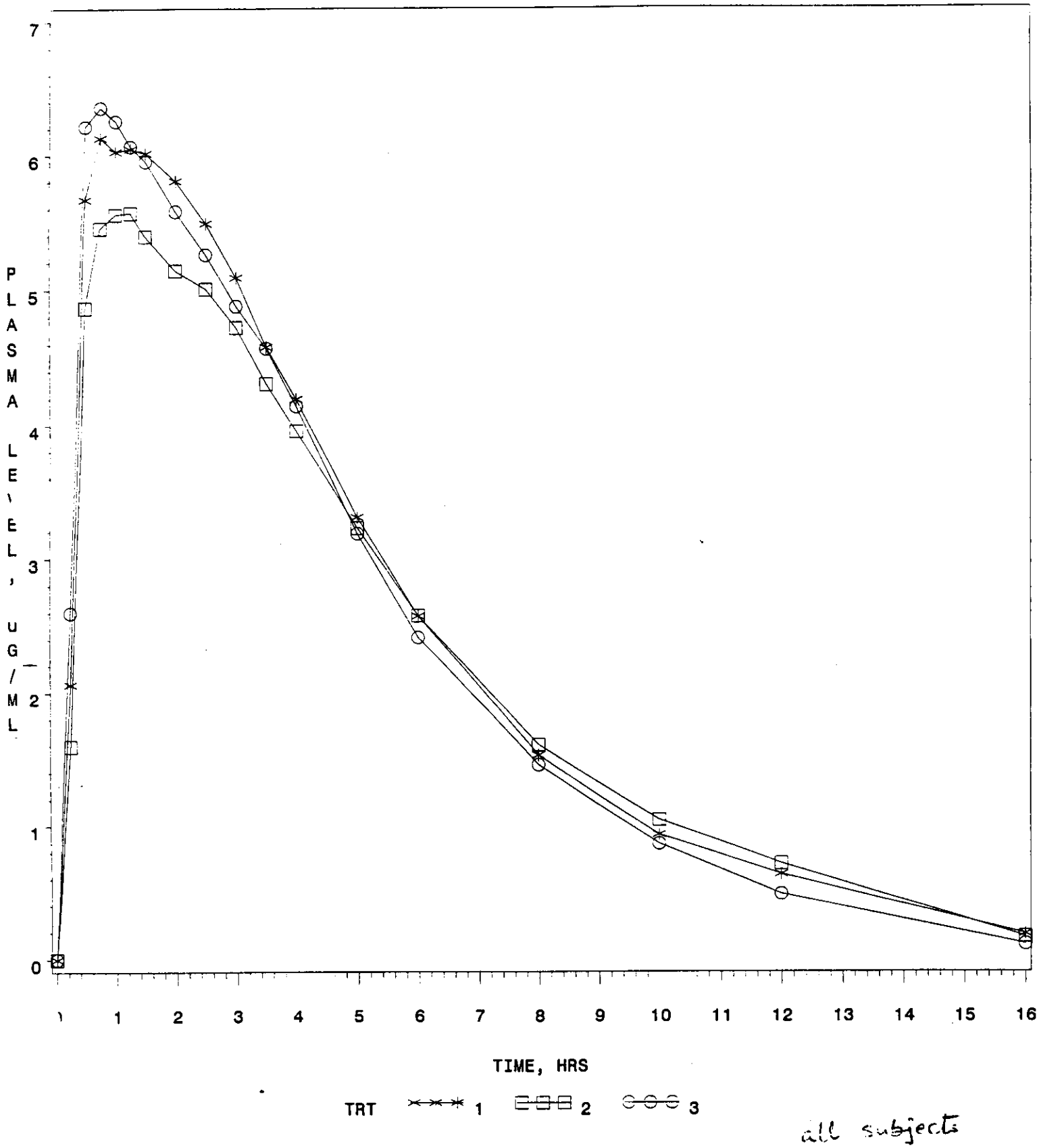
TABLE 13

CMIN AND FLUCT IN INDIVIDUAL SUBJECTS

OBS	SUB	PER	CMIN	FLUC1
1	1	1		4
2	2	2		7
3	3	1		2
4	4	2		8
5	5	2		9
6	6	1		6
7	7	1		1
8	9	2		0
9	10	1		4
10	11	2		4
11	12	1		1
12	13	2		4
13	14	1		0
14	15	2		5
15	16	1		6
16	17	1		5
17	18	2		2
18	20	1		4
19	21	2		3
20	22	1		4
21	23	1		3
22	24	2		3
23	25	1		7
24	26	2		3
25	27	2		5
26	1	2		5
27	2	1		7
28	3	2		2
29	4	1		5
30	5	1		9
31	6	2		7
32	7	2		5
33	9	1		3
34	10	2		1
35	11	1		3
36	12	2		.
37	13	1		.
38	14	2		9
39	15	1		.
40	16	2		0
41	17	2		7
42	18	1		2
43	20	2		3
44	21	1		1
45	22	2		1
46	23	2		5
47	24	1		5
48	25	2		9
49	26	1		7
50	27	1		3

FIG P-1. PLASMA ACETAMINOPHEN LEVELS

ACETAMINOPHEN ER CAPLETS, 650 MG, ANDA #75-077
UNDER FASTING CONDITIONS
DOSE=1 X 650 MG



all subjects

FIG P-2. PLASMA ACETAMINOPHEN LEVELS

ACETAMINOPHEN ER CAPLETS, 650 MG, ANDA #75-077
UNDER NONFASTING CONDITIONS
DOSE=1 X 650 MG

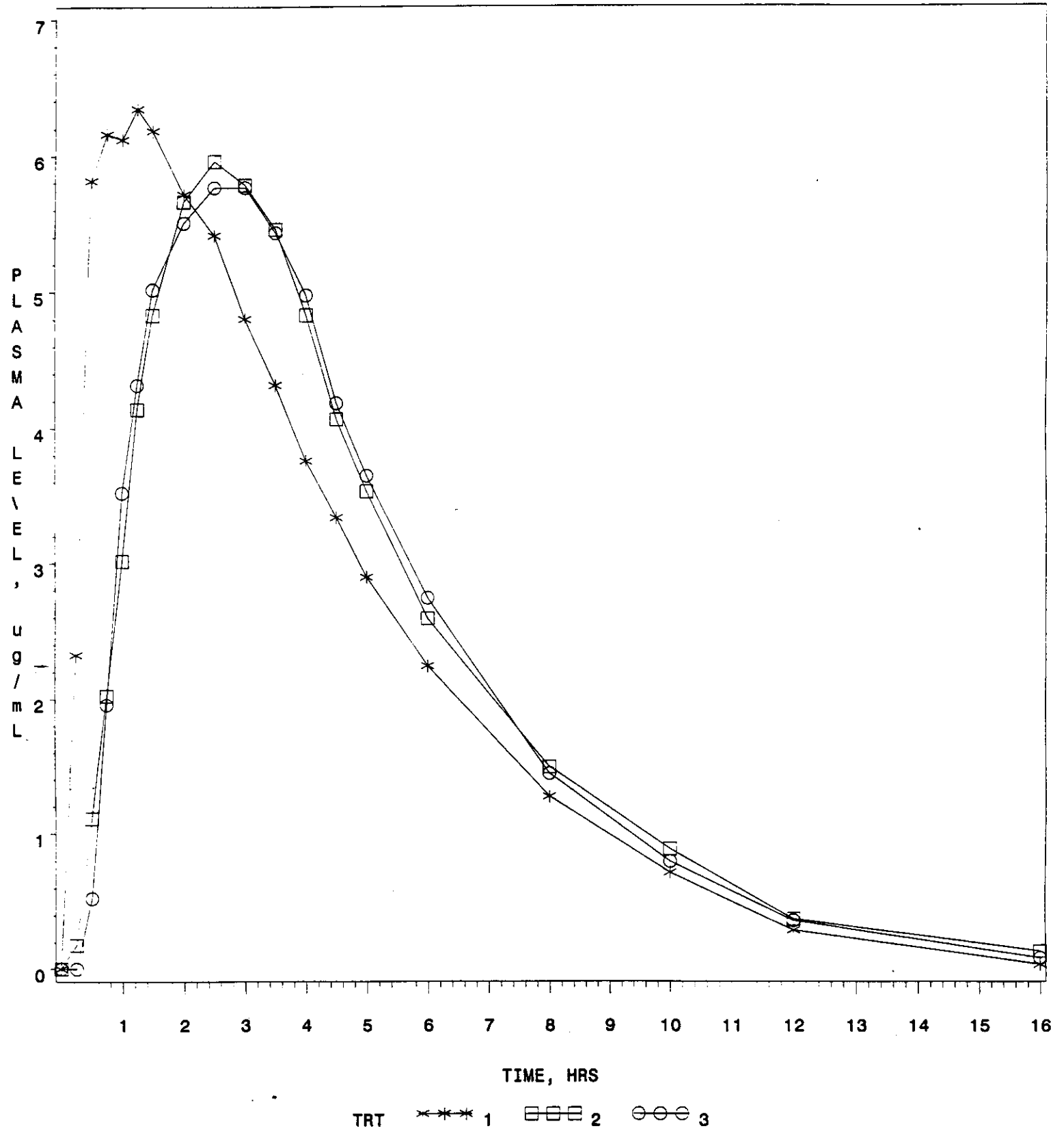


FIG P-3. PLASMA ACETAMINOPHEN LEVELS IN THE LAST DOSING INTERVAL

ACETAMINOPHEN ER CAPLETS, 650 MG, ANDA #75-077
UNDER MULTIPLE-DOSE STEADY-STATE CONDITIONS
DOSE=1 X 650 MG, DOSING INTERVAL(TAU)=8 HOURS

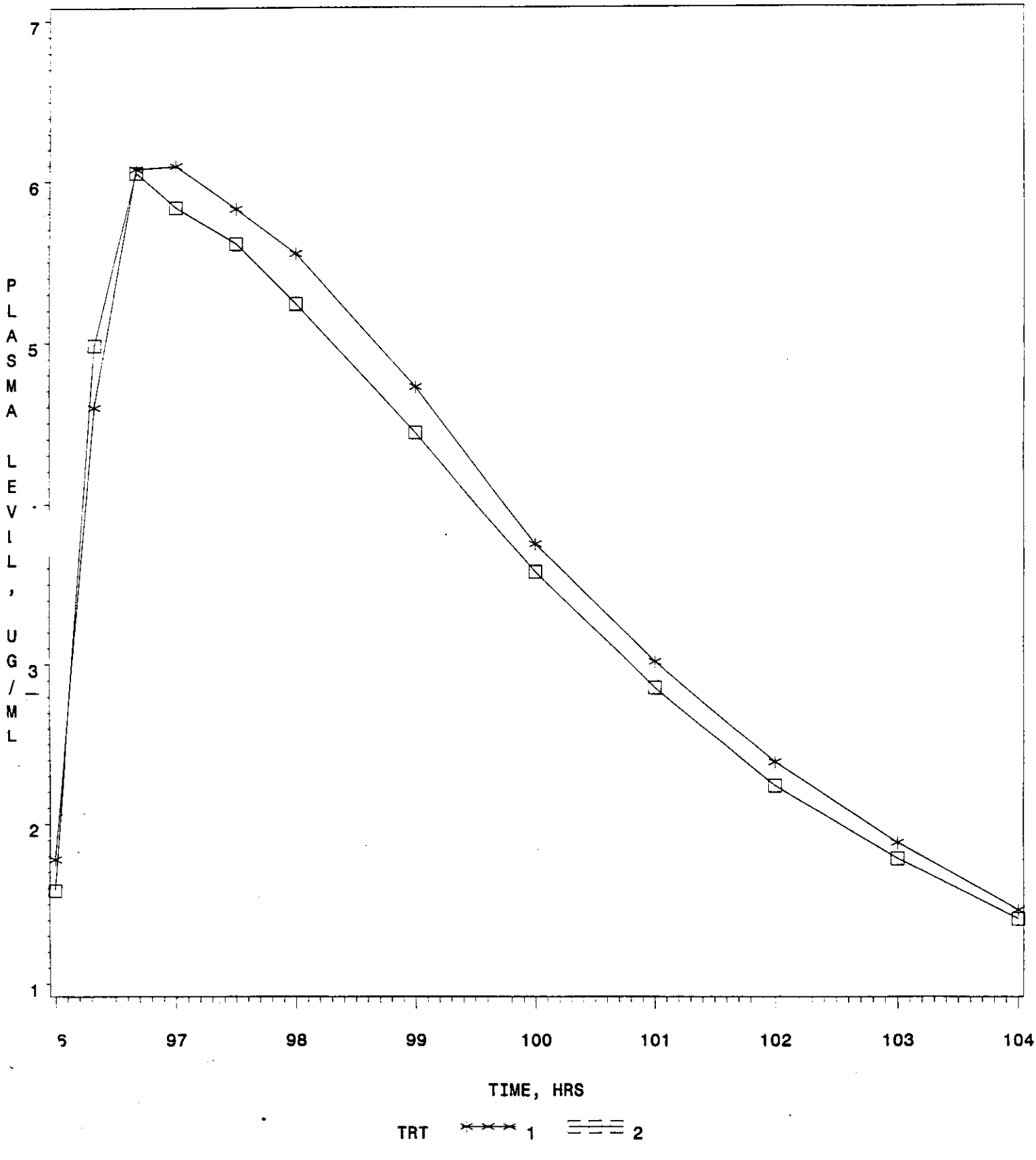
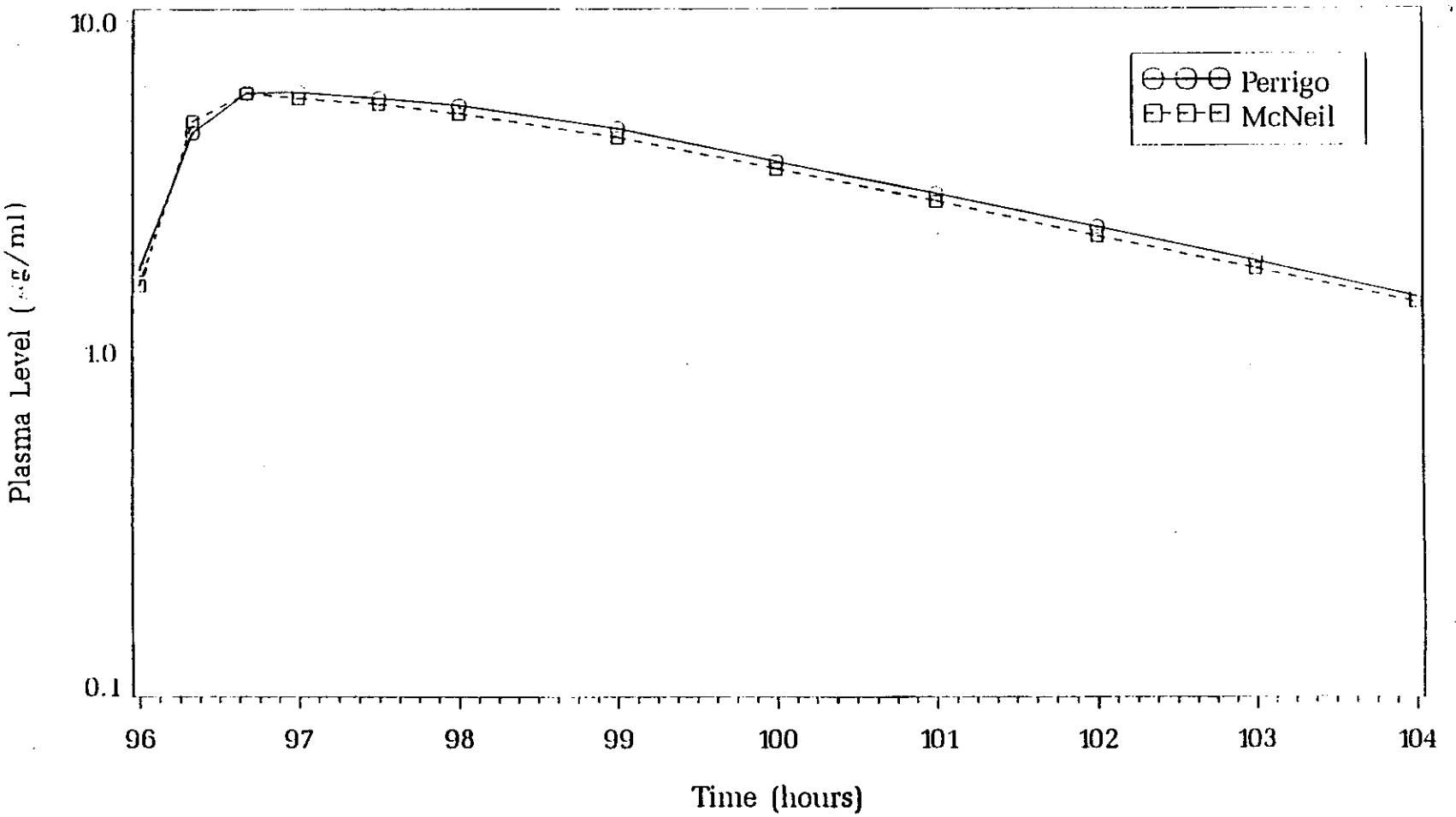


Figure 4: Mean Acetaminophen Plasma Levels (Semi—log Scale)
Steady State Interval
#116—16—10973
N = 25



PERRIGO COMPANY
ANALYTICAL R&D
SPECIAL ASSAY REQUEST

SAMPLE (S): Extented Release Acetaminophen — **NO:** 11321

PRODUCT CODE: 544XC / N.B. — **LOT:** 6N0778 / MPM492

SOURCE: Tablet R&D — **REQUESTED BY:** S. Gylys

TESTED BY: A. Pifer — **REFERENCE:** AD172P115-9

OBJECTIVE: Compare the Acetaminophen release rates of the Perrigo PC544XC (Lot 6N0778) to the release rates of the National Brand (Lot MPM492) using the same dissolution conditions.

DISSOLUTION CONDITIONS: 900mL of 37°C (± 0.5°C) degassed water, USP Apparatus II (Paddles) at 50rpm

DISSOLUTION RESULTS:

PC544XC LOT#6N0778							
TABLET SAMPLE	TIME (In minutes) OF EACH SAMPLING						
1							
2							
3							
4							
5							
6							
7							
8	30	43	58	69	83	89	
9							
10							
11							
12							
Avg %	35	43	53	64	80	88	93

SC

NATIONAL BRAND LOT#MPM492							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	52	56	64	77	93	99	99

PREPARED BY: D. Andrew-Pfizer **DATE:** 10/30/96 **CHK BY:** SG

COPIES: S. Gylys, D. Jespersen, B. Pileggi, J. Eaton, S. Shah, P. Gogineni

PERRIGO COMPANY
ANALYTICAL R&D
SPECIAL ASSAY REQUEST

SAMPLE (S): Extented Release Acetaminophen

NO: 11322

PRODUCT CODE: 544XC / N.B.

LOT: 6N0778 / MPM492

SOURCE: Tablet R&D

REQUESTED BY: S. Gylys

TESTED BY: A. Pifer

REFERENCE: AD162P69
AD163P55-6

OBJECTIVE: Compare the Acetaminophen release rates of the Perrigo PC544XC (Lot 6N0778) to the release rates of the National Brand (Lot MPM492) using the same dissolution conditions.

DISSOLUTION CONDITIONS: 900mL of 37°C (± 0.5°C) degassed water, USP Apparatus II (Paddles) at 75rpm

DISSOLUTION RESULTS:

PC544XC LOT#6N0778							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	51	54	62	74	89	95	97

NATIONAL BRAND LOTMPM492							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9	5						
10							
11							
12							
Avg %	54	58	68	83	97	98	98

PREPARED BY: D Andrew Pfau **DATE:** 10/30/96 **CHK BY:** SG

COPIES: S. Gylys, D. Jespersen, B. Pileggi, J. Eaton, S. Shah, P. Gogineni

PERRIGO COMPANY
ANALYTICAL R&D
SPECIAL ASSAY REQUEST

SAMPLE (S): Extented Release Acetaminophen **NO:** 11323

PRODUCT CODE: 544XC / N.B. **LOT:** 5N0778 / MPM492

SOURCE: Tablet R&D **REQUESTED BY:** S. Gylys

TESTED BY: A. Pifer **REFERENCE:** AD172P115-9

OBJECTIVE: Compare the Acetaminophen release rates of the Perrigo PC544XC (Lot 6N0778) to the release rates of the National Brand (Lot MPM492) using the same dissolution conditions.

DISSOLUTION CONDITIONS: 900mL of 37°C (± 0.5°C) degassed pH 1.3 Simulated Gastric Fluid (without enzyme) USP Apparatus II (Paddles) at 50rpm

DISSOLUTION RESULTS:

PC544XC LOT6N0778							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	38	41	49	60	76	85	90

84

NATIONAL BRAND LOTMPM492							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	50	55	63	74	89	96	98

PREPARED BY: D. Andrew Apt **DATE:** 10/30/96 **CHK BY:** SG

COPIES: S. Gylys, D. Jespersen, B. Pileggi, J. Eaton, S. Shah, P. Gogineni

PERRIGO COMPANY
ANALYTICAL R&D
SPECIAL ASSAY REQUEST

SAMPLE (S): Extented Release Acetaminophen **NO:** 11324

PRODUCT CODE: 544XC / N.B. **LOT:** 6N0778 / MPM492

SOURCE: Tablet R&D **REQUESTED BY:** S. Gylys

TESTED BY: A. Pifer **REFERENCE:** AD172P115-9

OBJECTIVE: Compare the Acetaminophen release rates of the Perrigo PC544XC (Lot 6N0778) to the release rates of the National Brand (Lot MPM492) using the same dissolution conditions.

DISSOLUTION CONDITIONS: 900mL of 37°C (± 0.5°C) degassed pH 1.3 Simulated Gastric Fluid (without enzyme) USP Apparatus II (Paddles) at 75rpm

DISSOLUTION RESULTS:

PC544XC LOT6N0778							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							97
9							
10							
11							
12							
Avg %	50	53	61	73	88	94	97

NATIONAL BRAND LOTMPM492							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	55	60	69	82	97	99	99

PREPARED BY: D. Andrew Ffa **DATE:** 10/30/96 **CHK BY:** SG

COPIES: S. Gylys, D. Jespersen, B. Pileggi, J. Eaton, S. Shah, P. Gogineni

PERRIGO COMPANY
ANALYTICAL R&D
SPECIAL ASSAY REQUEST

SAMPLE (S): Extented Release Acetaminophen — **NO:** 11325

PRODUCT CODE: 544XC / N.B. — **LOT:** 6N0778 / MPM492

SOURCE: Tablet R&D — **REQUESTED BY:** S. Gylys

TESTED BY: A. Pifer — **REFERENCE:** AD172P115-9

OBJECTIVE: Compare the Acetaminophen release rates of the Perrigo PC544XC (Lot 6N0778) to the release rates of the National Brand (Lot MPM492) using the same dissolution conditions.

DISSOLUTION CONDITIONS: 900mL of 37°C (± 0.5°C) degassed pH 4.3 Sodium Acetate Buffer
USP Apparatus II (Paddles) at 50rpm

DISSOLUTION RESULTS:

PC544XC LOT#6N0778							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	40	43	50	62	76	84	89

NATIONAL BRAND LOT#MPM492							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	50	55	63	76	91	97	97

PREPARED BY: D. Andrew Pfeiffer **DATE:** 10/30/96 **CHK BY:** SG

COPIES: S. Gylys, D. Jespersen, B. Pileggi, J. Eaton, S. Shah, P. Gogineni

PERRIGO COMPANY
ANALYTICAL R&D
SPECIAL ASSAY REQUEST

SAMPLE (S): Extented Release Acetaminophen **NO:** 11326

PRODUCT CODE: 544XC / N.B. **LOT:** 6N0778 / MPM492

SOURCE: Tablet R&D **REQUESTED BY:** S. Gylys

TESTED BY: A. Pifer **REFERENCE:** AD172P115-9

OBJECTIVE: Compare the Acetaminophen release rates of the Perrigo PC544XC (Lot 6N0778) to the release rates of the National Brand (Lot MPM492) using the same dissolution conditions.

DISSOLUTION CONDITIONS: 900mL of 37°C (± 0.5°C) degassed pH 4.3 Sodium Acetate Buffer
USP Apparatus II (Paddles) at 75rpm

DISSOLUTION RESULTS:

PC544XC LOT#6N0778							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	48	52	60	72	86	92	94

NATIONAL BRAND LOT#MPM492							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	53	57	68	83	96	97	97

PREPARED BY: D. Andrew Yen **DATE:** 10/30/96 **CHK BY:** SG

COPIES: S. Gylys, D. Jespersen, B. Pileggi, J. Eaton, S. Shah, P. Gogineni

PERRIGO COMPANY
ANALYTICAL R&D
SPECIAL ASSAY REQUEST

SAMPLE (S): Extented Release Acetaminophen — **NO:** 11327

PRODUCT CODE: 544XC / N.B. — **LOT:** 6N0778 / MPM492

SOURCE: Tablet R&D — **REQUESTED BY:** S. Gylys

TESTED BY: A. Pifer — **REFERENCE:** AD172P115-9

OBJECTIVE: Compare the Acetaminophen release rates of the Perrigo PC544XC (Lot 6N0778) to the release rates of the National Brand (Lot MPM492) using the same dissolution conditions.

DISSOLUTION CONDITIONS: 900mL of 37°C (± 0.5°C) degassed pH7.5 Potassium Phosphate Buffer
USP Apparatus II (Paddles) at 50rpm

DISSOLUTION RESULTS:

PC544XC LOT#6N0778

TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12				--	--	--	--
Avg %	35	42	51	62	77	84	89

[1]Sampling probes not in vessels 1 and 2 at 10 minutes.

92

NATIONAL BRAND LOT#MPM492							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	51	55	63	76	92	97	98

PREPARED BY: D Andrew PK **DATE:** 10/30/96 **CHK BY:** SG

COPIES: S. Gylys, D. Jespersen, B. Pileggi, J. Eaton, S. Shah, P. Gogineni

PERRIGO COMPANY
ANALYTICAL R&D
SPECIAL ASSAY REQUEST

SAMPLE (S): Extented Release Acetaminophen — **NO:** 11328

PRODUCT CODE: 544XC / N.B. — **LOT:** 6N0778 / MPM492

SOURCE: Tablet R&D — **REQUESTED BY:** S. Gylys

TESTED BY: A. Pifer — **REFERENCE:** AD172P115-9

OBJECTIVE: Compare the Acetaminophen release rates of the Perrigo PC544XC (Lot 6N0778) to the release rates of the National Brand (Lot MPM492) using the same dissolution conditions.

DISSOLUTION CONDITIONS: 900mL of 37°C (± 0.5°C) degassed pH7.5 Potassium Phosphate Buffer
USP Apparatus II (Paddles) at 75rpm

DISSOLUTION RESULTS:

PC544XC LOT#6N0778							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	51	55	63	75	90	95	98

NATIONAL BRAND LOT#MPM492							
TABLET SAMPLE	TIME (in minutes) OF EACH SAMPLING						
	10	15	30	60	120	180	240
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Avg %	54	58	67	82	97	97	98

PREPARED BY: D. Andrew **DATE:** 10/10/96 **CHK BY:** SG

COPIES: S. Gylys, D. Jespersen, B. Pileggi, J. Eaton, S. Shah, P. Gogineni

2-1

Acetaminophen
Extended Release Tablets, 650 mg
ANDA #75-077
Reviewer: Kuldeep R. Dhariwal
File name: 75077DSI.699

L. Perrigo Company
117 Water Street
Allegan, MI 49010

Addendum to Review
(Review of DSI report: June 21, 1999)

This ANDA for first generic was reviewed and found acceptable to the Division of Bioequivalence (file name: 75077SD.297). At our request, the Division of Scientific Investigations (DSI) conducted an audit of the bioequivalence studies submitted in this ANDA (report attached). Following the inspection, the DSI recommends that the OGD reviewer should evaluate if the following two findings would impact the outcome of the studies:

1. The smoking and alcohol history information reported in the screening worksheets was inconsistent. For example, screening worksheets obtained on 7/19/96 for study-15-10972 (food study) stated that subject 8 stopped using tobacco in January 96, while an earlier (4/23/96) screening chart for the same subject reported that he stopped using tobacco in March 96. Note that subject 8 would have been ineligible for study-15-10972 based on his smoking history reported on 4/23/96, as the protocol excludes subjects who smoked within 6 months prior to the study. Similar findings were also uncovered for subject 12 in study-15-10972 and subjects 2 and 18 in study-16-10973 (multi-dose study). As a result, the accuracy of smoking and alcohol history for these subjects could not be verified.

Reviewer's comment:

This should not affect the outcome of the food and multi-dose studies.

2. There was no documentation to confirm that subject 9 in period III (food study) met the criterion of no alcohol consumption or OTC medication for at least 24 hours prior to dosing. His Check-In Assessment form was not signed or dated by the attending nurse. Hence, it was not possible to verify if the study nurse questioned subject 9 for concomitant medication and alcohol consumption prior to dosing in period III.

Reviewer's comment:

This should not affect the outcome of the study.

Conclusions:

The above DSI findings do not affect the outcome of the studies. The earlier recommendations remain unchanged.

Kuldeep [illegible] Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ /S/ Date 7/9/99

Concur: _____ Date 7/14/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-077 Major Amendment APPLICANT: L. Perrigo

DRUG PRODUCT: Acetaminophen Extended Release Tablets, 650 mg

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

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

The dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2, at 37°C, using USP Apparatus II(paddles) at 50 rpm. The test product should meet the following interim specifications:

0%

1

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

2.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-077 Major Amendment APPLICANT: L. Perrigo

DRUG PRODUCT: Acetaminophen Extended Release Tablets, 650 mg

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

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

> The dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2, at 37°C, using USP Apparatus II(paddles) at 50 rpm. The test product should meet the following interim specifications:

75%

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Acetaminophen
Extended Release Tablets, 650 mg
Caplets (capsule shaped tablet)
ANDA #75-077
Reviewer: Kuldeep R. Dhariwal
File name: 75077SD.598

L. Perrigo Company
117 Water Street
Allegan, MI 49010
Submission Date:
May 8, 1998

Review of Amendment

Background:

Perrigo submitted ANDA #75077 on February 10, 1997 for first generic acetaminophen extended release tablets, 650 mg. The bioequivalence studies were reviewed by this reviewer and were found acceptable (file name: 75077SD.297). The dissolution testing conducted by the firm were found acceptable. The firm was informed that dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2 using USP apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

The firm submitted a major amendment on may 8, 1998 responding mainly to the chemistry deficiencies. In this amendment, firm has also responded to the above dissolution specifications given by the Division of Bioequivalence.

The firm states the following:

1. Based on dissolution testing performed on the bio-lots, our product meets these specifications but the reference listed drug does not.

2. At this time we have not manufactured a sufficient number of batches of the drug product to ascertain that these limits are appropriate in consideration of the unique controlled drug release mechanism used for the Perrigo product. We will evaluate the applicability of the recommended specifications

following the manufacture and stability testing of an adequate number of batches following the approval of this application.

Comments:

1. The specifications were given for test product and the firm should not be concerned if the reference drug does not meet the specs.

2. The dissolution method and specifications will not be changed at this time. The firm will be informed that these specifications are interim.

/S/ 9/98
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

/S/
RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 9/28/1998

Concur: /S/ Date 10/2/98
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-077

ADMINISTRATIVE DOCUMENTS

Tentative

Nebraska, St.
10.5.99
9.1

(APPROVAL SUMMARY, FIRST GENERIC)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-077** Date of Submission: **September 23, 1999**

Applicant's Name: **Perrigo Company**

Established Name: **Acetaminophen Extended-release Tablets, 650 mg**

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 24s & 300s

Satisfactory in computer generated printer's proof as of 9/23/99 submission

Carton Labeling: 24s

Satisfactory in computer generated printer's proof as of 9/23/99 submission

Revisions needed post-approval:

None

Before full approval, check to see whether RLD is in the new "Drug FACTS" format.
• WARNINGS BOLDED & CAPS (Not as of 12/8/99 Chan)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Tylenol® extended Relief

NDA Number: 19-872

NDA Drug Name: Acetaminophen extended-release tablets

No labeling revision approved in CCMS

NDA Firm: McNeil

Date of Approval of NDA Insert and supplement #: no labeling supplements. NDA 19-872 was approved June 8, 1994.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: listed Drug

Basis of Approval for the Carton Labeling: listed drug

Other Comments:

The sponsor has requested for determination of eligibility for Market Exclusivity in this submission of September 23, 1999.

FOR THE RECORD:

1. Review based on the listed drug Tylenol (ANDA 19-872 McNeil; Approved June 8, 1994). There is no labeling supplement approved.

2. There are three patents. # 4968509 11/6/2007
5004613 7/27/2007
4820522 7/27/2007

The firm has filed a Paragraph IV patent non-infringement certification.

3. This appears to be the first generic. The firm has requested that the Agency make a determination as eligibility for 180 days of market exclusivity for this product.

4. Storage and Dispensing Statement

NDA: Store at room temperature. Avoid excessive heat ($40^{o}C$).
ANDA: same

USP: not a USP item.

5. Package size - Both the listed drug and generic have the 24 tablet package size. ANDA has 300s package size as well. Both with CRC snap caps page 386.

6. Note that the text found on the listed drug labeling regarding the mechanism of how the extended release tablets works is missing from the generic. I find this to be OK.

7. The composition statement is consistent with the DESCRIPTION section. page 111 red vol.

8. See e-mail dated July 12, 1999 from Kerry Rothschild (PM for the RLD, Tylenol® Extended-release tablets) in the file folder regarding the term "Extended Relief". "Extended Relief" is merely descriptive and not considered part of the proprietary name of the RLD.

9. It appears that the innovator has changed the name of this product to be "Tylenol® Arthritis" as appearing on the revised labeling. However, this revision has not been approved as found in the COMIS. It is confirmed with the PM for the RLD in the new drug division. The PM stated that the new name most likely wouldn't be approved. Refer to the e-mail dated July 13, 1999 in the file folder for detail.

10. The firm has deleted "Arthritis formula" from the labeling per Agency's request.

Date of Review: October 8, 1999 Date of Submission: 9/23/99

Primary Reviewer: /S/ 10/8/99

Team Leader: Date:

/S/ 10/8/99

cc:

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

ANDA Number: **75-077** Date of Submission: **January 15, 1999**

Applicant's Name: **Perrigo Company**

Established Name: **Acetaminophen Extended-release Tablets, 650 mg**

Labeling Deficiencies:

GENERAL COMMENT

1. We acknowledge your comment regarding "Extended Relief". Upon further review, we believe that this phrase is merely descriptive and should not be considered part of the proprietary name for Tylenol® Extended-release tablets.

2. Please note that the new name "Tylenol® Arthritis" appearing on the labeling of the reference listed drug has not yet been approved by the Agency. We consider the use of the phrase "Arthritis Formula" on your labeling to be promotional in tone and could mislead the public in the use of your product, since your product is indicated for **the temporary relief of the minor pains of arthritis** as well as other indications listed in the labeling. We ask that you delete "Arthritis formula" from labels and labeling.

Please revise your labels and labeling, as instructed above, and submit final printed container labels and carton labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

/S/

Robert W. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

(FIRST GENERIC)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-077** Date of Submission: **January 15, 1999**

Applicant's Name: **Perrigo Company**

Established Name: **Acetaminophen Extended-release Tablets, 650 mg**

Labeling Deficiencies:

GENERAL COMMENT

1. We acknowledge your comment regarding "Extended Relief". Upon further review, we believe that this phrase is merely descriptive and should not be considered part of the proprietary name for Tylenol® Extended-release tablets.

2. Please note that the new name "Tylenol® Arthritis" appearing on the labeling of the reference listed drug has not yet been approved by the Agency. We consider the use of the phrase "Arthritis Formula" on your labeling to be promotional in tone and could mislead the public ir the use of your product, since your product is indicated for **the temporary relief of the minor pains of arthritis** as well as other indications listed in the labeling. We ask that you delete "Arthritis formula" from labels and labeling.

Please revise your labels and labeling, as instructed above, and submit final printed container labels and carton labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

Robert W. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

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

Container Labels:

Carton Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Tylenol Extended Relief

NDA Number: 19-872

NDA Drug Name: Acetaminophen extended-release tablets

NDA Firm: McNeil

Date of Approval of NDA Insert and supplement #: no labeling supplements

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: listed Drug

Basis of Approval for the Carton Labeling: listed drug

Other Comments:

FOR THE RECORD:

1. **Review based on the listed drug Tylenol (ANDA 19-872 McNeil; Approved June 8, 1994). There is no labeling supplement approved.**

2. **There are three patents. # 4968509 11/6/2007**
   # 5004613 7/27/2007
   # 4820522 7/27/2007

   The firm has filed a Paragraph IV patent non-infringement certification.

3. **This appears to be the first generic. The firm has requested that the Agency make a determination as**

eligibility for 180 days of market exclusivity for this product.

4. Storage and Dispensing Statement

NDA: Store at room temperature. Avoid excessive heat (40°C).
ANDA: same

USP: not a USP item.

5. Package size - Both the listed drug and generic have the 24 tablet package size. ANDA has 300s package size as well. Both with CRC snap caps page 386.

6. Note that the text found on the listed drug labeling regarding the mechanism of how the extended release tablets works is missing from the generic. I find this to be OK.

7. The composition statement is consistent with the DESCRIPTION section. page 111 red vol.

8. See e-mail dated July 12, 1999 from Kerry Rothschild (PM for the RLD, Tylenol® Extended-release tablets) in the file folder regarding general comment #1 on "Extended Relief".

9. It appears that the innovator has changed the name of this product to be "Tylenol® Arthritis" as appearing on the revised labeling. However, this revision has not been approved as found in the COMIS. It is confirmed with the PM for the RLD in the new drug division. The PM stated that the new name most likely wouldn't be approved. Refer to the e-mail dated July 13, 1999 in the file folder for detail.

Date of Review: July 13, 1999 Date of Submission: 1/15/99

Primary Reviewer: Date: C Pale 7/14/99

Team Leader: Date:

A. Vezza for C. Hopper 7/14/99

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cc:

) cc)
:V\75077NA3.1

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

ANDA Number: **75-077** Date of Submission: **May 8, 1998**

Applicant's Name: **Perrigo Company**

Established Name: **Acetaminophen Extended-release Tablets, 650 mg**

Labeling Deficiencies:

GENERAL COMMENT

1. We acknowledge your comments regarding the phrase "Extended Relief". However, please note that this phrase appears to be part of the proprietary name of the reference listed drug as recognized by the new drug division (See enclosed cover letter for approval). Furthermore, please note that the innovator uses the proprietary name "TYLENOL® Extended Relief Caplets" in the text of the carton labeling. Please delete the statement "Extended Relief" in the text (*i.e.*, Extended Relief Caplets) as well as on the principal display panel of container labels and carton labeling.

2. We refer you to 21 CFR 201.61(c) which states that the statement of identity (established name followed by the pharmacological category) shall be presented in bold face type on the principal display panel and shall be in a size reasonably related to the most prominent printed matter on such panel. Please increase the prominence of expression of the pharmacological category.

Please revise your labels and labeling, as instructed above, and submit final printed container labels and carton labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

Enclosure: A copy of the cover letter for approval of the reference listed drug.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-077

CORRESPONDENCE

PERRIGO®

CONFIRMATION OF FAX
Sent 12/22/99

December 20, 1999

TELEPHONE AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: Acetaminophen Extended Release Tablets, 650 mg (Over-the-Counter)
ANDA 75-077 Telephone Amendment

Dear Mr. Sporn:

Reference is made to ANDA 75-077, Acetaminophen Extended Release Tablets, 650 mg (Over-the-Counter), filed on February 10, 1997, and to subsequent communication regarding this ANDA as follows:

- FDA's "not approvable" fax dated December 19, 1997
- L. Perrigo's May 8, 1998, major amendment in response to FDA's December 19, 1997 fax
- FDA's "not approvable" fax dated October 16, 1998
- L. Perrigo's January 15, 1999, major amendment in response to FDA's October 16, 1998 fax
- FDA's "not approvable" fax dated July 15, 1999
- L. Perrigo's September 23, 1999, minor amendment in response to FDA's July 15, 1999 fax
- FDA's Bioequivalence comments fax dated December 16, 1999
- Telephone comments received from FDA's Dr. Karen Bernard on December 16, 1999

We hereby amend this application in accordance with 21 CFR 314.120 to address the comments in the December 16, 1999 fax from the Division of Bioequivalence (copy attached hereto) and to address the telephone comments received from Dr. Karen Bernard on December 16, 1999.

Bioequivalence Comments:

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

   The dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2, at 37°C, using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following interim specifications:

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 22 1999
OGD

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

ר 70%

Response:

The finished product and stability specifications with dissolution conditions and limits as noted above were previously submitted in the September 23, 1999 minor amendment in Section 3 at pages 28 and 29. They are attached hereto in accordance with this request.

We understand that OGD approves modified release drug products with tentative specifications. Upon approval of this ANDA with this proposed tentative specification, Perrigo commits to reviewing and finalizing the dissolution specification when adequate data has been generated to support a post-approval Supplement.

Comments received by telephone on December 16, 1999, from Dr. Bernard:

1. Provide excipient functionalities for the drug product formulation using the terms noted in the FDA SUPAC-MR guidance document.

   Response:

   A revised component/composition table is attached. Where possible, the role/function category noted in the Component/Composition table submitted in the original submission in Section 7 at page 111 has been revised to note the function/role example category terms used in the 1997 FDA SUPAC-MR guidance document. In those cases where the excipient does not fall into one of the example categories used in the SUPAC-MR guidance document, the USP, EP, or NF functionality category is noted.

2. Provide the acceptance specification for the SR beads that are manufactured by IPC.

   Response:

   The acceptance specification for the SR beads material (. Material: Coated Particle) was previously submitted in the original submission in Section 11 at page 292 and Section 12 at page 377. It is attached herein in accordance with this request.

Please note that the May 8, 1998, the January 15, 1999, and the September 23, 1999, amendments contained a request that the Food and Drug Administration make a determination regarding eligibility for 180 days of market exclusivity for Acetaminophen Extended Release Tablets, 650 mg. We continue to await FDA's determination.

In accordance with 21 CFR 314.50, I certify that a field copy, which is a true copy of this amendment, has been mailed to the Detroit District FDA Office.

Should you require additional information to facilitate final review and approval of this ANDA submission, please contact me directly by telephone at 616-673-9367 or by fax at 616-673-7655.

Sincerely,

Valerie Gallagher
ANDA Regulatory Affairs Administrator

PERRIGO

NDA
FA 9/30/99

September 23, 1999

MINOR AMENDMENT

BIOAVAILABILITY

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/Rm.

Re: Acetaminophen Extended Release Tablets, 650 mg (Over-the-Counter)
ANDA 75-077 Minor Amendment

Dear Mr. Sporn:

Reference is made to ANDA 75-077, Acetaminophen Extended Release Tablets, 650 mg (Over-the-Counter), filed on February 10, 1997, and to subsequent communication regarding this ANDA as follows:

- FDA's "not approvable" fax dated December 19, 1997
- L. Perrigo's May 8, 1998, major amendment in response to FDA's December 19, 1997 fax
- FDA's "not approvable" fax dated October 16, 1998
- L. Perrigo's January 15, 1999, major amendment in response to FDA's October 16, 1998 fax
- FDA's "not approvable" fax dated July 15, 1999

We hereby amend this application in accordance with 21 CFR 314.120 to provide the additional information requested in the July 15, 1999, correspondence (copy attached hereto). This is a minor amendment as indicated in the FDA Fax including comments from the Chemistry, Bioequivalence, and Labeling Divisions.

Chemistry Comments:

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

9/23/99

Bioequivalence Comments:

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

   The dissolution testing should be conducted in 900 mL of simulated gastric fluid w/o pepsin, pH 1.2, at 37°C, using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following interim specifications:

Response:

During a telephone call with the FDA on 8/19/99, Perrigo sought clarification of how FDA established the proposed specification noted above for dissolution. Perrigo was informed that the proposed specification was based on the data provided in Special Assay Report (SAR) 11323 (attached here in Section 2, previously submitted in the original ANDA at Pages 84 and 85, and previously submitted in the May 1998 amendment at Pages 68 and 69).

Perrigo respectfully requests that FDA consider the following points in relation to setting the tentative dissolution specification for this product:

1. All stability data generated on the submission batch have used the test conditions of 900 mL of water at 37^{0}C with Paddles @ 75 RPM, with the exception of the 24 months real time sample. The 24 months real time data was generated in accordance with FDA's recommendations in the December 19, 1997 "not approvable" fax as well as Perrigo's original dissolution conditions and limits (SAR 12916 attached in Section 2, previously submitted in the May 1998 amendment at pages 70 and 71). A lack of adequate stability data generated using the FDA proposed method, particularly for samples stored under accelerated conditions (40^{0}C/75%RH), makes it difficult to justify changing to the proposed specification at this time.

2. As can be seen from the 12 tablet dissolution data of the submission batch recorded on SAR 11323 (Attached in Section 2), the percent of drug released at the 15 minutes time point varied from a low of to a high of In light of this information, FDA's proposed dissolution specification does not make allowance for the following:

   - the 3.0% variability allowed in the assay of the Acetaminophen raw material should be considered when establishing dissolution specifications because the formula contains ≈ . active (See Acetaminophen monograph from USP 24, Page 17, attached in Section 2);
   - the variability associated with analytical techniques and test equipment;
   - batch-to-batch variability;
   - and, that slower paddle speeds may be associated with higher variability.

3. Because dissolution testing is intended to be a discriminatory quality control tool, the specification should be based on the data generated and submitted. One suggested method of calculating the upper and lower limits for dissolution is to use the average ± 2.5 to 3.0 standard deviations of the data submitted (Attached in Section 2, USP General Chapter 1088, page 2055, Establishment of Dissolution Specification Ranges by Convolution method).

4. The data generated on several lots of the reference listed drug, Tylenol Arthritis, (attached in Section 2, Report No. 14367 and SAR 11323) shows that it does not meet FDA's proposed specification even though the Perrigo drug product was found to be bioequivalent to the RLD.

In light of all the information presented above, Perrigo respectfully proposes for consideration and approval to conduct dissolution testing using the conditions proposed by the FDA with the following modification to FDA's proposed tentative specification:

Media : 900 mL of S G F W/O Pepsin, pH 1.2 Apparatus : Paddles @ 50 RPM

Time (minutes)	Drug Release (%)
	%

Attached in Section 3 are Drug Release Procedure 1403 and finished product and stability specifications with revised dissolution conditions and limits as noted above.

We understand that OGD approves modified release drug products with tentative specifications. Upon approval of this ANDA with this proposed tentative specification, Perrigo commits to reviewing and finalizing the dissolution specification when adequate data has been generated to support a post-approval Supplement.

Labeling Comments:

1. We acknowledge your comment regarding "Extended Relief". Upon further review, we believe that this phrase is merely descriptive and should not be considered part of the proprietary name for Tylenol® Extended-release tablets.

Response:

Thank you for your consideration and acknowledgement of our previous comment. Perrigo will not consider "Extended Relief" to be part of the proprietary name for Tylenol® Extended-release tablets as the phrase is merely descriptive.

2. Please note that the new name ' appearing on the labeling of the reference listed drug, has not yet been approved by the Agency. We consider the use of the phrase " ' on your labeling to be promotional in tone and could mislead the public in the use of your product, since your product is indicated for **the temporary relief of the minor pains of arthritis** as well as other indications listed in the labeling. We ask that you delete ' " from labels and labeling.

Response:

Perrigo has deleted reference to " from the labels and labeling for this product in accordance with this request. Final printed labeling is attached in Section 4 with the noted changes. In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the proposed final labeling with our

last submission is included with all differences annotated and explained in Section 4.

The L. Perrigo company notes that the Agency reserves the right to request further changes to the labels and/or labeling based upon changes in the approved labeling of the reference listed drug or upon further review of the application prior to approval.

Request for Determination of Eligibility for Market Exclusivity:

Please note that the May 8, 1998 and the January 15, 1999, amendments contained the following request regarding market exclusivity:

On February 10, 1997, L. Perrigo submitted the first substantially complete ANDA for this drug product, which contained a "paragraph IV", patent non-infringement certification. The patent owner/NDA holder, McNeil Consumer Products (a subsidiary of Johnson and Johnson), did not bring a patent infringement action against L. Perrigo within 45 days of the date that McNeil received notice of the ANDA submission.

Pursuant to Section 505(j)(4)(B)(iv) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. Section 355(j)(4)(B)(iv), the L. Perrigo Company hereby requests that the Food and Drug Administration made a determination regarding eligibility for 180 days of market exclusivity for Acetaminophen Extended Release Tablets, 650 mg.

In accordance with 21 CFR 314.50, I certify that a field copy, which is a true copy of this amendment, has been mailed to the Detroit District FDA Office.

Should you require additional information, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at the address on this letterhead.

Sincerely,

Valerie Gallagher

Valerie Gallagher
ANDA Regulatory Affairs Administrator

PERRIGO

January 15, 1999

Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

Major Amendment

Subject: **Acetaminophen Extended Release Tablets, 650 mg**
ANDA 75-077
Major Amendment

NDA ORIG AMENDMENT
N/A

Dear Mr. Sporn:

Reference is made to ANDA 75-077, Acetaminophen Extended Release Tablets, 650 mg, (Over-the-Counter), filed on February 10, 1997, and to the FDA 'not approvable' Fax dated October 16, 1998. Further reference is made to the conference call of October 27, 1998, in which the details of this fax were discussed. In attendance at the call were Brian Schuster, Andrew Pifer, and Prasad Gogineni from the Perrigo Company, and Kassandra Sherrod, Dr. Karen Bernard, and Brenda Arnwine from the Office of Generic Drugs.

We hereby amend this application in accordance with 21 CFR 314.120 to provide the additional information requested in the October 16, 1998, correspondence. This is a major amendment as indicated in the FDA letter.

A. Deficiencies

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

1/15/99

We understand that the proposed dissolution testing parameters may require further review and communication from the Division of Bioequivalence concerning this application.

Labeling Deficiencies:

General Comment:

Comment1
We acknowledge your comments regarding the phrase "Extended Relief". However, please note that this phrase appears to be part of the proprietary name of the reference listed drug as recognized by the new drug division (See enclosed cover letter for approval). Furthermore, please note that the innovator uses the proprietary name "Tylenol® Extended Relief Caplets" in the text of the carton labeling. Please delete the statement "Extended Relief" in the text (i.e. Extended Relief Caplets) as well as on the principal display panel of container labels and carton labeling.

Response
In reviewing the Summary Basis of Approval for NDA 19-872, it was noted that the product was described as Tylenol® SR (for sustained release). At the commercial launch of this product, McNeil listed Tylenol® Extended Relief on the package. Now, McNeil has changed the packaging and title of the product to Tylenol® Arthritis. Please see the new labeling for McNeil's NDA 19-872 enclosed in Attachment 2.

"Extended Relief Caplets" still appears on the listed drug's labeling, however it is not as prominent as Tylenol® Arthritis. Again, McNeil has not pursued a trademark registration on "Extended Relief" or "Extended Relief Caplets" with the Federal Trademark & Patent Office. The most probable cause of not pursuing registration of this phrase is that it is descriptive and not fanciful and would therefore not qualify for trademark registration and protection.

Concerning "Extended Relief", the Agency noted "...this phrase *appears* to be part of the proprietary name..." (emphasis added). However, because McNeil has changed the product title, the phrase no longer even appears to be part of the proprietary name. For these reasons, the Perrigo Company will retain "Extended Relief Caplets" on the labeling of our product.

Comment 2
We refer you to 21 CFR 201.61(c) which states that the statement of identity (established name followed by the pharmacological category) shall be presented in bold face type on the principal display panel and shall be in a size reasonably related to the most prominent printed matter on such panel. Please increase the prominence of expression of the pharmacological category.

Response
The established name of the drug (acetaminophen extended-release tablets, 650 mg) and the pharmacological category (pain reliever/fever reducer) which make up the statement of identity have been brought into closer proximity of size. The statement of identity has also been bolded to increase the prominence of expression per the request of the Agency.

Please see final printed labeling enclosed in Attachment 2 with changes as described above.

The L. Perrigo Company notes that the Agency reserves the right to request further changes in our labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

In order to facilitate review of our submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), a side-by-side comparison of our proposed Final Printed Labeling with our last submission is included, with all differences annotated and explained.

Request for Determination of Eligibility for Market Exclusivity

Please note that the May 8, 1998, amendment contained the following request regarding market exclusivity:

On February 10, 1997, Perrigo submitted the first substantially complete ANDA for this drug product which contained a 'paragraph IV' patent non-infringement certification. The patent owner/NDA holder, McNeil Consumer Products (a subsidiary of Johnson & Johnson), did not bring a patent infringement action against Perrigo within 45 days of the date that McNeil received notice of the ANDA submission.

Pursuant to section 505(j)(4)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j)(4)(B)(iv), the L. Perrigo Company hereby requests that the Food and Drug Administration make a determination regarding eligibility for 180 days of market exclusivity for Acetaminophen Extended Release Tablets, 650 mg.

In accordance with 21 CFR 314.50, I certify that a field copy which is a true copy of this amendment has been mailed to the Detroit District FDA Office.

Should you require additional information, please contact me directly by telephone at 616-673-9745, by FAX at 616-673-7655, or at the address on this letterhead.

Sincerely,

Brian R. Schuster
Regulatory Affairs Manager

PERRIGO

April 8, 1997

AMENDMENT
ANDA 75-077

Douglas Sporn, Director
FDA, CDER, OPS, Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

Re: Acetaminophen Extended-Release Tablets
ANDA 75-077

Dear Mr. Sporn:

As a follow-up to the Amendment filed March 27, 1997, the L. Perrigo Company is filing another amendment to its ANDA 75-077 Acetaminophen Extended-Release Tablets, in accordance with 21 CFR 314.95(e).

Documentation of receipt and evidence of the date of "Notice of Non-Infringement of a Patent" (hereinafter Notice) is attached which was sent to the patent owner, Johnson & Johnson, and holder of the approved New Drug Application, McNeil Consumer Products (hereinafter McNeil), for the listed drug as described in the Amendment dated March 27, 1997. This Notice was sent to Johnson & Johnson and McNeil via certified mail, return receipt requested. A copy of each "DOMESTIC RETURN RECEIPT" PS Form 3811 (hereinafter Receipt) is attached which serves to document receipt by Johnson & Johnson and McNeil of the Notice sent to them.

The Receipt for the Notice addressed to Johnson & Johnson is postmarked March 31, 1997 by the U.S. Postal Service. The date of delivery on box no. 7 of the form is blank.

The Receipt for the Notice addressed to McNeil is not postmarked by the U.S. Postal Service. The date of delivery on box no. 7 of the form is blank. The Notice was mailed to McNeil on March 27, 1997.

Please contact me at telephone 616-673-9745 if you have any questions.

Respectfully submitted,

David A. Jespersen
Director of Technical Services
DAJ/lem
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RECEIVED
APR 09 1997
GENERIC DRUGS

505(j)(2)(A)(ii)
Anamarie H. Weikel
3/11/97

bruary 10, 1997

Douglas Sporn, Director
DA, CDER, OPS, Office of Generic Drugs
cument Control Room
tro Park North II
00 Standish Place, Room 150
ckville, MD 20855-2773

VOLUME 1 OF 1

E: **Abbreviated New Drug Application**
Acetaminophen Extended Release Tablets, 650 mg
Over-the-Counter Product

Dear Mr. Sporn:

The L. Perrigo Company is submitting for your review and approval, an ANDA for Acetaminophen Extended Release Tablets 650 mg pursuant to 505(j) of the Federal Food, Drug, Cosmetic Act. Acetaminophen Extended Release Tablets are identical in strength, indications, active ingredient, route of administration and dosage form to McNeil Consumer Products' Tylenol® Extended Release Tablets.

Tylenol® Extended Release Tablets (NDA #19-872) are listed in the Sixteenth Edition of Approved Drug Products with Therapeutic Equivalence Evaluations as an OTC drug with protection. A paragraph IV patent certification is enclosed is Section 3 of this application which states that the unexpired patents will not be infringed by Perrigo's proposed new drug product. Tylenol® Extended Release Tablets have market exclusivity until June 8, 1997.

Bioequivalence studies conducted under fasted, fed and multi-dose/steady-state conditions, sponsored by Perrigo, are also included in this ANDA. Perrigo is requesting approval to market only the 544XC formula; not the 544XE formula.

Attached is an additional copy of this cover letter. Please stamp the date of receipt on it and return to me in the attached self-addressed stamped envelope.

Should you require additional information, please contact Brian Shuster, Regulatory Affairs Manager, by telephone at 616-673-7745, FAX at 616-673-7655, email at BSHUSTE@PERRIGO.COM or the address on this letterhead.

RECEIVED
FEB 14 1997
GENERIC DRUGS

Respectfully submitted,

J. M. Eaton

Jacqueline M. Eaton
Regulatory Affairs

1