

# Appendix

## **Section I - Documents Reviewed for the 325 mg Strenght, Immediate-Release APAP**

- A. Proposed Rule for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products (21 CFR Part 343, 42 FR 35345)

## **Section II - Documents Reviewed for the 500 mg Strenght, Immediate-Release APAP**

- A. February 20, 1973 Medical Officer's Summary of NDA 17-053
- B. April 6, 1973 Statistical Review of NDA 17-053
- C. April 10, 1973 Statistical Review of Bioavailability Study contained in NDA 17-053
- D. March 29, 1974 Medical Officer's Summary of NDA 17-552
- E. January 3, 1974 Pharmacologist's Review of NDA 17-552
- F. March 5, 1974 Biopharm Review of NDA 17-552
- G. The Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products (53 FR 46204)

## **Section III - Documents Reviewed for the 650 mg Strenght, Sustained-Release APAP**

- A. Undated Biopharm Review for NDA 19-872
- B. January 26, 1994 Medical Officer's Review of NDA 19-872

**Appendix**  
**Section I - Documents Reviewed for the 325 mg**  
**Strength, Immediate-Release APAP**

a combination of 65 mg isometheptene, 325 mg acetaminophen and 100 mg dichloralphenazone, (b) 325 mg acetaminophen and (c) placebo. Only the combination showed to be superior to placebo in this type of headache.

In another study, not controlled, a combination of acetaminophen and Vitamin C was studied in 45 patients with pain of different etiology (Ref. 18). The doses used were four to six tablets (containing 330 mg acetaminophen) per 24 hours. Nine of these patients had headache, and positive, favorable results were obtained in all of them. Four of these patients had pain described as neuralgia and all four obtained relief using this dose.

In another uncontrolled study by Perin (Ref. 19) acetaminophen in combination with Vitamin C (doses not given) was evaluated in 1,000 patients with pain of different etiology. Of these, 96 patients were admitted into the study for headache. The results are mostly analyzed in global form for all patients included. However, the following statement is made: "patients with headache reacted well and were alleviated rapidly." Unfortunately, the doses and dosage regimen are not specified for these patients. An additional 66 patients in the study are identified as having "neuralgias and neuritis" but the response of this group of patients is not stated.

In another single-blind study (Ref. 20), 500 mg acetaminophen was compared with a combination of 300 mg acetaminophen, 5 mg hydroxyzine, 30 mg propoxyphene hydrochloride and 30 mg caffeine. One to two tablets of each preparation were given to patients suffering from tension headache. The results showed that 45 percent success was obtained with acetaminophen alone and 90 percent with the combination. This superiority was attributed to the "potentiation of the analgesic agents by hydroxyzine."

The Panel concludes that acetaminophen is effective in relieving the pain of headache, and that it is a general analgesic of proven efficacy as shown by clinical testing. Thus, acetaminophen is considered to be equivalent to aspirin in its analgesic effects, although the lack of anti-inflammatory action might make it less useful in conditions having an inflammatory component (Ref. 21).

(2) *Safety.* Numerous clinical studies have shown that acetaminophen, when taken in recommended doses, is relatively free of adverse effects in most age groups, even in the presence of a variety of disease states. There was no increase in fecal blood loss (Ref. 22). There were no stomach mucous membrane reactions in patients with gastrointestinal illnesses (Ref. 23). There was no interference with the action of drugs which promote uric acid excretion in the urine (Ref. 24). No effects on clotting were seen in hemophiliacs (Ref. 25). However, several studies have shown small increases in blood clotting time in patients using acetaminophen, but concurrent anticoagulant therapy was considered manageable with conventional precautions (Ref. 26).

Larger than normal doses were required to produce a mild methemoglobinemia (a reversible blood disorder) (Ref. 27). The safety of acetaminophen is discussed in detail below. The metabolism of acetaminophen was considered and has been reviewed by the Panel elsewhere in this document. (See part II, paragraph L. above—Absorption, Distribution, Bio-transformation (Metabolism) and Excretion of Acetaminophen.)

A few cases of hypersensitivity to acetaminophen have been reported, as manifested by skin rashes (Ref. 28), thrombocytopenic purpura (characterized by "black and blue" patches on skin and mucous membranes) (Ref. 29), rarely hemolytic anemia (anemia due to red blood cell destruction) and the very serious blood disorder agranulocytosis (Ref. 30). Occasional individuals respond to ordinary doses with nausea and vomiting or diarrhea.

The only contraindications to the use of acetaminophen presently well-established are known hypersensitivities to the drug. Definitive studies are not available on whether or not acetaminophen should be used in patients with certain preexisting liver diseases. The Panel concludes that increased risk may be a possibility in these individuals and recommends that high priority be given to well-designed studies to resolve this issue.

(i) *Animal toxicity.* With regard to the acute toxicity of acetaminophen, the large doses of acetaminophen required to evoke toxic reactions in the studies cited below are considered by the Panel to reflect a wide range of safety. This is especially true when those dosages are compared to the Panel's recommended single dose and daily intake.

The single-dose oral LD<sub>50</sub> (dose that kills 50 percent of the animals) of acetaminophen in male rats was reported to be 3,710 mg/kg (Ref. 31), as compared to the previously reported LD<sub>50</sub> of 1,650 mg/kg for phenacetin in the female rat (Ref. 32). The LD<sub>50</sub> of acetaminophen in the rat is about 300 to 400 times the usual single dose in 50 to 70 kg (110 to 150 lb) adult humans.

In an acute toxicity study by Boyd and Bereczky (Ref. 31), acetaminophen produced early pathologic effects in the rats similar to those seen in the same laboratory in an earlier study (Ref. 32) with phenacetin. Rats dying in 24 hours showed extensive capillary-venous congestion, tubular nephritis and centrilobular hepatitis (kidney and liver inflammatory conditions, respectively). When deaths occurred later with acetaminophen the hepatitis had progressed into hepatic necrosis.

A 100-day LD<sub>50</sub> of acetaminophen in the rat was found to be 770 mg/kg daily; the 100-day LD<sub>50</sub> was estimated to be 409 mg/kg daily (Ref. 33). Extrapolating to humans ranging in weight from 50 to 70 kg (110 to 150 lb) the latter dose represents about 5 to 7 times the usual maximum recommended daily dose of 3,900 mg.

Boyd further found that his 100-day LD<sub>50</sub> in the rat produced atrophy of the

testes and inhibition of the production of sperm in rats and guinea pigs as well (Ref. 34). The sex organs of females were affected to a lesser degree. Other effects noted by Boyd and Hogan (Ref. 33), in rats receiving the 100-day LD<sub>50</sub> dose, included kidney and liver damage.

(ii) *Acute toxicity in man.* Several recent reports have also described numerous cases of poisoning in man by large single doses of acetaminophen, apparently usually taken for suicidal purposes. Prescott, Roscoe, Wright and Brown (Ref. 35) observed liver damage in 17 of 30 patients who had taken at least 15 g; one went into a coma induced by liver degeneration and died. In this report, no estimate was given of the lowest dose thought to have caused liver damage. Clark et al. (Ref. 36) studied a series of 60 patients who took doses of acetaminophen claimed to range from 13 to 100 g. Forty-nine developed liver damage, 17 progressed to hepatic encephalopathy (brain damage), and 12 died from fulminant liver failure. Death occurred in 4 to 18 days after the ingestion of the drug. Proudfoot and Wright (Ref. 37) studied 41 cases of acute acetaminophen poisoning, 17 of which showed liver damage. One patient died, 3 developed jaundice and the others showed only biochemical evidence of liver dysfunction. These authors stated that "liver damage is a toxic effect which is present in most patients who ingest more than 15 g of paracetamol" (acetaminophen). In all these series it was noted that other drugs were, or may have been, also taken.

In the U.S. in 1972, 61 cases of acetaminophen overdosage were reported to the National Clearinghouse for Poison Control Centers, Food and Drug Administration (Ref. 38). Of these, 15 reported the ingestion of less than 3.5 g, 23 between 3.5 and 15 g, and 7 ingested more than 15 g. Two of the latter developed toxic hepatitis. No effects of this nature were reported from doses lower than 15 g. In 1971 there were only 3 cases reported in which more than 15 g were ingested. One of these had no symptoms, another experienced some lethargy, and the other experienced nausea, vomiting and abdominal pain. The Panel concludes that single doses less than 15 g are not usually associated with serious liver damage. The much lower incidence of reported acetaminophen acute toxicity in the U.S.A. compared to England has been attributed to the well known axiom, if the diagnosis is not suspected, it is not seen, since one investigator reported 156 cases with 4 fatalities in one city alone (Ref. 39).

A dose of 15 g is 23 times the usual recommended single dosage of acetaminophen (650 mg) and about 4 times the maximum recommended daily intake. In estimating the range of safety, the single dosage comparison is probably more appropriate than the comparison of the single toxic dose with the daily divided therapeutic dose. The toxic effect of acetaminophen on the liver is related to glutathione depletion (Ref. 40).

Since acetaminophen is metabolized by the liver the question of the safety of its use in the presence of liver disease should be considered.

In a study of 72 patients with various forms of liver disease given 10 mg/kg of acetaminophen, Fevery and de Groote (Ref. 41) found an increase in both the serum levels and urinary excretion of unconjugated acetaminophen in the presence of certain liver diseases (parenchymal disease with hyperbilirubinemia or obstructive jaundice). Patients with cirrhosis exhibited plasma levels 2 to 3 times higher than those observed in subjects with no liver damage indicating decreased rates of metabolism. No decrease in the blood levels of conjugated acetaminophen or total urinary excretion of the drug could be demonstrated indicating that these two types of observations would not be expected to show differences in metabolism of free drug as would be expected from the pharmacokinetic characteristics of this drug. Vest and Fritz (Ref. 42) observed a lowered ability of the liver to conjugate acetaminophen in six children with infectious hepatitis given 10 or 20 mg/kg of the drug intravenously. In the acute phase of the hepatitis the excretion of conjugated acetaminophen was decreased. However, urinary excretion of free drug or excretion of total conjugated acetaminophen is an insensitive method to observe changes in metabolism of acetaminophen. Direct comparison of blood levels of unchanged drug indicates that the relative rate of conjugation can be decreased significantly without significant differences in urinary excretion of total conjugates. Free acetaminophen disappeared more slowly from the blood. The effects on excretion and blood levels of the conjugates and free acetaminophen reflected a partial inhibition of the conjugation of the drug to its glucuronide and the sulfate resulting in a moderate delay in the total elimination of the drug from the body. In 33 patients with liver cirrhosis, Jirsa and Hykes (Ref. 43) found no effect on the excretion of conjugated acetaminophen but did find a significant decrease in diabetics. Schmid and Hamaker (Ref. 44) observed no significant reduction in the formation of conjugated acetaminophen in five patients with Gilbert's disease (congenital liver disorder) after the administration of 30 mg/kg of acetaminophen but did not study blood levels of unchanged drug. In studies on infants prior to the development of their ability to metabolize this drug, no significant hematologic or other toxic effect were produced by single oral doses of acetaminophen up to 16.6 mg/kg (Ref. 45), or by 100 mg 3 times daily rectally for 3 days (Ref. 46).

There have been no clinical studies of the effect of liver disorders on metabolic pathways other than the glucuronide and sulfate conjugation pathways through which acetaminophen may be metabolized. In this connection Mitchell et al. (Ref. 40) have postulated that a minor but as yet unidentified highly reactive metabolite formed by nonconjugating

enzymes (mixed oxidase) is responsible for the liver toxicity of acetaminophen. In normal subjects the concentration of this metabolite is low, and it is further conjugated with glutathione to a nontoxic metabolite. At high doses glutathione stores may be overwhelmed and the reactive metabolite reacts chemically with other compounds in the cell which results in necrosis. It is pertinent to know whether liver disease might affect the liver toxicity of acetaminophen by interfering with the production of this toxic metabolite by nonconjugating pathways and further conjugation with cysteine to a nontoxic substance.

There is evidence in the results of the above studies that in some forms of liver disease there is a decrease in the conjugation of acetaminophen. This effect significantly increases the half-life of acetaminophen to 3 to 4 hours in some cases. It is perhaps significant that in toxic reactions to overdoses of acetaminophen the half-life is usually increased to 4 hours (Ref. 35).

Decreased metabolism of acetaminophen by normal conjugation mechanisms (glucuronide and sulfate) observed in some patients with chronic liver disease, could potentially increase toxicity of acetaminophen by increasing the relative fraction metabolized through nonconjugating pathways to the toxic metabolite. Decreased conjugation could also indicate decreased capacity of the liver to further conjugate the toxic metabolites with glutathione to a less toxic conjugate.

An alternative explanation for the increased susceptibility of chronic alcoholics to the hepatotoxicity of acetaminophen (Ref. 47) is the induction of the microsomal enzyme systems (nonconjugating) by chronic use of alcohol (Ref. 48). However, recent evidence suggests that the overall elimination by conjugation is decreased in alcoholics similar to that observed in other cases of decreased liver function.

Shamszad et al. found that preexisting liver disease significantly decreases the rate of elimination of drug (as evidenced by the increased half-life of unchanged drug in the plasma in patients with cirrhosis (half-life  $3.5 \pm 1.3$  hours) and active alcoholic hepatitis ( $4.5 \pm 1.5$  hours) compared to chronic alcoholics with normal liver function ( $2.2 \pm 0.39$  hours) and chronic alcoholics off alcohol for 7 days ( $2.8 \pm 0.7$  hours)) (Ref. 49).

Thus several types of liver disease result in prolonged half-lives of unchanged drug which are about the same increase (about 4 hours) observed in patients who suffer liver damage after acetaminophen overdose.

One cannot conclude that because an increased acetaminophen half-life occurs in association with acute liver damage caused by acetaminophen, that increased acetaminophen half-life caused by preexisting liver disease will increase the potential or severity of acetaminophen hepatotoxicity. Well designed studies to answer this question are needed. Although the Panel does not have evidence to warrant a warning to persons

with liver disorders at this time, it is noted that there is no evidence to exclude this possibility and the considerations discussed above require that this possibility not be dismissed.

Although the Panel concludes that additional studies are needed to determine if a warning is required for normal doses in adults or infants with liver disease, overdose may result in such severe liver damage that a label warning regarding this effect is obligatory. The basis for such a warning is well documented in several recent reviews of the hazards of acetaminophen overdosage, especially with respect to the harmful effects on the liver (Refs. 39, 48, and 50 through 52).

The warning should state: "Do not exceed recommended dosage because severe liver damage may occur".

Kidney damage has been described in numerous cases in which the liver injury has been of primary concern in acute poisoning by acetaminophen, as previously discussed. The nature of the injury to the kidney observed in such acute cases is apparently not related to the type of injury (papillary necrosis) which typically results from long-term abuse of analgesic drugs.

One case of the papillary necrosis type of kidney injury has been reported (Ref. 53) following prolonged use of acetaminophen at a dose of 11 to 18 g daily for 6 months in combination with proportionately large doses of chlorzoxanone. Two other cases, though questionably attributed to acetaminophen (Ref. 54), involved in one case this type of kidney injury which continued after switching to acetaminophen after the consumption of phenacetin-containing analgesics for 14 years. In the other case, the kidney damage developed after 5 years of intake of 1.5 g acetaminophen daily along with other drugs including some drugs containing phenacetin. Master (Ref. 55) reported a case of analgesic-induced kidney injury in a woman who took an average of 1.5 g acetaminophen daily for 10 years, though other analgesics were consumed previously or concurrently. Nanra (Ref. 56) mentioned two other cases of analgesic-induced kidney injury occurring in Australia. He attributed these to acetaminophen alone but he described no details. In none of the above six cases, in which the consumption of acetaminophen was involved, is it clear that this drug was the sole cause of the analgesic-induced kidney damage or that it was the primary drug of abuse.

Abel (Ref. 57) and the Royal Australasian College of Physicians (Ref. 58) have stated that patients fail to recover from kidney injury when their intake of phenacetin combinations is replaced by acetaminophen either alone or in combinations.

In studies on healthy adult human subjects, Prescott (Ref. 59) and Prescott, Sansur, Leven and Conney (Ref. 60) observed a slight increase in the excretion of kidney tubule cells in the urine following the intake of 3.6 g acetaminophen daily for 5 days. In the latter

study the increase was significant in one of eight subjects on acetaminophen and two of nine subjects on the same dosage schedule of phenacetin. This effect was considerably less than that seen in subjects taking similar doses of aspirin.

Edwards, Edwards, Huskisson and Taylor (Ref. 61) found only a minor impairment of urine concentrating ability in 6 of 13 patients after their intake of 2 to 30 kg acetaminophen over a period of 2 years. Batterman and Grossman (Ref. 7) noted no blood, liver or kidney disturbances in human subjects receiving 3.6 g daily for up to 116 weeks.

In an experiment on dehydrated dogs, Bluemle and Goldberg (Ref. 62) found a high concentration of acetaminophen in the papillae of the kidney after a single dose of phenacetin, and a similar concentration of the drug in the renal papillae was observed after a single dose of acetaminophen. However, in this study, no concentration of acetaminophen was found in nondehydrated dogs.

Acetaminophen has not been reported to produce effects on the central nervous system like those produced by phenacetin, variously described as euphoria, stimulation, sedation, depression, etc. These effects of phenacetin are considered to constitute the basis of the potential for abuse of analgesic preparations containing this drug. In comparing the subjective effects of phenacetin and acetaminophen in 20 healthy male volunteers, Eade and Lasagna (Ref. 63) found that phenacetin "depressed mood, energy and mentation," while acetaminophen in the same dose, 28 mg/kg, had no such effects and did not differ from aspirin or placebo. However, Nakra et al. recently reported that some patients, especially housewives, have used acetaminophen as a "pick-me-up" and raises the possibility that some will abuse it (Ref. 64).

No comparison has yet been made with regard to the relative abuse potential of analgesic mixtures of phenacetin and similar mixtures of acetaminophen. A longer history of use of acetaminophen combinations, especially those with aspirin, will be required before this question can be answered. However, considering the lack of effects of acetaminophen on the sensorium similar to those of phenacetin it is justifiable to conclude that acetaminophen, as a single entity or in analgesic mixtures, does not have the abuse potential demonstrated for analgesic mixtures containing phenacetin. Reports from Australia (Ref. 59) showing that established abusers of phenacetin-containing drugs continued to abuse acetaminophen combinations after the removal of phenacetin from proprietary products, do not indicate a primary abuse potential of acetaminophen or of its analgesic mixtures.

The Panel concludes from observations reviewed above that acetaminophen may be taken in recommended doses without undue risk.

The Panel has examined the regulations of the Poison Prevention Packaging

Act of 1970 as set forth in 21 CFR 1700.15 (a), (b) and (c), that provide for poison prevention packaging standards for aspirin-containing products in a dosage form intended for oral administration. The standards for child-resistant safety closures required on the containers of these products are intended to protect children from intentional or accidental ingestion without hampering the adult use effectiveness of the products. The Panel concurs with these standards and is of the opinion that the standards for child-resistant safety closures should apply to the containers in which acetaminophen oral products are packaged as well as to aspirin-containing products.

The Panel further concludes that the restrictions on the maximum number of tablets permitted in containers of aspirin products for child use should also apply to acetaminophen products formulated for use in children only. Therefore, acetaminophen products containing 80 mg (1.23 g) tablets intended for oral use in children should contain no more than 36 tablets to reduce the hazard of accidental poisoning, as set forth in 21 CFR 201.314(c)(2) for products containing 80 mg (1.23 gr) tablets of aspirin for pediatric use.

The Panel concludes that the OTC packaging requirements for safety closures and the restriction on the maximum number of tablets in the containers of aspirin products for pediatric use should also apply to acetaminophen products for use in children.

## REFERENCES

- (1) Woodbury, D. M., "Analgesic-Antipyretics, Anti-Inflammatory Agents, and Inhibitors of Uric Acid Synthesis," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, Macmillan and Co., New York, pp. 314-347, 1970.
- (2) Brodie, B. B. and J. Axelrod, "The Estimation of Acetanilide and Its Metabolic Products, Aniline, N-Acetyl-p-Aminophenol and p-Aminophenol (Free and Total Conjugated) in Biological Fluids and Tissues," *Journal of Pharmacology and Experimental Therapeutics*, 94:22-28, 1948.
- (3) Brodie, B. B. and J. Axelrod, "The Fate of Acetanilide in Man," *Journal of Pharmacology and Experimental Therapeutics*, 94:29-38, 1948.
- (4) Brodie, B. B. and J. Axelrod, "The Fate of Acetophenetidin (Phenacetin) in Man and Methods for the Estimation of Acetophenetidin and Its Metabolites in Biological Material," *Journal of Pharmacology and Experimental Therapeutics*, 97:58-67, 1949.
- (5) Flinn, F. B. and B. B. Brodie, "The Effect on the Pain Threshold of N-Acetyl-p-Aminophenol, A Product Derived in the Body From Acetanilide," *Journal of Pharmacology and Experimental Therapeutics*, 94:76-77, 1948.
- (6) Zelvelde, W. O., "Mededelingen Afdeling Klinisch Geneesmiddelenonderzoek T. N. O., Nederlandsche Vereniging voor Geneeskunde, 109:1734-1736, 1965.
- (7) Batterman, R. C. and A. J. Grossman, "Analgesic Effectiveness and Safety of N-Acetyl-para-Aminophenol," *Federation Proceedings*, 14:316-317, 1955.
- (8) Wallenstein, S. L. and R. W. Houde, "Clinical Comparison of Analgesic Effectiveness of N-Acetyl-para-Aminophenol Salicylamide and Aspirin," *Federation Proceedings*, 13:414, 1954.
- (9) Lasagna, L., M. Davis and J. W. Pearson, "A Comparison of Acetophenetidin and Acetaminophen; I. Analgesic Effects in Postpartum Patients," *Journal of Pharmacology and Experimental Therapeutics*, 155:296-300, 1967.
- (10) Kantor, T. G., M. Meisner, E. Laska and A. Sunshine, "A Computer Program for the Clinical Study of Analgesic Compounds," *Federation Proceedings*, 23:176, 1964.
- (11) Kantor, T. G., E. Laska, M. Meisner and A. Sunshine, "Studies of Oral Pentazocine (WIN 20,228) and Other Compounds at Bellevue Hospital, New York City," in "Drug Addiction and Narcotics Bulletin," pp. 3921-3931, 1964.
- (12) Parkhouse, J. and P. Hallinon, "A Comparison of Aspirin and Paracetamol," *British Journal of Anaesthesia*, 39:146-154, 1967.
- (13) Moertel, C. G., D. L. Ahmann, W. F. Taylor and N. Schwartz, "A Comparative Evaluation of Marketed Analgesic Drugs," *New England Journal of Medicine*, 286:813-815, 1972.
- (14) "Para-Aminophenol Derivatives," in "AMA Drug Evaluations," 2d. Ed., American Medical Association, Chicago, p. 262, 1973.
- (15) OTC Volume 030154.
- (16) OTC Volume 030155.
- (17) Diamond, S., "Treatment of Migraine with Isometheptene, Acetaminophen, and Dichloralphenazone Combination: A Double-Blind, Crossover Trial," *Headache*, 15:282-287, 1976.
- (18) Vivien, P., J. Turpin and H. Allannic, "Essai Clinique d'un Paracetamol Effervescent," *Ouest Medical*, 27:551-556, 1974.
- (19) Perrin, L. F., "Evaluation Clinique d'un Nouvel Antalgique (etude de 1000 observations)," *Therapeutique*, 48:689-692, 1972.
- (20) Borges, J. and C. Zavaleta, "Study of a New Analgesic Compound in the Treatment of Tension Headache," *Journal of Internal Medicine Research*, 4:74-78, 1976.
- (21) Anonymous, "Acetaminophen, Valium and Analgesic Renal Injury," *The Medical Letter*, 13:74-76, 1971.
- (22) Goulston, K. and A. Skyring, "Effect of Paracetamol (N-Acetyl-p-Aminophenol) on Gastrointestinal Bleeding," *Gut*, 5:463-466, 1964.
- (23) Vickers, F. N., "Mucosal Effects of Aspirin and Acetaminophen: Report of a Controlled Gastroscopic Study," *Gastrointestinal Endoscopy*, 14:94-99, 1967.
- (24) Kersley, G. D. and A. R. Gibbs, "Uricosuric Agents in the Treatment of Gout," *Annals of the Rheumatic Diseases*, 19:351-355, 1960.
- (25) Mielke, C. H., Jr. and A. F. H. Britten, "Use of Aspirin or Acetaminophen in Hemophilia," *New England Journal of Medicine*, 282:1270, 1970.
- (26) Antlitz, A. M., J. A. Mead and M. A. Tolentino, "Potentiation of Oral Anticoagulant Therapy by Acetaminophen," *Current Therapeutic Research*, 10:501-507, 1968.
- (27) Thomas, J., S. Mexican, G. A. Starmer and P. R. Carroll, "Paracetamol and Methemoglobinemia," *Lancet*, 2:1360, 1966.
- (28) Henriques, C. C., "Acetaminophen Sensitivity and Fixed Dermatitis," *Journal of the American Medical Association*, 214:2336, 1970.
- (29) Heading, R. C., "Purpura and Paracetamol," *British Medical Journal*, 3:743-744, 1968.
- (30) Lloyd, T. W., "Agranulocytosis Associated with Paracetamol," *Lancet*, 1:114-115, 1961.
- (31) Boyd, E. M. and G. B. Berczky, "Liver Necrosis from Paracetamol," *British Journal of Pharmacology*, 26:606-614, 1966.
- (32) Boyd, E. M., "The Acute Oral Toxicity of Phenacetin," *Toxicology and Applied Pharmacology*, 1:240-249, 1959.

**Appendix**  
**Section II - Documents Reviewed for the 500 mg**  
**Strength, Immediate-Release APAP**

February 20, 1973 80-100

MEDICAL OFFICER'S SUMMARY OF NDA 17-053

Sponsor: McNeil Laboratories, Inc.  
Fort Washington, PA

Trademark: Capsules Tylenol - 500

Nonproprietary Name: Acetaminophen 500 mg

Clinical Indications: As a mild analgesic. The sponsor had been asked to provide new data to show an additional analgesic effectiveness of Tylenol 500 (given as a 1000 mg dose) when compared to Tylenol 650 mg.

Conclusion:

- a. The requested evidence that the new capsule of Tylenol 500 mg, given in the recommended dosage of two capsules (1000 mg acetaminophen), is more effective as an analgesic than Tylenol 325 mg (tablets) given in the dose of two tablets at a statistically significant level, has been provided.
- b. The new bioavailability study compared, as requested, mean plasma levels of acetaminophen in volunteers, given either 975 mg of acetaminophen as tablets (the presently marketed Tylenol 325 mg) to those following the ingestion of 1000 mg of acetaminophen as capsules, the new proposed Tylenol 500 mg. Mean peak plasma levels obtained at identical times (45 minutes) were not significantly different ( $p < .05$ ) from each other.

Recommendations: Approvable

Pivotal Studies:

Controlled studies: Four double-blind, randomized analgesic studies have been performed in 338 post-partum patients with episiotomy pain comparing the efficacy of 1000 mg Tylenol (versus 650 mg Tylenol versus placebo as single dose medication) in identical appearing capsules.

Initial pain intensity, relief scores over a four hours post medication time interval and a global evaluation at four hours post medication were the evaluation criteria. Side effects as well as additional analgesic medications used in study drug failures have been recorded also.

1.                     

This study involved a total of 75 patients, 25 in each treatment group. Patients were comparable as to age, weight and time interval from delivery to entering the study. None of the patients had received an analgesic since the delivery. The anesthetic used for the delivery was not recorded.

Patients admitted to the study were suffering from ( ) moderately severe, ( ) severe and ( ) very severe pain due to their episiotomies.

Initial Pain	A	B	C	Time Interval from Delivery in Hours								Succ.	Fail.
	500	325	Placebo	1	1-2	2-3	3-4	4-5	5-6	6-7			
Very severe	18	19	11	A	0	0	12	3	3	0	0	14	4
				B	0	2	7	6	4	0	0	9	10
				C	0	4	4	3	0	0	0	0	11
Severe	5	6	11	A	0	1	1	2	0	0	1	4	1
				B	0	1	1	3	1	0	0	3	3
				C	0	1	8	2	0	0	0	1	10
Moderately severe	2	none	3	A	0	0	1	1	0	0	0	2	0
				B	0	0	0	0	0	0	0	0	0
				C	0	1	0	1	1	0	0	0	3
	25	25	25										
Total:													
Success	20	12	1										
Failure	5	13	24										

500 mg vs 325 mg Chi Square  $p < .01$

325 mg vs placebo Chi Square  $p < .001$

Conclusion: The — study provided the evidence requested to show a statistically significant difference in efficacy as an analgesic for Tylenol capsules 500 mg, given in a 2 capsule (1000 mg acetaminophen) single dose when compared to a single dose of 600 mg acetaminophen (two Tylenol 325 mg).



No safety problem arose. Of the 75 patients studied, two patients experienced side effects, both in the 500 mg drug group with initially very severe pain. The first patient complained of "warmness of her face" one hour post medication and five hours post delivery, which improved with reassurance. The second one was nauseated two hours post ingestion of the 500 mg Tylenol medication and five hours post delivery. Reassurance cleared the nausea. The sponsor presented several tables of comparative evaluations of different parameters of the study group which are acceptable and correct.

2.                     

This study involved a total of 150 patients, 50 in each treatment group. The three treatment groups were comparable as to age, weight, time interval since delivery and previous drug administration.

In contrast to the        study, all of the        patients were entered into the study on days 1-4 (average 2 days) post partum and all of these patients with the exception of one, had received a mild analgesic 12 hours prior. (Darvon N with ASA in the majority of the cases.)

Initial Pain	500	325	Placebo	S	F	Time Interval From Delivery in Days			
						1	2	3	4
Very severe	11	12	8	8	3	A 3	5	3	0
				3	9	B 4	7	1	0
				1	7	C 3	3	2	0
Severe	24	19	19	19	5	A 7	9	7	1
				14	5	B 6	7	5	1
				3	16	C 8	8	3	0
Moderately severe	15	19	23	13	2	A 7	6	0	2
				10	7	B 4	14	0	1
				8	15	C 6	9	7	1
TOTAL	50	50	50						
Successful	40	29	12						
Failure	10	21	38						

S = Success (global rating excellent and good)

F = Failure (global rating fair, poor, no effect)

500 mg vs 325 mg Chi Square p <.01

325 mg vs placebo Chi Square p <.001

Conclusion: The \_\_\_\_\_ study provided the requested evidence that efficacy as an analgesic for Tylenol 1000 mg when compared to Tylenol 650 mg occurred at a statistically significant level. No safety problem arose. Side effects reported for the 150 patients were as follows:

Total Side Effects: 12 of 150 patients

	500	325	Placebo
Dizzy	6		
Drowsy		1	1
Dry mouth	1		
Sleepy	1*	2	
Skin rash and itching			1

\* Occurred in one of the dizzy patients

11%

3. \_\_\_\_\_ This investigator was to evaluate 75 patients, but due to lack of patients, a total of 38 post-partum women only entered into the study. A statistical evaluation of the study results was neither done by the investigator nor the sponsor, however, the firm included the study results when the pooled data were analyzed (i.e., \_\_\_\_\_ studies).

The investigator presented case reports for 12 Tylenol 500 mg  
13 Tylenol 325 mg and  
13 placebo patients.

Patients in the three treatment groups appear comparable. Ten patients in each group entered the study one day post-partum, and two each in the Tylenol 500 and Tylenol 325 group received the drug within hours of delivery and three patients in the placebo group. One of the 325 mg patients entered on the second post-partum day. The majority of the patients in each group did not receive prior analgesic drugs.

Results:

	A	B	C		
Initial Pain	500	325	Placebo	S	F
Very severe	5	7	6	A	5
				B	5
				C	1
Severe	5	3	3	A	3
				B	3
				C	1
Moderately severe	2	3	4	A	2
				B	2
				C	1
TOTAL	12	13	13		
Success	10	10	3		
Failure	2	3	10		

Conclusion: This study, although limited in numbers of subjects participating, showed a significant superiority of both active drugs over placebo, but no difference between the two dosage forms of acetaminophen.

One patient in the Tylenol 500 group experienced "light headedness".

4.                      This study included a total of 75 patients, 25 for each treatment.

The study protocol, as well as the actual execution of this study, was identical to the previous ones, however, the results obtained were in the opinion of both, the investigator himself and the sponsor, "Completely atypical for the study of an analgesic used to treat episiotomy pain. The placebo response was essentially the same as that for the two medications. The investigator proposed that the data of this study should be rejected based on a statistical analysis ( $p < .01$ , ranked "t" test).

Comment: Since placebo and both drug treatments came out alike, there was inadequate assay sensitivity. The study therefore must be considered a "no test" situation.

Side effects occurred in 11 patients, none of which was considered serious. They have been listed as:

Sleepiness - 8 patients

Dizziness - 2 patients

Drowsiness - 1 patient.

5.                     : This investigator conducted a bioavailability study of the cross-over design in 15 volunteer subjects. Drug treatments compared were two capsules Tylenol 500 (1000 mg acetaminophen). Mean peak plasma levels obtained were not statistically significantly different ( $p < .05$ ) and occurred at identical times (i.e., 45 minutes post medication). Areas under the curves are comparable. The statistical department, Mr. Sloboda, has been asked to do a crossover analysis of the two tables with individual plasma-level results to confirm the validity of the statistical evaluation as presented. The intra- and inter-patient variability of the levels obtained is rather wide.

Summary: McNeal originally submitted on June 15, 1971 this NDA for a new Tylenol 500 mg capsule, claiming greater analgesic efficacy than the presently marketed Tylenol 325 mg tablet and proposed to make the Tylenol 500 prescription only.

Three-hundred patients had been clinically studied in double-blind studies comparing the new formulation to placebo in a variety of painful conditions.

The assigned M.O. considered the submission unapprovable.

A letter issued April 3, 1972 informing the sponsor of the deficiencies. The firm's representatives subsequently met with Dr. Finkel and discussed FDA's requests for well controlled clinical studies to provide evidence that the new formulation, capsules Tylenol 500 (500 mg of acetaminophen), when administered in the two capsule dosage, (i.e., 1000 mg) single dose, does indeed provide additional analgesia not obtained by the ingestion of two 325 mg Tylenol tablets (650 mg of acetaminophen) at a statistically significant level. FDA secondly requested that bioavailability studies should be performed comparing three tablets (975 mg of acetaminophen) with two capsules (1000 mg of acetaminophen) to show comparable plasma levels.

The firm resubmitted the NDA dated December 19, 1972. The five volumes were received by me on January 10, 1973.

This submission provided data (individual patient records were included) of four double-blind post-partum pain studies in a total of 338 patients. Of these 112 received Tylenol 1000 mg (2 caps.)  
113 received Tylenol 650 mg (2 caps)  
113 received placebo 2 capsules.

The results of two of the four studies, involving a total of 225 patients, 75 for each treatment group, provided evidence, at a statistically significant level ( $p < .01$  Chi Square) that two Tylenol 500 capsules (1000 mg acetaminophen) are more efficacious than two Tylenol 325 capsules (650 mg acetaminophen) administered as a single, oral dose in patients with post-partum episiotomy pain when pain relief is evaluated over a four hour post medication period.

Because of some differences in the patient population of these two studies (i.e., time interval since delivery to entering the study as well as analgesic drug administration 12 hours prior to entering the study) ~~study~~ study) I do not agree that it is appropriate to pool the results of these two studies. Each of these studies evaluated separately, however, did result in a statistically significant difference in analgesic efficacy.

The ~~study~~ study, although rather limited in numbers of subjects evaluated, did not show a difference between the two active drug treatments. The sponsor, however, included the results in the pooled data for the statistical evaluation. The fourth clinical study by ~~study~~ must be considered a "no test" situation because of poor assay sensitivity, i.e., active drugs and placebo provided essentially the same response). It is known that acetaminophen has been demonstrated in many studies as an effective mild analgesic-antipyretic.

The OTC panel on internal analgesics in its preliminary evaluation agreed that efficacy for acetaminophen has been demonstrated and documented as an analgesic and antipyretic at a single dose of 650 mg. The bioavailability study provided evidence for comparable plasma availability of acetaminophen for the two different formulations. The question if the "crushing" of the tablet formulation and "encapsulation" for the purpose of identical appearing medications for use in the clinical studies and possible alterations in this process has been answered satisfactorily. Results of the assay's performed on these comparison capsules indicate a 95% availability of acetaminophen in the "crushed" encapsulated tablets. For details please see Chemist's review.

Safety: Adverse reactions reported from the first three studies were as follows:

Side Effects	Tylenol 500	325	Placebo
Dizziness	6	0	1
Drowsiness	0	1	1
Sleepiness	1	2	0
Light headedness	1	0	0
Dry mouth	1	0	0
Rash	0	0	1
Itching	0	0	1
Headache	0	1	0
Warmness of face	1	0	0
Nausea	1	0	0
TOTAL	11	4	4
Patients with side effects	10	3	3
Patients treated	87	88	88

75 patients reported the following:

Sleepiness	4	3	1
Dizziness	1	1	0
Lightheadedness	1	0	0
Drowsy	0	1	0
TOTAL	6	5	1

None of these adverse effects were considered as serious or required any other treatment than reassurance.

Comment: The reported side effects and the incidence of their occurrence are no different from those observed with other mild analgesics.

Review of the Package Insert:

The firm has submitted labeling (a package insert) for Tylenol 500 as a prescription drug.

Before the acceptability of this labeling can be considered in detail, a policy decision will have to be made as to whether we will allow the manufacturer to market Tylenol 500 as an Rx medication or whether we will insist that the drug be marketed on an OTC basis with appropriate OTC labeling. The Office of Scientific Evaluation should take the following points into consideration when arriving at such a policy decision:

1. As a general policy matter does the FDA wish to permit a firm to make minor revisions in the formulation of an OTC drug (such as marketing a dosage form containing a somewhat larger amount of drug per dosage unit or formulating the drug as a capsule as opposed to a tablet) and thereby "create" a "new" prescription medication? This question is particularly cogent in a case such as Tylenol 500 where the rationale is completely one of permitting a marketing or promotional advantage for the company which will probably result in a disadvantage to the consumer, who will be forced to pay a higher price to have a prescription filled for a mild analgesic which he can presently obtain OTC at considerably less expense.
2. Sections 502(f) and 503(b) of the FD and C Act and section 1.106(a) of the regulations would seem to require that the drug be marketed on an OTC basis if it can be labeled in such a way that it can be used safely and effectively by the layman and does not pose a drug abuse hazard. If acetaminophen 325 mg tablets can be so labeled, it is obvious that acetaminophen 500 mg capsules can also be labeled to permit safe use on an OTC basis.
3. Since acetaminophen is one of the OTC internal analgesics presently being evaluated by the OTC panel, the labeling of Tylenol 500 should take into account the panel's recommendations for acetaminophen products in general. While these recommendations have not been finalized as yet, the preliminary draft sets the usual adult dose as 650 mg every four hours, yielding a total 24 hour dose of 3900 mg. Tylenol 500 mg capsules could therefore be labeled to recommend either two capsules (1000 mg) every six hours or one capsule (500 mg) every three or four hours and still still yield a total relative 24 hour dose recommended by the panel for OTC use.

4. If the firm desires to provide the prescribing physician or dentist with more detailed information than appears in an OTC label, additional information can be provided in promotional material and advertising directed at the profession, as documented in this NDA.

Recommendation:

Tylenol 500 is approvable as a mild OTC analgesic-antipyretic. Labeling should conform with forthcoming OTC labeling.

*Brigitta Dassler*  
Brigitta Dassler, M.D.

cc:

Orig.

Dup.

BD-100

BD-120

BD-120:BDassler:2/20/73

R/D signed:WBeaver:2/20/73

F/T:pkb:2/22/73

*WBeaver*  
2-22-73





Brigitta Bessler, M.D.

Division of Neuropharmacological Drug Products, BD-120

April 10, 1973

McNeil Laboratories, Inc.  
Fort Washington, PA  
AF 12-610

Division of Statistics, BD-230

ADA 17-053, Tylenol (Acetaminophen) - Bioavailability study by  
M.D.

1. Fifteen normal, male volunteers were used in this study. These were divided into two groups of 7 and 8 patients respectively. Random assignment was made to 325 mg. and 500 mg. treatment of acetaminophen on a crossover basis.

a. Heparinized blood was collected at 0 (pre-dose), 10, 20, 30, 45, 60 and 90 minutes and at 2, 3, 4, 6, 8, and 10 hours following dosing.

b. Blood levels were analyzed using a gas chromatograph.

2. Our analysis of these data indicate that no significant differences were observed between the two drugs at any sampling point, nor for the time-to-peak, peak or area under the time-action curve measures.

3. The average blood level values are presented in Table I, as well as values for time-to-peak, peak and area under the time-action curve. The model for the crossover analysis can be found in Appendix A.

4. Power calculations indicated that for  $p = 0.05$  and a 25% difference, power was greater than 0.95, i.e., sufficient sensitivity was shown to have detected a difference of 25% had there been one.

5. Summary - The analysis of variance for a crossover design failed to detect statistically significant differences in blood levels between Tylenol 325 and Tylenol 500 at any of the sampling points. Similar lack of significance was obtained for time-to-peak, peak and area under the time-action curve.

Charles DeWitt Roberts, Ph.D.

Walter Sloboda  
Statistical Evaluation Branch, BD-232

cc: Orig., Dup. Trip., BD-106

BD-200, BD-230/Dr. Anello

BD-232/Dr. Dubey

BD-232/Dr. Roberts, BD-232/Mr. Sloboda, CA-228, AF 12-610, BD-120/Dr. Gardner  
BD-100, chron file, CRoberts/WSloboda/mjm 4-11-73

Table I. Averages Blood Level Values per Observation Point and for Time-to-Peak, Peak, and Area Under the Time-Action Curve.

Measure	Tylenol 325	Tylenol 500
10 Min.	1.3340	0.3607
20 Min.	4.3913	6.9107
30 Min.	6.7967	7.9220
45 Min.	9.6433	11.3847
60 Min.	8.7367	10.0473
90 Min.	9.2207	8.7840
2 Hr.	7.6967	7.8653
3 Hr.	5.9980	6.2847
4 Hr.	4.4120	4.6020
6 Hr.	2.4833	2.4873
8 Hr.	1.1267	1.0527
10 Hr.	0.5553	0.5560
Time-to-Peak	0.9444	0.8944
Peak	11.8053	13.6813
Area	38.8315	40.6009

## Appendix A

### Statistical Model for the Analysis of Variance

$$Y_{ijkm} = a + t_i + d_j + s_k + P_{n(k)} + e_{ijkm}$$

where

$Y_{ijkm}$  is the blood level at a particular time

$a$  is the mean effect

$t_i$  is the treatment effect 1 = Tablet, 2 = Capsule

$d_j$  is the day effect ( $j = 1, 2$ )

$s_k$  is the sequence effect 1 = Tablet First, 2 = Capsule First

$P_{m(k)}$  is the subject effect, nested within sequence

$m = 1, 2, \dots, 7$  for  $k = 1$

$= 1, 2, \dots, 8$  for  $k = 2$

$e_{ijkm}$  is the random error



Brigitta Bassler, M.D., BD-120  
Division of Neuropharmacological Drug Products

April 6, 1973

Division of Statistics, BD-230

BDA 17-053, Tylenol (acetaminophen). Studies by Dr.                     

1. This is a response to your memorandum requesting comments regarding the statistical methodology employed, the statistical significance between the two formulations and the appropriateness of tables presented.
2. Statistical Methodology - See discussion in Section 4 of this memorandum.
3. Efficacy - We have evaluated the studies by Drs.                      with regard to efficacy. Two measures were used. Total pain intensity and total change in pain intensity. Total pain intensity consisted of summing the pain scores over the total time of observation. Total change in pain intensity was calculated by subtracting the initial pain intensity from each subsequent observation and adding these differences.
  - a.                      b. The purpose of this study was to compare the effectiveness and safety of two capsules of Tylenol (1000 mg. acetaminophen) and capsules containing two tablets of Tylenol (650 mg. acetaminophen) and placebo as analgesics for the treatment of pain following episiotomy. A total of 75 patients (25 per group) were used. All were experiencing moderately severe to very severe pain. Results of our analysis are presented in Table I. Comparisons against Placebo were significant for both drugs, however, Tylenol 500 was not statistically significant from Tylenol 325 for total intensity of pain. For total change in pain intensity over 4-hours, all comparisons were statistically significant. Figures 1 and 2 show these results graphically.
  - b.                      M.D. - This study was conducted on 150 post partum patients with moderately severe to very severe episiotomy pain. The same dosage and drugs were used in this study as in Dr. Zar's study. The results are also presented in Table I. Significance was found for all 3 comparisons using both measures of efficacy. The point-by-point mean values are presented in Figures 3 and 4.

Dr. Bassler

c. Pooled Results. A statistically significant difference was found for all 3 comparisons using both measures (Table I). Since no significant interactions nor investigator differences were found, pooling appears to be appropriate in this case.

4. Appropriateness of Tables. We question the use of the chi-square statistic in a repeated measures design as shown in the tables on pp. 102-104 and 122-124 of Vol. 1. The multiple classification of each patient, i.e., classifying the patient on both his initial pain level and his final pain score, violates the assumption of the chi-square regarding the independence of the cell entries. We further note that the Applicant has not provided references and support for the application of the "Mantel-Lasagna Modified Chi-Square" or for the "Ranked 't' test."

5. Summary and Conclusions

a. Two studies, (Dr. \_\_\_\_\_) were analyzed using total pain intensity and total change in pain intensity. In Dr. Bare's study, no difference was found between Tylenol 325 and Tylenol 500 for total pain intensity, although Tylenol 500 did show less pain. For change in pain intensity, Tylenol 500 was more effective than either Tylenol 325 or Placebo. All comparisons to Tylenol 500 were significant in Dr. \_\_\_\_\_ study.

b. Pooling of these two studies appeared to be justified on statistical grounds. Pooled results indicated Tylenol 500 to be statistically superior to Tylenol 325 and Placebo for both measures.

c. We question the application of the Chi-Square statistic on these data since the assumption of independence of observations has been violated.

Walter Sloboda  
Statistical Evaluation Branch, BD-232

cc:  
Orig. Dup. Trip., BD-106  
~~BD-100~~  
BD-200  
BD-230  
BD-232/Dr. Dubey\_\_\_\_\_  
BD-232/Mr. Sloboda  
BD-120/Dr. Gardner  
BD-232/chron file  
ca-228  
WSloboda/mjm 4-6-73

Table 1. Results of the Analysis of Variance.  
(Appendix A presents the models for this analysis).

Investigator	Measure	Tylenol 500 (1)		Tylenol 325 (2)		Placebo (3)		Significance (P)		
		Mean	SD	Mean	SD	Mean	SD	1-2	1-3	2-3
—	Total Pain	9.60	5.02	11.80	5.86	15.38	5.68	<.01	<.01	<.01
	Change in Pain	10.00	4.03	7.50	4.67	3.22	4.55	<.01	<.01	<.01
—	Total Pain	13.12	4.12	15.72	4.33	19.28	4.51	-	<.01	<.01
	Change in Pain	10.68	4.05	8.08	3.87	2.92	3.50	<.05	<.01	<.01
—	Total Pain	10.77	5.00	13.11	5.68	16.68	5.58	<.01	<.01	<.01
	Change in Pain	10.23	4.02	7.69	4.40	3.12	4.20	<.01	<.01	<.01

- not significant



Appendix A.

1. The model for Total Pain Intensity was:

$$Y_{ijk} = \mu + t_i + b_j + (tb)_{ij} + e_{ijk}$$

where:

$Y_{ijk}$  is the dependent variable of Total Pain Intensity

$\mu$  is the overall mean effect

$t_i$  is the treatment effect where  $i = 1, 2, \text{ or } 3$

(Tylenol 500, Tylenol 325 or Placebo, respectively)

$b_j$  is the baseline pain intensity where  $j = 1, 2 \text{ or } 3$  (Very severe, severe, and moderately severe pain respectively)

$(tb)_{ij}$  is the interaction term

$e_{ijk}$  is the random model error.

2. For Change in Pain Intensity, the following model is used:

$$Y_{ij} = \mu + t_i + e_{ij}$$

when

$Y_{ij}$  is the dependent variable of Total Change in Pain intensity.

$\mu$  is the overall mean effect

$t_i$  is the effect of treatment,  $i = 1, 2, 3$

(Tylenol 500, Tylenol 325 or Placebo, respectively)

$e_{ij}$  is the random model error.

3. For the combined studies:

$$Y_{ijkl} = \mu + t_i + b_j + I_k + (tb)_{ij} + (tI)_{ik} + (Ib)_{jk} + e_{ijkl}$$

where

$Y_{ijk}$  is the Total Pain Intensity, the dependent measure

$\mu$  is the overall mean effect

$t_i$  is the effect of treatment;  $i = 1, 2, 3$  (Tylenol 500, Tylenol 325 or Placebo).

$b_j$  is the baseline, pain effect;  $j = 1, 2, 3$  (Very severe, severe or moderately severe pain, respectively)

$I_k$  is the effect of investigators;  $k = 1, 2$   
Bare or Hopkinson, respectively)

$(tb)_{ij}$ ,  $(tI)_{ik}$  and  $(Ib)_{jk}$  are two-way interactions

$e_{ijk}$  is the random model error variance.

4. For the combined studies testing Total Change in Pain Intensity:

$$Y_{ijk} = \mu + t_i + I_j + (tI)_{ij} + e_{ijk}$$

where

$Y_{ijk}$  is the Total change in Pain Intensity

$\mu$  is the overall mean effect

$t_i$  is the treatment effect;  $i = 1, 2, 3$  (Tylenol 500, Tylenol 325 or Placebo, respectively).

$I_j$  is the effect of the investigator  $j = 1, 2$  \_\_\_\_\_ respectively

$(tI)_{ij}$  is the interaction term

$e_{ijk}$  is the random effects model error term.

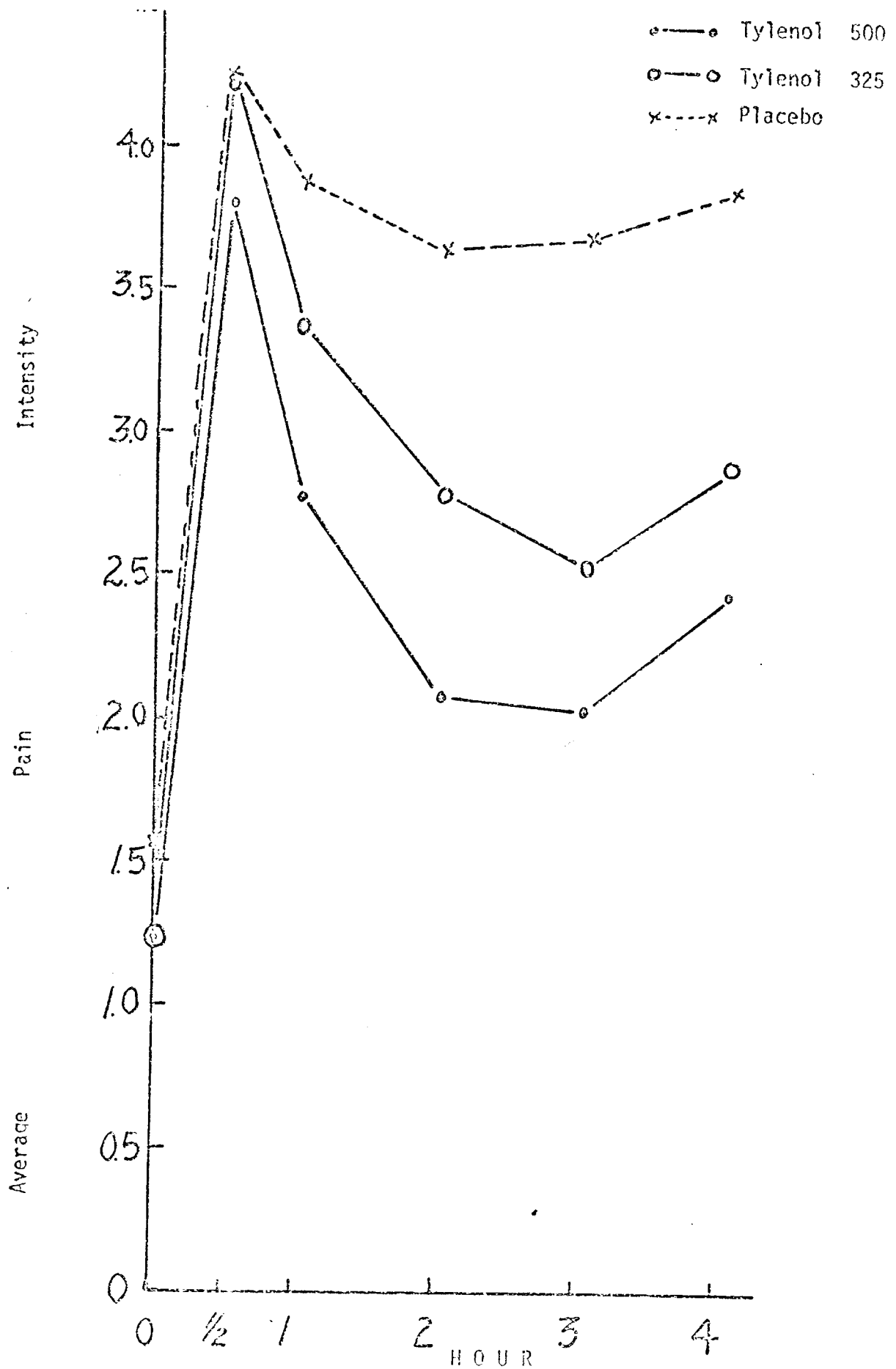


Figure 1. Average pain intensity per observation point. Dr — Study.

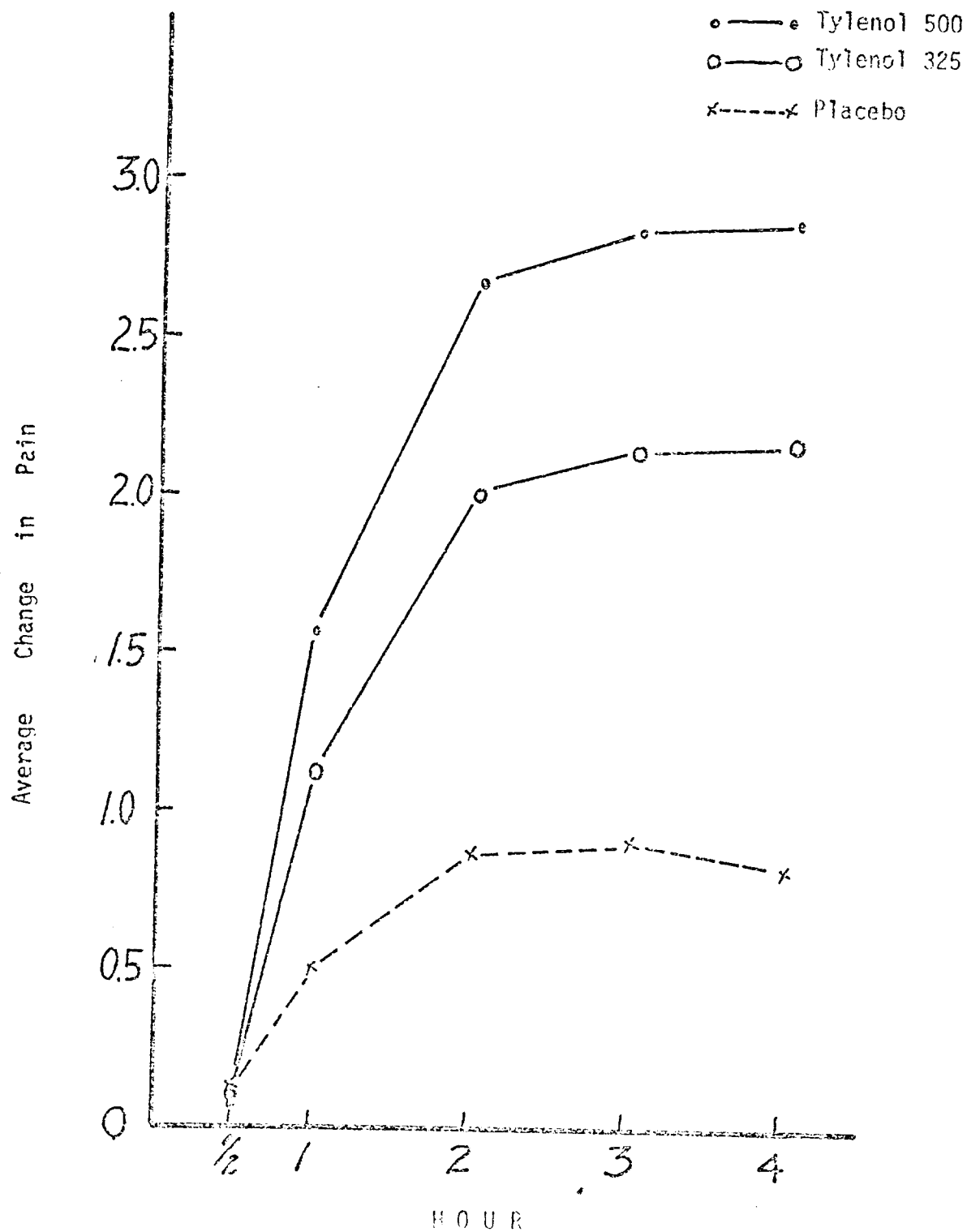


Figure 4 . Average change in pain intensity. Dr. ——— Study.

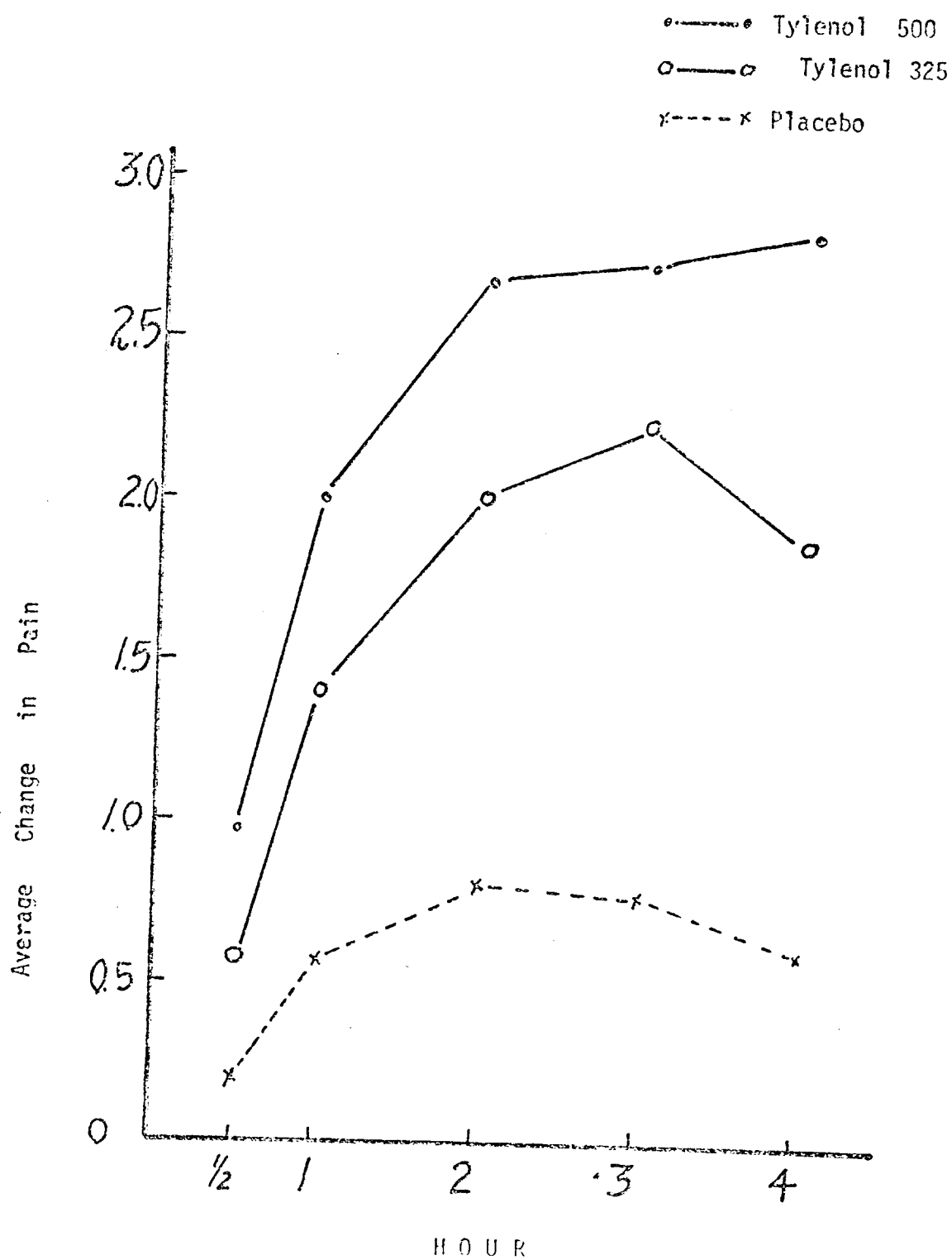


Figure 2. Average change in pain intensity. Dr. — Study.

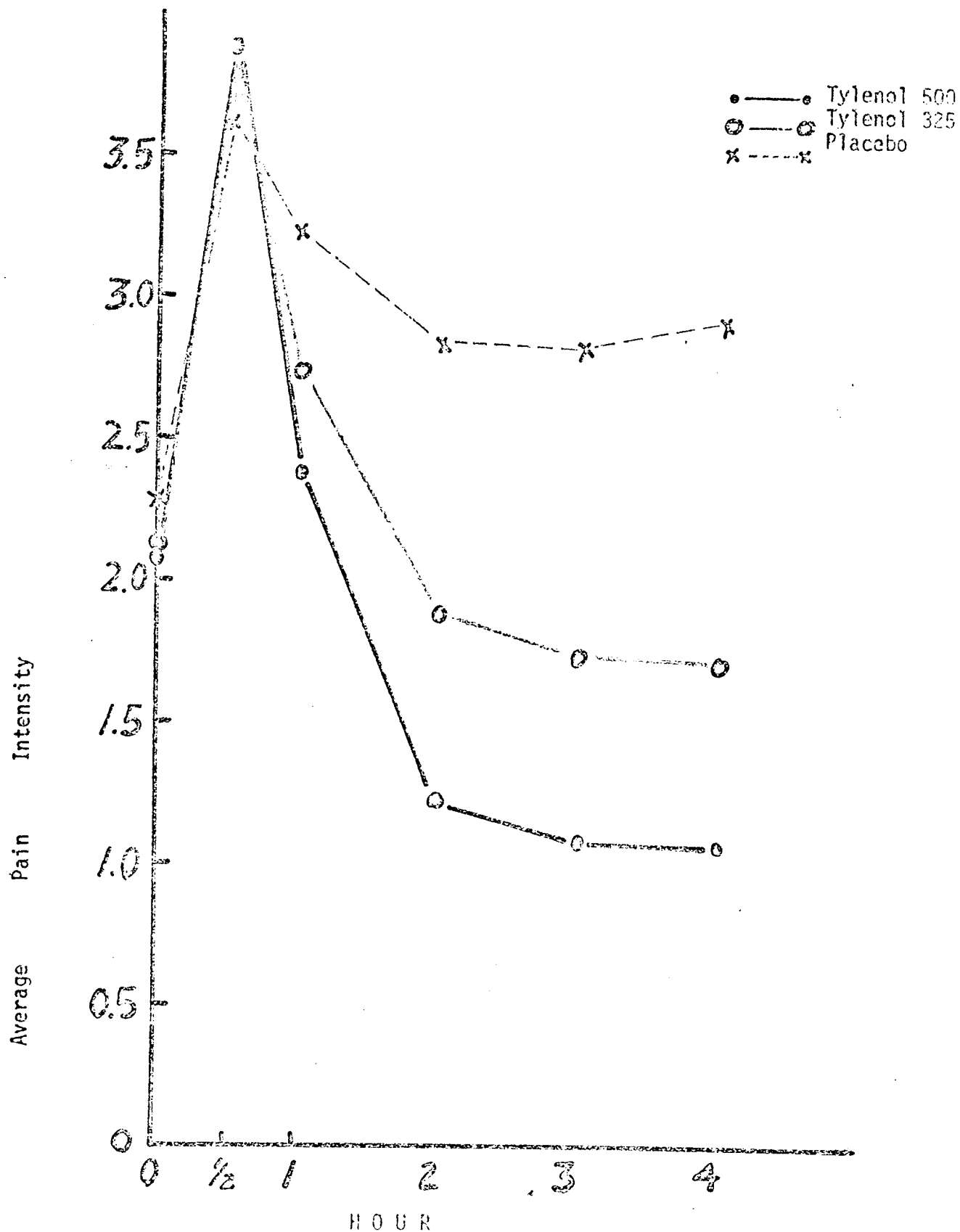


Figure 3. Average pain intensity per observation point. Dr. \_\_\_\_\_ Study.



March 29, 1974

*Orig*

Medical Officer Summary of NDA 17-552

- 1) Sponsor: McNeil Laboratories, Inc.  
Camp Hill Road  
Fort Washington, Pa. 19034  
  
    Originally submitted: December 18, 1974  
  
    Review Completed: March 29, 1974
- 2) Trademark: Tablets tylenol- 500 mg.
- 3) Nonproprietary Name: Acetaminophen 500 mg.
- 4) Clinical Indication: As a mild analgesic-antipyretic
- 5) Conclusion: The evidence provided in this NDA is in the form of two bio-equivalent studies comparing the approved tylenol 500 capsule (NDA 17-053) to the new formulation tylenol 500 tablet (the NDA 17-552). Although the tablets in both studies gave somewhat lower and flatter peaks than the capsules, the areas under the curve and the amount of drug absorbed were similar. The bioavailability study is acceptable.

Recommendations: Approvable

Pivotal studies as reviewed by the Division of Clinical Research.

1. Submitted is a bioavailability study on the above product with acetaminophen 500 mg capsules as the reference product. Eighteen subjects were used. The dose was 2 capsules or tablets (1000 mg) and the crossover was done 7 days after the first administration. Blood was collected at 0, 20, 40, 60 and 90 minutes and 2, 3, 4, 6, 8, and 10 hours. The study was conducted by \_\_\_\_\_ and the samples assayed by \_\_\_\_\_.
2. The assay used was the gas-liquid chromatographic method of Prescott (J. Pharm. Pharmac. 23: 111 and 807, 1971) and had a limit of sensitivity of about 1  $\mu$ g/ml plasma.



3. The peak values occurred in about 40 minutes and averaged 11.64 and 8.32 ug/ml for the reference and test drugs. The respective half-life of the two products were 124.0 and 126.5 minutes, and the area under the curves were 2513 and 2391. There was practically 100% absorption of the drug from both products (102% and 95%).

4. Analysis of variance revealed significant differences due to peak height but not due to half-life or area. The difference in peak heights is of questionable clinical significance.

5. A second study was done at the \_\_\_\_\_ in which three 325 mg tablets were compared with two 500 mg capsules. The results were almost identical with the results of the study on the 500 mg tablets. The average peak values being 9.64 and 11.38 ug/ml. The half-life was 2.10 and 2.03 hours and the areas under the curve were 2402 and 2508 for the tablets and capsules respectively.

Recommendations:

Although the tablets in both studies gave somewhat lower and flatter peaks than the capsules, the areas under the curve and the amount of drug absorbed were similar. Acceptance of the bioavailability study is recommended.

Labeling: The labeling should be identical to that recommended by OSE for the 500 mg capsule.

Recommendations:

Tablet tylenol 500 is approvable as an OTC analgesic - antipyretic.

cc:  
Orig  
Dup  
HFD-100  
HFD-120  
HFD-120/BDassler  
HFD-120/FJordan  
FT:cld/4/3/74  
Trip

*Brigitta Dassler, M.D.*  
Brigitta Dassler, M.D.

4-4-74

*FJordan 4/4/74*



Initial Submission  
12/18/73

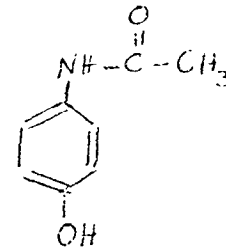
SPONSOR: Mc Neil Laboratories, Inc.  
Camp Hill Road  
Fort Washington, Pennsylvania 19034

DRUG: Acetaminophen, Tylenol<sup>R</sup>

GATEGORY: Analgesic, antipyretic

DOSAGE FORM: Tablets

RELATED NDA: McNeil Tylenol Capsules NDA 17-053



#### NON-CLINICAL STUDIES:

Pharmacology-Toxicology: Acetaminophen has been extensively reviewed by other pharmacologists (e.g., above NDA and IND). It has been demonstrated to be an effective analgesic in various animal models including squeezing of inflamed rat paw, protection of neck and foreleg flexion after intra-arterially injected bradykinin and chemical induced writhing test. The antipyretic activity of acetaminophen has been demonstrated in rat, guinea pig and rabbit models including yeast induced, streptobacillus and "E" pyrogen induced fevers. The anti-inflammatory activity has been shown in carrageenin induced edema, cotton pellet granuloma and other paw edema tests.

No serious toxic effects have been reported by the sponsor at the usual dosages. Considerable human pharmacology and toxicology data are now available on acetaminophen.

Absorption and Disposition: Human bioequivalence study indicates that acetaminophen is well absorbed from tablets as well as capsules and these 2 dosage forms are almost similar in absorption patterns (975 mg in tablets vs 1000 mg in capsules). The plasma blood levels thus obtained are also therapeutically effective. The plasma  $t_{1/2}$  for acetaminophen (500 gm) formulations ranged from 1.9 - 2.3 hr. Adequate evidence is presented to show that Tylenol tablets are bioequivalent to Tylenol capsules.

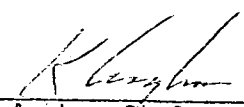
#### EVALUATION

Acetaminophen is known to be an effective analgesic and antipyretic agent in humans. Recently published reports of Mitchell et al. (JPET 187: 185-217, Oct. 1973) indicate that excessive doses of acetaminophen can produce hepatic necrosis in mice and rats especially when these animals were pre-treated with inducers of drug metabolising enzymes. This hepatic toxicity is considered to be mediated by a metabolic intermediate of acetaminophen. However, information is lacking on the effect on liver of concurrent administration of only moderately high doses of acetaminophen and enzyme inducing substances over a period of months.

There also have been human cases where massive doses of acetaminophen have produced liver toxicity. In view of these findings caution should be advised when high doses of acetaminophen are administered for prolonged periods to patients who are heavy users of coffee, alcohol or are taking any other enzyme-inducing drug or substance.

RECOMMENDATION:

1. The bioequivalence aspect of Tylenol capsules and tablets should be approved.
2. The labeling of all acetaminophen preparations should contain a caution that the use of high doses of acetaminophen over prolonged periods may produce liver toxicity in those patients taking high amounts of coffee, alcohol, barbiturates or other enzyme inducing substances.

  
\_\_\_\_\_  
K. Asghar, Ph.D.  
Pharmacologist

cc:  
Orig.  
Dup.  
DO-PHI  
HFD-1  
HFD-100  
HFD-120  
HFD-120/init. by VCGlocklin/1-7-74/KAsghar  
F/T/ag:1-16-74  
Dr. Dossler



TYLENOL Tablets  
(acetaminophen) 500 mg  
NDA 17-552

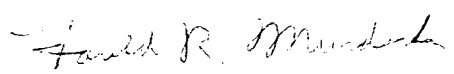
McNeil Laboratories  
AF 12-610  
Submission December 18, 1973

REVIEW OF A BIOAVAILABILITY STUDY

1. Submitted is a bioavailability study on the above product with acetaminophen 500 mg capsules as the reference product. Eighteen subjects were used. The dose was 2 capsules or tablets (1000 mg) and the crossover was done 7 days after the first administration. Blood was collected at 0, 20, 40, 60, and 90 minutes and 2, 3, 4, 6, 8, and 10 hours. The study was conducted by \_\_\_\_\_ and the samples assayed by \_\_\_\_\_.
2. The assay used was the gas-liquid chromatographic method of Prescott (J. Pharm. Pharmac. 23: 111 and 807, 1971) and had a limit of sensitivity of about 1 ug/ml plasma.
3. The peak values occurred in about 40 minutes and averaged 11.64 and 8.32 ug/ml for the reference and test drugs. The respective half-life of the two products were 124.0 and 126.5 minutes, and the area under the curves were 2513 and 2391. There was practically 100% absorption of the drug from both products (102% and 95%).
4. Analysis of variance revealed significant differences due to peak height but not due to half-life or area. The difference in peak heights is of questionable clinical significance.
5. A second study was done at the \_\_\_\_\_ in which three 325 mg tablets were compared with two 500 mg capsules. The results were almost identical with the results of the study on the 500 mg tablets. The average peak values being 9.64 and 11.38 ug/ml. The half-life was 2.10 and 2.03 hours and the areas under the curve were 2402 and 2508 for the tablets and capsules respectively.

RECOMMENDATIONS:

Although the tablets in both studies gave somewhat lower and flatter peaks than the capsules, the areas under the curve and the amount of drug absorbed were similar. Acceptance of the bioavailability study is recommended.



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cc: NDA Orig, Dup., Trip., HFD-200, HFD-220, HFD-222, HFD-106, AF FILE, HFD-107 (Dr. Seife), HFD-120 (J. Purvis), HFD-222 (Medical and Technical Research Associates) (Development Corporation)

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R/D init. by JPSKELLY 3/4/74



revised 10-day and 5-day warnings for analgesic drug products in § 343.50(c)(1)(i), (2)(i), and (3) in this tentative final monograph adequate to warn consumers to obtain professional help if symptoms persist or get worse or if new symptoms occur.

22. Two comments objected to the 5-day limitation of use of analgesic and antipyretic drug products by children under 12 years of age in the Panel's recommended warning statement in § 343.50(c)(1)(ii). The comments agreed with the Panel that the period of OTC use of analgesic and antipyretic drugs in children under 12 years of age should be limited, but disagreed over the length of time. Suggested alternatives were 2 or 3 days. One comment argued that this warning implies that OTC analgesic drug products are unsafe or toxic if used longer than 5 days.

The agency is proposing the following revised warning for children 2 years to under 12 years of age in § 343.50(c)(2)(i): "Do not give this product for pain for more than 5 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition." (see comment 18 above).

The comments submitted no data to support their suggestions for shorter time limitations. The Internal Analgesic Panel based its recommendation of a 5-day limitation for children on reports from poison control center data and on computer simulations that demonstrated that the plasma salicylate level could exceed 20 milligrams per 100 milliliters (mg/mL) (a toxic level) "among some smaller children of a particular age category following the recommended dosage schedule after 5 days" (42 FR 35368). The agency believes these data provide sufficient reason to propose the Panel's recommended 5-day use limitation for children.

23. Several comments opposed the number and length of warning statements the Panel recommended for OTC analgesic and antipyretic drug products. One comment expressed concern that an extensive list of warnings for products containing aspirin, compared to a shorter list for acetaminophen drug products, will lead consumers to conclude that aspirin drug products are more toxic and less useful than acetaminophen drug products. Other comments urged FDA to limit warning statements to those that are scientifically documented, clinically significant, and important to the appropriate use of the products by the average consumer. These comments

further urged that the statements be combined and condensed for ease of consumer understanding and to avoid label clutter that may cause consumers to ignore cautions and warnings in the labeling. One comment suggested the use of supplementary circulars, etc.

FDA agrees that the warning statements for OTC drug products should be limited to those that are scientifically documented, clinically significant, and important for the safe and effective use of the products by consumers. The agency is requiring warning statements for each ingredient on this basis, not on the basis of a comparable number of warnings for each ingredient. Warning statements are also being combined and condensed whenever possible for ease of consumer understanding. In addition, manufacturers are free to design ways of incorporating all required information in labeling, e.g., using flap labels, redesigning packages, or using a package insert.

24. Many comments opposed warnings that cite organs of the body as possible sites of damage by internal analgesic drug products, with some comments referring specifically to the Panel's recommended liver warning for acetaminophen in § 343.50(c)(5)(i). These comments argued that naming an organ that may be injured from an acute overdose or from excessive use of an analgesic drug would place the responsibility of recognizing organ damage on the consumer, who would then be assuming the role of a physician. The comments further argued that this kind of label warning may be misunderstood and may either alarm or cause anxiety in consumers who use drugs rationally. On the other hand, the comments added, such labeling may provide information that may induce individuals to harm themselves.

The comments favored a single, more general warning for all OTC internal analgesic drug products, such as the following: "Do not take this product for more than 10 days unless directed by a physician. Excessive use over a long period of time may cause permanent injury." One comment suggested that, if such a general warning is not adopted, all OTC drug products should bear labeling which fully discloses the conditions under which damage may occur.

The agency is not proposing to include the general warning suggested by the comments in this tentative final monograph. FDA believes that the self-medicating consumer should be made aware of potential risks of a particular OTC drug product through label warnings. As discussed in comment 25

below, the agency agrees that the warnings need not specify the toxic effects on particular organs of the body that can be caused by acute overdose of a drug, as in a suicide attempt, and is not proposing the Panel's recommended liver warning for acetaminophen in this tentative final monograph. However, the agency concludes that the warnings should include specific information on the known side effects or adverse reactions that may occur from use of the drug according to labeled directions, as well as potential dangers that may occur if the labeled directions are exceeded.

The agency concludes that when medical evidence shows that toxicity is associated with the use of an OTC drug, either within its recommended dosage or when used beyond its recommended time limit or dosage (except for acute overdose), it is appropriate to warn consumers of the potential toxicity. In such cases it may be necessary to include organ-specific warnings as well as general labeling statements.

25. Many comments opposed the liver warning recommended by the Panel for acetaminophen drug products in § 343.50(c)(5)(i). "Do not exceed recommended dosage because severe liver damage may occur." Some comments argued that acetaminophen taken in recommended OTC dosage ranges shows no evidence of hepatotoxicity and that the labeling required in § 330.1(g), "Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately," provides sufficient warning to consumers. The comments expressed concern that the liver warning recommended by the Panel may discourage consumers from ever using acetaminophen and that this warning may also encourage suicidal persons to abuse acetaminophen drug products. The comments also argued that "liver warning is especially inappropriate for children's acetaminophen drug products because there is a lack of documented fatalities and serious liver damage in children from acute acetaminophen overdose. The comments stated there may be differences between the metabolism and pharmacokinetics of acetaminophen in children and adults that would cause children to be less vulnerable to acetaminophen toxicity.

Other comments endorsed the recommended liver warning and pointed out that there are no unique signs of acetaminophen toxicity, such as ringing in the ears (tinnitus), and that symptoms of acetaminophen toxicity do not appear until a few days after the overdose.



Noting that consumers are increasing their use of acetaminophen and that fatalities and liver damage have occurred in children, the comments argued that the recommended warning may discourage consumers from exceeding the recommended daily OTC dosage of acetaminophen and make consumers and doctors aware of the consequence of acetaminophen overdose. One comment, concerned about toxicity from the chronic use of acetaminophen in dosages of less than 4 grams (g) per day, suggested that the proposed liver warning be revised to place additional emphasis on the recommended limit of self-treatment with acetaminophen as follows: "Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur." Another comment suggested that the recommended warning be revised to state the dosage that will cause hepatotoxicity, for example, 40 or more 325-mg tablets taken as a single dose.

After evaluating the data and information submitted, the agency has tentatively decided not to adopt the liver warning recommended by the Panel in § 343.50(c)(5)(i). The agency is aware that liver damage can occur from acetaminophen overdose, as explained by the Panel (42 FR 35414). However, the agency believes that warnings need not include information on the specific toxic effects on organs of the body caused by acute overdose of a drug, as in suicide. (See comment 24 above.) The agency also considers it inadvisable to specify hepatotoxic dosage levels in consumer labeling, as one comment suggested, because such labeling could be suggestive to suicidal individuals.

The agency has noted two reports of hepatotoxicity in children who overdosed on acetaminophen. Arena, Rourke, and Sibrack (Ref. 1) described a 3-year-old girl who ingested 35 tablets of acetaminophen 325 mg and suffered decreased consciousness, vomiting, and enlargement of the liver and spleen. At that time the serum ammonia level was 82 micrograms per deciliter ( $\mu\text{g}/\text{dL}$ ). She was admitted to the hospital about 24 hours after ingestion. The serum acetaminophen level was 94 micrograms per milliliter ( $\mu\text{g}/\text{mL}$ ) 24 hours after ingestion; 49 hours after ingestion it dropped to 26  $\mu\text{g}/\text{mL}$ . Seventy-two hours after the overdose, serum transaminase (liver enzyme) levels revealed a peak serum glutamic-oxaloacetic transaminase of 20,376 International Units (I.U.) and a peak serum glutamic-pyruvic transaminase of 13,503 I.U. The patient was alert and in

good spirits by the second day in the hospital and was discharged 1 week later. Seven weeks after discharge her liver enzymes were normal.

Although this child weighed only 31 pounds and had ingested 11,375 g acetaminophen, resulting in phenomenal transaminase levels and a high plasma level of acetaminophen at 24 hours, she survived without any aftereffects. As one comment noted, this case suggests that a child's liver may be less vulnerable to the hepatotoxic effects of acetaminophen overdose than an adult's. The agency points out, however, that before conclusions can be made on the potential toxicity of acetaminophen in children, more data are needed on the metabolism of acetaminophen and clinical observations in children (Ref. 2).

Carlross (Ref. 3) reported the death of a 3½-year-old girl who had an upper respiratory infection and was being treated with acetaminophen. The child was given 120 mg of acetaminophen syrup every 4 hours for three doses. Her doctor later increased the dose to 720 mg every 3 hours. During the next 24 hours she took 5.04 g acetaminophen and was hospitalized for nausea and vomiting. Fourteen hours after the last dose, the acetaminophen level was 5.3 mg/dL (therapeutic range, 1 to 3 mg/dL), well in the range of hepatotoxicity. The child was discharged from the hospital the next morning, but was readmitted 16 hours later with a serum glutamic-oxaloacetic transaminase level of 22,000 I.U. and subsequently died.

The child described by Carlross (Ref. 3) was approximately the same age as the one described by Arena, Rourke, and Sibrack (Ref. 1). Neither child had been treated with an antidote for acetaminophen poisoning, such as *N*-acetylcysteine. It is difficult to explain why the child who had ingested 5.04 g acetaminophen died, and the child who had ingested 11,375 g acetaminophen survived.

Regarding chronic use of acetaminophen within recommended OTC dosages, the agency at this time does not believe that the labeling suggested by the comment, "Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur," is needed. The warnings proposed in § 343.50(c) (1)(i) and (3) in this tentative final monograph already state a 10-day limitation for adults on OTC analgesic self-medication. Furthermore, the agency is aware of only one somewhat convincing case report of acetaminophen hepatotoxicity associated with chronic acetaminophen usage in a normal individual (Ref. 4). A second case has

been reported, but rechallenge results were inconsistent (Ref. 5). As discussed in detail in comment 27 below, Olsson (Ref. 4) described a 55-year-old male who was hospitalized for a flareup of hepatitis while taking a product containing acetaminophen and chlormezanone. He had no recent history of drug or alcohol use, but had a 1-year history of alcohol abuse 7 years before hospitalization. Because this individual developed hepatotoxicity on a low dose of acetaminophen, it is possible that some other problem was also present. (This patient was using a drug containing acetaminophen and chlormezanone, which could have induced the liver injury.) No similar report has appeared despite the wide use of acetaminophen.

A case of chronic use of 325 mg acetaminophen (12 tablets daily for 1 year) was described in which the patient's serum glutamic-oxaloacetic transaminase level was normal before acetaminophen use (Ref. 5). After 1 year of acetaminophen use, liver function tests showed an abnormal serum glutamic-oxaloacetic transaminase level and enlargement of the liver and spleen. After the drug was discontinued, the patient's serum glutamic-oxaloacetic transaminase level returned to normal. After being discharged from the hospital, the patient resumed using 12 tablets of 325 mg acetaminophen daily. Within 2 months he developed pain and was rehospitalized. A monitored rechallenge with one dose of 1,325 mg acetaminophen caused a rise in liver enzyme levels (serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase levels) within 12 to 18 hours. A liver biopsy revealed "bridging necrosis, spanning two portal and two central areas." After discontinuing acetaminophen for 4 months, the individual developed abdominal pain and enlargement of the spleen and had to be treated with azathioprine and prednisone. One year later, when liver function tests were back to normal, the individual again was rechallenged with 1,325 mg acetaminophen without any development of symptoms or rise in liver enzyme levels. This raises the possibility that this patient might have been developing chronic active hepatitis exacerbated by acetaminophen.

Rosenberg et al. (Ref. 6) described two individuals who had taken 3.6 g acetaminophen daily for 1 to 2 weeks. One person had a history of Gilbert's disease (characterized by mild jaundice). Both developed jaundice during a course of infectious mononucleosis. However, because

jaundice can occur in 5 to 10 percent of patients with infectious mononucleosis, the jaundice in these two patients could not definitely be attributed to acetaminophen.

Johnson and Tolman (Ref. 7) described a patient who had been taking 3 g acetaminophen daily and complained of fatigue and loss of appetite. The patient had used no other drugs and was not exposed to toxins other than unidentified cleaning solvents used occasionally. On medical examination there was liver tenderness, and a liver function test showed abnormal results. A liver biopsy revealed evidence of chronic active hepatitis with cirrhosis. The patient had a positive rechallenge, and the liver enzymes increased during the 2 weeks following the rechallenge, indicating that acetaminophen may have caused this elevation. It is possible that the patient had chronic active hepatitis and that acetaminophen exacerbated it. This case was also complicated by the concomitant occasional use of unidentified cleaning solvents.

The agency has noted instances where only a mild overdose of 5 to 7 g of acetaminophen may have produced hepatotoxicity. Ware et al. (Ref. 8) described a person who developed disorientation, jaundice, and fever after using acetaminophen and prescription drugs daily for headaches. Liver enzyme levels were elevated, and a liver biopsy showed centrilobular fibrosis and bridging necrosis with evidence of both an acute and a chronic process. The patient improved after 8 days of unspecified conservative treatment. This case does not prove acetaminophen hepatotoxicity because the other drugs the patient had been taking can cause hepatitis.

Toxic hepatitis was reported in three persons who were regularly ingesting acetaminophen in higher amounts than the recommended OTC dosage (Ref. 9). One patient was an alcoholic who for years had used up to 10 300-mg tablets of acetaminophen daily. During the 4 days before admission to the hospital, this individual drank no alcohol, but used about 100 tablets of acetaminophen. On admission to the hospital, the patient's liver enzymes were elevated, but they fell rapidly over the next 2 to 3 days. The amount of acetaminophen ingested and the subsequent pattern of serum liver enzyme abnormality found in this patient were consistent with a substantial overdose of acetaminophen 2 to 3 days before admission.

The second individual used as much as 5.2 g acetaminophen daily. This patient had disseminated bronchial

cancer, with general ill health and malnutrition. This patient's liver enzymes were elevated while using acetaminophen. After the liver enzymes returned to normal, the patient was rechallenged. The rechallenge of 5.2 to 6.5 g acetaminophen daily produced elevated liver enzyme levels. The plasma acetaminophen level at 24 hours was 37  $\mu\text{g/mL}$ , corresponding to an overdose of the drug.

The third individual had reportedly used 5.2 to 6.5 g acetaminophen daily for 3 weeks before hospitalization. Forty hours after the last dose, the plasma acetaminophen concentration was 15  $\mu\text{g/mL}$ , consistent with an overdose.

Although it is not inconceivable that chronic use of acetaminophen within recommended OTC dosage ranges produces chronic active hepatitis in a very low percentage of people, and although it is possible that acetaminophen can exacerbate preexisting chronic active hepatitis, the agency concludes that the above data do not provide an adequate basis for requiring a labeling statement on liver damage from chronic use of acetaminophen, that is, within recommended daily OTC dosages for longer than 10 days.

Although the liver warning recommended by the Panel in § 343.50(c)(5)(i) is being deleted, the agency shares the comments' concern that symptoms of acetaminophen toxicity do not appear until a few days after an overdose. Following acetaminophen overdose, there is a 24- to 48-hour period of relative well-being, when symptoms of hepatotoxicity do not appear despite the occurrence of liver damage. This "silent period" may create a false sense of security that could delay the use of an antidote, which must be administered promptly in order to be effective (Refs. 10 and 11). To alert consumers that prompt medical attention is essential to the proper management of acetaminophen overdose, the agency is proposing the following overdose warnings for acetaminophen drug products: For products labeled for adults (§ 343.50(c)(1)(iii)), "Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms," or for products labeled for children (§ 343.50(c)(2)(iii)), "Prompt medical attention is critical even if you do not notice any signs or symptoms." For products labeled both for adults and children, the warning for adults would apply, as described in § 343.50(c)(3). Both warnings would be required to follow the general overdose warnings in § 330.1(g) that are required for all OTC drugs.

## References

- (1) Arena, J.M., M.H. Rourke, and C.D. Sibrack, "Acetaminophen: Report of an Unusual Poisoning," *Pediatrics*, 61:68-72, 1978.
- (2) Peterson, R.G., and B.H. Rumack, "Pharmacokinetics of Acetaminophen in Children," *Pediatrics* (Supplement), 62:877-879, 1978.
- (3) Carlsson, H.W., "Misuse of a 'Harmless' Drug," *Archives of Internal Medicine*, 139:688-689, 1979.
- (4) Olsson, R., "Increased Hepatic Sensitivity to Paracetamol," *Lancet*, 2:152-153, 1978.
- (5) Bonkowsky, H.L., G.H. Mudge, and R.I. McMurtry, "Chronic Hepatic Inflammation and Fibrosis Due To Low Doses of Paracetamol," *Lancet*, 1:1016-1018, 1978.
- (6) Rosenberg, D.M., et al., "Acetaminophen and Hepatic Dysfunction in Infectious Mononucleosis," *Southern Medical Journal* 70:660-661, 1977.
- (7) Johnson, G.K., and K.G. Tolman, "Chronic Liver Disease and Acetaminophen," *Annals of Internal Medicine*, 87:302-304, 1977.
- (8) Ware, A.J., et al., "Acetaminophen and the Liver" (letter to the editor), *Annals of Internal Medicine*, 88:267-268, 1978.
- (9) Barker, J.D., D.J. de Carle, and S. Anuras, "Chronic Excessive Acetaminophen Use and Liver Damage," *Annals of Internal Medicine*, 87:299-301, 1977.
- (10) Rumack, B.H., and R.G. Peterson, "Acetaminophen Overdose: Incidence, Diagnosis, and Management in 416 Patients," *Pediatrics* (Supplement), 62:898-903, 1978.
- (11) Ameer, B., and D.J. Greenblatt, "Acetaminophen," *Annals of Internal Medicine*, 87:202-209, 1977.

26. Several comments urged the adoption of a warning statement that advises consumers who have preexisting liver disease, such as hepatitis or infectious mononucleosis, or who may have Reye syndrome, against the use of acetaminophen unless directed by a doctor. The comments cited reports in the medical literature concerning acetaminophen toxicity in persons with liver disease (Refs. 1 through 13). Two comments asserted that there is no evidence to warrant a warning regarding acetaminophen and preexisting liver disease. One of these comments submitted two clinical studies (Refs. 14 and 15) and a report (Ref. 16) to support its position.

In reviewing and evaluating the data and information submitted by the comments, the agency has concluded that there is insufficient evidence at present to propose a warning against the use of acetaminophen at recommended OTC dosages by individuals with preexisting liver disease.

The data and information in Refs. 1 through 7, Refs. 9 through 13, and Ref. 16 presented no evidence to show that OTC dosages of acetaminophen cause



*Gender*

**COPY**

Acetaminophen 650mg SR Tablet  
Tylenol Extra Strength SR  
NDA 19-872  
Reviewer: E.D. Bashaw, Pharm.D.

McNeil Pharmaceutical  
Spring House, PA

Submission Date:  
8/3/90, 10/29/92, 2/25/93  
12/6/93, 1/17/94, 3/15/94  
4/1/94

**Review of an NDA**

**Background**

This NDA has been submitted to provide for a sustained release formulation of acetaminophen. It was originally submitted in 1988 to HFD-120. In a letter dated 11-July-88 the sponsor was notified that the application was refused for filing as the submission lacked clinical efficacy trials and that the supporting biopharmaceutics information was insufficient for approval. Upon receipt of this letter the sponsor undertook a series of clinical efficacy trials. This current submission contains the results of the in-vivo clinical efficacy trials and the results of new supportive in-vivo biopharmaceutic trials.

**Study Overview**

A total of six in-vivo biopharmaceutic trials were done in support of this NDA. Two of them (Studies 58 and 65) were pilot biopharmaceutic trials using experimental formulations. As the sustained release drug product tested in these studies was not intended for clinical development these studies are not included in this NDA.

**Recommendation**

From a biopharmaceutic standpoint, provided that the sponsor commits to the requested phase IV data analysis (Comment #3) and the revisions to the labeling outlined in Comments #4 and #5, the product that is the subject of this application is approvable.

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In this NDA the sponsor has evaluated four different formulations of acetaminophen bi-layer tablets. These formulations were all designed to have slightly different release characteristics. The formulations are summarized below:

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[illegible]

### Analytical

For the biopharmaceutic portion of the NDA, the sponsor used three different analytical methods over the period of time that studies were done. Studies 75, 91, and 92 used a similar extraction and sampling preparation procedures but used different chromatographic columns and conditions, they are referred to in the NDA text as Methods 1 and 2 respectively. Study 117 was done by \_\_\_\_\_ which used their own internal method. The precise conditions, column, and mobile phase of the \_\_\_\_\_ method is not contained in the analytical report. However, sufficient validation information is submitted to validate the assay for Study 117. It was partially for this lack of a "full" analytical report that the study report was downgraded by this reviewer from pivotal to supportive in the classification scheme used in this NDA review.

## Comparison of Methods

As noted above Methods 1 and 2 differed in the specifics of the column and conditions used. Both methods utilize \_\_\_\_\_ The differences between the two methods are summarized below:

Method 1 \_\_\_\_\_

Method 2 \_\_\_\_\_

Functionally these differences were not significant in their impact on the outcome of this study. In an effort to assess the cross-study performance of the assay methods reproduced below are the summary data tables for the standard curves used throughout Studies 75, 91, 92 and 117.

Biostudy 75

Standard	Average (µg/mL)	N	% of Theor.	% C.V.
0.5 µg/mL	0.39	39	79.8	31
1.0 µg/mL	0.88	39	87.5	13
2.0 µg/mL	2.3	39	115	7.5
5.0 µg/mL	4.9	39	97.1	1.1
10.0 µg/mL	10.0	39	99.9	1.5
15.0 µg/mL	15.0	39	100	1.1
20.0 µg/mL	19.9	39	99.3	2.8
25.0 µg/mL	25.0	39	100	0.64

Biostudy 117

Standard	Average (µg/mL)	N	% of Theor.	% C.V.
0.5 µg/mL	0.48	12	96.4	7.2
1.0 µg/mL	1.0	12	101	6.0
2.0 µg/mL	2.0	12	102	3.9
5.0 µg/mL	5.2	12	103	3.0
10.0 µg/mL	9.8	12	97.7	2.4
20.0 µg/mL	20.1	12	101	2.2

Biostudy 91

Standard	Average (µg/mL)	N	% of Theor.	% C.V.
0.5 µg/mL	0.49	42	98.4	15
1.0 µg/mL	1.02	42	102	4.6
2.0 µg/mL	2.02	42	101	3.4
5.0 µg/mL	5.0	42	99.9	1.3
10.0 µg/mL	9.9	42	99.3	1.0
15.0 µg/mL	15.0	42	100	0.92
20.0 µg/mL	20.0	42	100	0.67
25.0 µg/mL	25.0	42	100	0.44

Biostudy 92

Standard	Average (µg/mL)	N	% of Theor.	% C.V.
0.5 µg/mL	0.51	53	102	7.5
1.0 µg/mL	1.0	53	99.4	3.1
2.0 µg/mL	2.0	53	100	1.9
5.0 µg/mL	5.0	53	100	1.2
10.0 µg/mL	10.1	53	101	1.1
15.0 µg/mL	15.0	53	100	1.3
20.0 µg/mL	19.8	53	99.1	1.4
25.0 µg/mL	25.1	53	100.4	1.0

As shown above on a daily basis the assays are quite comparable in the variability associated with the daily standard curves used, except for the 0.5 µg/mL standard used in Study 75. In this study the %CV approaches 35%. This is at variance with the %CV for the same standard

concentration in Studies 91, 92, and 117 (7.2, 15, 7.5% respectively). However, this increased variability at low concentrations is not significant as less than 10% of all concentrations in this study were below this limit and the next higher standard at 1 ng/ml had a 13% C.V.

### Analytical Summary

Although the sponsor used a series of analytical methods over time the sponsor has submitted sufficient information to validate the individual methods. Each of the study summary sheets accompanying this review contain a summary section dealing with the quantification limits, ranges of the assay, and the mean recovery. In light of the information submitted with the individual summary reports in the NDA all three methods can be considered validated for the purposes of this NDA.

### Pivotal Trials Overview

In this NDA the sponsor has done three trials that can be considered pivotal from a biopharmaceutical perspective; study 75- a single dose study, study 91- a food/fasting study, and study 92 a multiple dose steady-state study. Detailed descriptions of the studies, results, and figures are included as Appendix A, pages 11-35 of this review. This section will discuss each of the studies in turn and the information gained from each of the trials.

#### Study 75

This study was a single dose study comparing the clinically studied caplet formulation C-112-7D to 2x500 Tylenol Extra-Strength Tablets and to 1300mg of Adult Tylenol liquid (39ml, 500mg/15ml). The study was carried out in 25 subjects as a three way, randomized crossover study, with one week between treatments. One subject (#1) discontinued from the trial for unknown reasons after the first treatment phase and was replaced by subject #25.

The results of this study (on a dose normalized basis) are summarized in Appendix A, pages 12-16. In general the results indicate that the SR-APAP product that is the subject of this NDA is bioequivalent to the liquid APAP reference in terms of AUC,  $AUC_{inf}$ , and  $C_{max}$  (90% Confidence Interval, Two 1-sided t-test). In relation to the dose normalized immediate release APAP tablet, the SR product is bioequivalent to it in terms of AUC (90% CI=85.5-102%) and  $AUC_{inf}$  (90% CI=84.9-100.6%). It is bioequivalent in term of  $C_{max}$  (90% CI=61.2-79%).

In terms of relative bioavailability, the sponsors product is 82.4% available relative to the solution and 93.9% available as compared to the reference tablet. The net result of this study is that the oral bioavailability of the SR tablet is equal to that of the reference tablet. Considering that these comparisons are that of a sustained release product to, an immediate release reference product, the differences seen are those that would normally be expected from such a comparison (i.e.,  $C_{max}$ ).

#### Study 91

This study was done to determine bioequivalency between the clinical lot of product C-112-7D and a full production batch of C-112-10C. In addition the study included a comparison of the effect of a high fat breakfast on the release of drug from the full production batch C-112-10C. Twenty-four subjects were enrolled in the study which was a randomized, four-way, crossover study with a one week washout period between doses. One subject (#20) discontinued



from the trial for unknown reasons after the first treatment phase and was replaced by subject #25.

The results of this study are summarized in Appendix A, pages 17-25 of this review. In regards to the comparison between the clinically studied lot and the full production lot the two lots are bioequivalent in terms of AUC,  $AUC_{inf}$  and  $C_{max}$ . Surprisingly, the products are bioinequivalent in terms of  $T_{max}$  (90% CI=63-126%). Visual inspection of the plasma level time curves for these two treatments (pages 18 and 19) suggest that this difference was due to the limitations of plasma sampling and variability in plateau phase of the plasma level time curve. An examination of the data reveals that the means for  $T_{max}$  are 1.21 and 1.27 hrs. for lots 7D and 10D, respectively and that the ANOVA shows no significant differences for this comparison. Given this information and the observed variability in the plasma level time curves themselves, the finding of  $T_{max}$  bioinequivalency should not be considered a failing.

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In relation to the other objectives of this study the sponsor included in this study a sub-standard high fat breakfast consisting of 2 eggs, 3 strips of bacon, toast, and coffee. This is not the diet required by the FDA for the testing of controlled release dosage forms. Even so the reduced fat breakfast in this study had a significant impact on the dosage form. In terms of product performance there are borderline differences in both the AUC and  $AUC_{inf}$  for this product. In terms of  $C_{max}$  and  $T_{max}$  there are statistically significant differences between the treatments with significant magnitude to question the effectiveness of this dosage form following meals, especially in terms of the onset of pain relief. It is this reviewer's belief that if the sponsor had used the FDA high fat breakfast that this effect would only be magnified. Because of the findings in this study the instructions for use of this product should include directions to "take on an empty stomach".

Finally, in this study the sponsor had the Adult Tylenol liquid (500mg/15ml) as a reference treatment for assessing oral bioavailability. Compared to the oral liquid the clinical lot is 84% bioavailable and the production batch is 90% bioavailable. From a cross-study perspective the oral bioavailability of the clinical batch is comparable to that determined in study 75 (82.4%).

The higher bioavailability of the production batch is consistent with the sponsor's development of this formulation to have a faster initial release rate. In terms of bioequivalency the findings are as one would expect when one compares a sustained release dosage form to an immediate release solution. Both tablets fail equivalency testing for  $C_{max}$  and  $T_{max}$  and pass  $AUC_{inf}$  testing.

Overall this study has demonstrated equivalency between the clinically studied lot and full production lot of product. In addition, the sponsor has demonstrated a significant food effect that should be reflected in the label.

### Study 92

This study was a multiple dose steady-state study in 24 subjects comparing 2x500mg Extra-Strength Tylenol tablets to 2x650mg APAP-SR caplets. Throughout the study five patients discontinued from the trial after completing one phase. Three patients for unknown reasons, one for hepatitis A, and two subjects for mildly elevated liver enzymes. The two subjects with mildly elevated liver enzymes had received the test (APAP-SR) treatment. Subsequent to this, all subjects had repeat liver enzymes done for surveillance purposes. All five subjects were replaced. No additional incidences of elevated liver enzymes were noted.

This study was done with a two day dosing period and a five day washout period between treatments. In order to facilitate the statistical comparison of these products the doses were

normalized to 1300mg. The results of this study are summarized on pages 26-36 of this review. Following the first dose statistically significant differences were noted for C<sub>max</sub> (90% CI=53.5-65.1%) between the test and reference products. The products were bioequivalent in terms of the extent of absorption.

Following repeat dosing, the test product was found to be bioequivalent to the reference product in terms of AUC, C<sub>max</sub>, C<sub>ps</sub>, and C<sub>min</sub> (i.e., 90% CI within the 80-125% reference bound).

### **Pivotal Trials Summary**

In the previous three studies the sponsor has adequately established links between the clinically studied and to be marketed dosage forms. From a biopharmaceutic perspective with the demonstration of bioequivalency to an appropriately dosed reference product at steady-state, and the performance of an acceptable food-fasting study, the sponsor has addressed all of the in-vivo biopharmaceutic issues required for approval.

### **Supportive Trials Overview & Summary**

Since the time of the original filing of this NDA the sponsor conducted an additional study with the intention of demonstrating bioequivalency to the marketed 325mg regular strength tablets and to validate some of the clinical work. This study #117 was a single dose comparison with a full production batch of C-112-10C (APAP-SR) compared to 2x325mg Tylenol tablets dosed q4h x 2 doses.

The summary data from this trial is contained on pages 36-42 of this review. In general the study demonstrated that a single dose of the APAP-SR product that is the subject of this formulation is bioequivalent 2x325mg q4h x 2 doses. As such this study validates the work done in study 75, 91, and the first dose of 92. However, using the data from this trial the sponsor has attempted to perform some very superficial cross-study pharmacodynamics.

Attached as pages 41 and 42 are the results, as presented by the sponsor, of clinical trials 88-856 and 88-857, respectively. On these pages the sponsor presents plots of the Pain Intensity Difference (PID) and Pain Relief scores. The sponsor has asked us, in their narrative, to note that the PID and Pain Relief scores appear to track the plasma level time curve of 117 in an almost 1 to 1 manner. From this they conclude that there is a pharmacodynamic relationship for acetaminophen and that even when plasma levels of the APAP-SR product fall below those of the immediate release treatment there are sufficient blood levels to maintain the clinical effect as measured by PID and Pain Relief.

While interesting, the data analysis carried out by the sponsor is lacking. In terms of the study itself, the sponsor should have made study 117 a true pk/pd trial with subjects undergoing molar extraction or any other validated pain model. Then the sponsor could have done a true pk/pd analysis instead of what was done. Even with the data in hand the sponsor should have made a general assumption that, as the studies were demographically indistinguishable, the plasma levels could be used in a true pk/pd analysis. The data should have been replotted as PID vs. Concentration, the degree and shape of hysteresis should have been noted, and the data should have been collapsed via any of the available pk/pd packages available to determine an EC<sub>50</sub> and a keo value. As APAP is an old drug doubtless literature estimates of EC<sub>50</sub> are available and these

literature values could have been compared to the calculated values. Then the sponsor would have been on firmer ground in making conclusions regarding the data, beyond asking the reader to make non-specific visual comparisons. As the sponsor has brought this issue up and tried to make claims from it, these comments will be sent to the sponsor as a phase IV commitment.

### Dissolution

As noted on the first page of this review this product is a bilayer tablet. The top layer is consists of 325mg of acetaminophen in a readily dissolvable form and the lower tablet contains 325mg of acetaminophen in a much slower dissolving form. Throughout the development dissolution testing has been a key element of their in-vitro testing protocols. For the purposes of setting a dissolution specification the sponsor has chosen the following method and specifications:

USP Apparatus 2  
Paddle Speed 50 rpm  
Simulated Gastric Fluid w/o Enzymes

Time	Limits
15 min.	—
1 hr.	—
3 hr.	—

Reproduced below is a summary table of the performance of lot C-112-10C (the lot used in studies 91, 92, and 117) in three media:

TIME	Percent Dissolved		
	SGF	SIF	Water
0			
10	—		
20	—		
40	—		
60	—		
90	—		
120	—		
150	—		
240	—		

The dissolution method as proposed and the proposed specifications are acceptable.

## Labeling

As this product is intended for OTC marketing there is no pharmacokinetic labeling, per se, for review. However, analysis of the data from these trials has indicated the need for food warning and for the need for the directions to mention that the dosage form should be taken intact. Failure to take the dosage form intact could cause rapid release of the entire dose in a large bolus like manner. These conclusions have been forwarded to the sponsor for action and reflected in the Comments section below.

## Comments

1.) The sponsor needs to improve their data checking procedures and how they handle their data. For example, in study 75, subject #16 had a 15min plasma level of 23.5 and a 30min level of 1.4ug/ml. While this might be possible with a drug that is rapidly and completely absorbed and extensively compartmentalized, this is not the case here as this subject received the SR-tablet. It is apparent from this and other examples throughout all of the studies that the sponsor merely analyzed the data and did not bother to look at it in a critical manner. Re-analysis of this subjects data with a 15min value of 1ng/ml reduced the total AUC by approximately 10%. While less instances of such data were seen with the other studies, the fact that it existed at all in this report without an explanation or comment in the narrative section of the NDA is cause for concern.

2.) The diet used in study 91 is not the recommended FDA high fat diet. The diet as spelled out in the controlled release guideline for a food/fasting study is as follows:

- 2 Eggs (fried in butter)
- 2 Pieces of Bacon
- 2 Pieces of Toast w/Butter
- 2-4oz. of Hash Brown Potatoes
- 8oz of Whole Milk

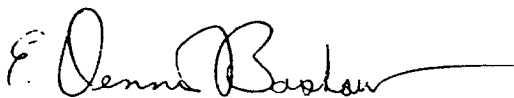
This guideline has been in place since 1984 and failure to use this diet is both a potential filing issue and an approvability issue. The only reason that the diet that the sponsor used in trial 91 was accepted was that even though it was a diet lower in fat content, it was still able to produce a robust food effect. The sponsor is put on notice that future studies using a non-FDA recommended high fat diet will be considered either as grounds for refusal to file or non-approval.

3.) In study 117 the sponsor has attempted to make implied pk/pd conclusions from a visual cross-study inspection of PID and Pain Relief score data and plasma levels. As the sponsor raised this issue the sponsor should, as a phase IV commitment, provide the following analysis. Assuming that the studies in question are demographically indistinguishable, the data from the trials should be combined and the clinical variables plotted as a function of plasma level. The direction of hysteresis should be noted, and the data should then be collapsed via any of the available pk/pd packages available to determine an EC50 and a keo value. Using literature estimates these values could be compared to the calculated values from the two trials. With such

information the sponsor would then be able to propose any pk/pd claims based on data and not the subjective nature of visual comparisons.

4.) As noted in study #91 there is a pronounced food effect with this product in relation to both Cmax and Tmax. The magnitude of this effect is sufficient to raise questions regarding the onset of relief when administered with meals. For this reason the label should instruct the patient to take the dosage form on an empty stomach.

5.) As this bi-layer tablet depends upon dosage form integrity to demonstrate sustained release package warnings should include a statement to the effect that the dosage form should be taken whole and not crushed, chewed, or broken in half, etc. Because of concerns on this matter this reviewer contacted the sponsor by phone on 3/14/94 and conveyed his concerns to Ms. Vivian Chester, Executive Director of Regulatory Affairs, McNeil. In a written response received 3/21/94, McNeil has included the following statement under directions for use, "Do not divide, crush, chew or dissolve the caplet.". This language was selected based on similar language used in the EFFIDAC/24 label<sup>1</sup>. This language is acceptable to the reviewer.



E. Dennis Bashaw, Pharm.D.  
Pharmacokineticist  
Pilot Drug Evaluation Staff

Peer Reviewer: Ruth E. Stevens, PhD. \_\_\_\_\_

CC: NDA19-872 (ORIG),  
HFD-007/DIV File  
HFD-007/CSO/ Barnes  
HFD-007(Bashaw x 2)  
HFD-426 (Drug, Chron, Fleischer)  
HFD-344(Viswanathan)  
HFD-19.

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<sup>1</sup> EFFIDAC/24 is a 24hr OTC product containing 240mg of pseudoephedrine approved for marketing last year by the FDA.

### Appendix A, Pivotal Trials

<b>Study 75</b>	Clinical lot vs. Extra Strength Adult Tylenol Liquid and Tablets									
	Single Dose	*	*	*	*	*	*	*	*	
<b>Study 91</b>	NDA formulation fed vs. fasted vs. Clinically studied formulation									12
	Single Dose	*	*	*	*	*	*	*	*	
<b>Study 92</b>	NDA formulation vs. Extra Strength Tylenol Tablets,									17
	Multiple Dose	*	*	*	*	*	*	*	*	26

NDA# 19-872/S-001 Submission Date: \_\_\_\_\_ Vol. \_\_\_\_\_

Study Type: A Comparison of Controlled Absorption and Conventional  
Acetaminophen Formulations Under Single-Dose Conditions.

(Protocol 87-777)

Study # 75

Investigator: /

Study Site: /

Single Dose: X Multiple Dose: \_\_\_\_\_

Subjects: Normal X Patients \_\_\_\_\_ Young X Elderly \_\_\_\_\_

Impaired: Renal \_\_\_\_\_ Hepatic \_\_\_\_\_ Other \_\_\_\_\_

Crossover 3-way Parallel \_\_\_\_\_ Washout 7 Days N= 24 ; M= 24 ; F= 0

Subject Healthy Adult Males  
Type: \_\_\_\_\_

Subject  
Type: \_\_\_\_\_

Weight Mean= 156 Range= 141-184 lb

Weight Mean= \_\_\_\_\_ Range= \_\_\_\_\_

Age Mean= 27 Range= 18-48 yr

Age Mean= \_\_\_\_\_ Range= \_\_\_\_\_

Treatment	Code	Dose	Dosage Form	Strength	Lot/Batch#	Size
Treatment	A	= 2 x 650mg acetaminophen in the fasted state	Acetaminophen SR Caplet	APAP 650mg/caplet	C-112-7D	103kg
Treatment	B	= 1300mg acetaminophen in the fasted state	Extra- Strength TYLENOL® Liquid	APAP 500mg/15mL	CAM143	--†
Treatment	C	= 2 x 500mg acetaminophen in the fasted state	Extra- Strength TYLENOL® Tablet	APAP 500mg/tablet	BPA178	--†
Treatment		=				

† Production-scale batch.

Fasted A, B & C ; overnight fast and 4 hrs. post-dosing.

Nonfast \_\_\_\_\_ Food Study No FDA High Fat Breakfast \_\_\_\_\_

Biostudy 75 (continued):

Samples: Plasma 8 mL ; 0, 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6,  
8, 10, 12, 16 and 24 hrs

Urine NA ;

Feces NA ;

Assay Method:

(McNeil CPC Bioanalytical Method 1)

Assay Sensitivity: Quantification Limit 0.5µg/mL; Range 0.5-25µg/mL

Assay Accuracy: Mean Recoveries 98.0-102.2% (10 determinations of range)

Labeling Claims from Study (Study Conclusions):

1. Acetaminophen was fully bioavailable (extent) from Acetaminophen SR Caplets (Formula C-112-7D) when compared with Extra-Strength TYLENOL® Tablets.
2. Acetaminophen was not as bioavailable from Acetaminophen SR Caplets when compared with Extra-Strength TYLENOL® Liquid, a more rigorous standard.

~~00-00001~~ 13



# Biostudy 75

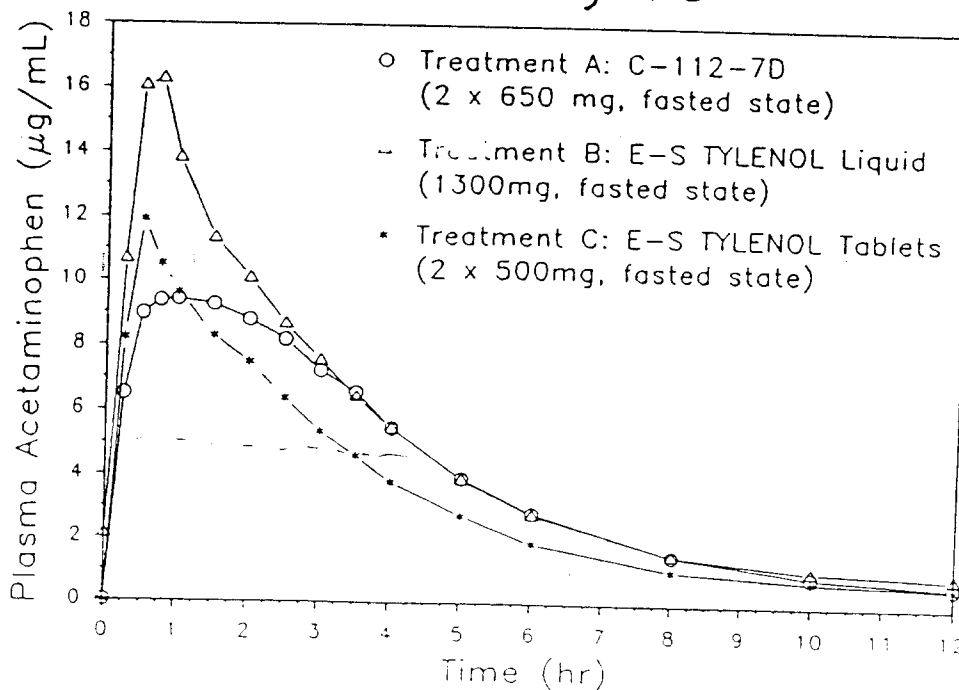
Mean Plasma Acetaminophen $\mu\text{g/mL}$ (S.D.)			
Time (hr)	C-112-7D (2 x 650mg, fasted)	Extra-Strength TYLENOL® Liquid (1300mg, fasted)	Extra-Strength TYLENOL® Tablet (2 x 500mg, fasted)
0.0	0.0 (0.0)	0.1 (0.4)	0.0 (0.0)
0.25	6.5 (6.4)	10.7 (6.9)	8.2 (6.6)
0.5	9.0 (5.8)	16.0 (6.7)	11.9 (6.8)
0.75	9.4 (5.0)	16.3 (4.8)	10.5 (4.8)
1.0	9.4 (3.5)	13.8 (3.4)	9.6 (3.0)
1.5	9.3 (2.6)	11.3 (2.4)	8.3 (1.6)
2.0	8.8 (2.0)	10.1 (1.9)	7.5 (1.4)
2.5	8.2 (2.0)	8.7 (1.7)	6.4 (1.2)
3.0	7.2 (1.9)	7.6 (1.7)	5.4 (1.2)
3.5	6.6 (1.9)	6.4 (1.6)	4.6 (1.0)
4.0	5.5 (1.5)	5.5 (1.5)	3.8 (1.0)
5.0	4.0 (1.3)	3.9 (1.3)	2.8 (1.0)
6.0	2.9 (1.1)	2.8 (1.0)	1.9 (0.8)
8.0	1.5 (0.7)	1.6 (0.7)	1.1 (0.5)
10.0	0.9 (0.3)	1.1 (0.4)	0.8 (0.2)
12.0	0.6 (0.2)	0.9 (0.3)	0.6 (0.1)
16.0	0.7 (0.1)	0.6 (0.1)	0.5 (0.0)
24.0	0.6 (0.0)	0.7 (0.3)	0.0 (0.0)

	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
C <sub>MAX</sub> ( $\mu\text{g/mL}$ )	12.7 (4.2)	19.1 (4.7)	18.7 (7.4) <sup>1</sup>
T <sub>MAX</sub> (hr)	1.16 (0.84)	0.69 (0.45)	0.80 (0.52)
AUC <sub>INF</sub> ( $\mu\text{g} \cdot \text{hr/mL}$ )	48.7 (14.8)	59.1 (16.5)	51.9 (12.9) <sup>1</sup>

<sup>1</sup>Solid reference data normalized for dose.

59/49.0

# Biostudy 75



00-000-14

**Table 1 (Revised 2/4/93): Pharmacokinetic Parameters — Clinical Formula vs Liquid Reference**

Mean ( $\pm$ S.D.)								
Parameter	C-112-7D (1300mg, fasted state)	Extra-Strength TYLENOL® Liquid (1300mg, fasted state)	90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power	Percent <sup>1</sup> Detectable Difference	
AUC ( $\mu\text{g} \cdot \text{hr/mL}$ )	46.5 (14.5)	56.6 (15.8)	-25.13	to -10.26	0.0002	0.9809	14.21	
AUC <sub>INF</sub> ( $\mu\text{g} \cdot \text{hr/mL}$ )	48.7 (14.8)	59.1 (16.5)	-24.91	to -10.15	0.0002	0.9822	14.11	
C <sub>MAX</sub> ( $\mu\text{g/mL}$ )	12.7 (4.2)	19.1 (4.7)	-44.80	to -22.47	0.0001	0.7429	21.35	
T <sub>MAX</sub> (hr)	1.16 (0.84)	0.69 (0.45)	28.99	to 107.38	0.0055	0.1054	74.94	
K <sub>EL</sub> (hr <sup>-1</sup> )	0.316 (0.084)	0.304 (0.079)	-4.62	to 12.43	0.4452	0.9364	16.30	
T <sub>1/2</sub> (hr)	2.36 (0.73)	2.48 (0.86)	-15.75	to 6.18	0.4677	0.7591	20.97	

<sup>1</sup>Difference detectable between two means with a power of 80%.

**Table 2 (Revised 2/4/93): Pharmacokinetic Parameters — Clinical Formula vs Solid Reference**

Mean ( $\pm$ S.D.)								
Parameter	C-112-7D (1300mg, fasted state)	Extra-Strength TYLENOL® Tablets (1000mg, fasted state)	90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power	Percent <sup>1</sup> Detectable Difference	
AUC ( $\mu\text{g} \cdot \text{hr/mL}$ )	46.5 (14.5)	49.1 <sup>1</sup> (13.1)	-13.78	to 3.34	0.3112	0.9346	16.37	
AUC <sub>INF</sub> ( $\mu\text{g} \cdot \text{hr/mL}$ )	48.7 (14.8)	51.9 <sup>1</sup> (12.9)	-14.48	to 2.33	0.2314	0.9427	16.07	
C <sub>MAX</sub> ( $\mu\text{g/mL}$ )	12.7 (4.2)	18.7 <sup>1</sup> (7.4)	-43.60	to -20.78	0.0001	0.7233	21.81	
T <sub>MAX</sub> (hr)	1.16 (0.84)	0.80 (0.52)	10.56	to 77.75	0.0325	0.1270	64.24	
K <sub>EL</sub> (hr <sup>-1</sup> )	0.316 (0.084)	0.350 (0.065)	-17.01	to -2.18	0.0352	0.9813	14.18	
T <sub>1/2</sub> (hr)	2.36 (0.73)	2.05 (0.38)	2.01	to 28.57	0.0595	0.5827	25.39	

<sup>1</sup>Difference detectable between two means with a power of 80%.

<sup>2</sup>Dose normalized to higher dose.

Table 5: *ln*-Transformed Pharmacokinetic Parameters for Biostudy 75 - Clinical Formula vs Liquid Reference

Parameter	Mean ( $\pm$ S.D., %C.V.)		Mean Ratio <sup>1</sup> (T/R %)	90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power (%)
	C-112-7D (1300mg, fasted)	ES-TYLENOL® Liquid (1300 mg, fasted)					
LAUC	3.792 (0.325, 8.6%)	3.999 (0.275, 6.9%)	81.3	74.4	to 88.8	0.0003	94
LAUC <sub>INF</sub>	3.841 (0.314, 8.2%)	4.043 (0.273, 6.8%)	81.7	75.0	to 88.9	0.0002	92
LC <sub>MAX</sub>	2.490 (0.322, 12.9%)	2.916 (0.279, 9.6%)	65.3	57.5	to 74.2	0.0001	62

<sup>1</sup>Mean Ratio = 100 \* exp(m<sub>1</sub> - m<sub>2</sub>) - reference for *ln*-transformed parameters.

Table 6: *ln*-Transformed Pharmacokinetic Parameters for Biostudy 75 - Clinical Formula vs Solid Reference

Parameter	Mean ( $\pm$ S.D., %C.V.)		Mean Ratio <sup>1</sup> (T/R %)	90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power (%)
	C-112-7D (1300mg, fasted)	ES-TYLENOL® Tablets (1000mg, fasted)					
LAUC	3.792 (0.325, 8.6%)	3.860 <sup>2</sup> (0.268, 6.9%)	93.4	85.5	to 102.0	0.2004	94
LAUC <sub>INF</sub>	3.841 (0.314, 8.2%)	3.920 <sup>2</sup> (0.248, 6.3%)	92.4	84.9	to 100.6	0.1259	92
LC <sub>MAX</sub>	2.490 (0.322, 12.9%)	2.853 <sup>2</sup> (0.399, 14.0%)	69.6	61.2	to 79.0	0.0001	62

<sup>1</sup>Mean Ratio = 100 \* exp(m<sub>1</sub> - m<sub>2</sub>) - reference for *ln*-transformed parameters.

<sup>2</sup>Data normalized to higher dose

NDA# 19-872/S-001 Submission Date: \_\_\_\_\_ Vol. \_\_\_\_\_

Study Type: A Comparison of Sustained-Release Acetaminophen Caplet Formulations in the Fed and Fasted States, and a Conventional Solution Formulation in the Fasted State Under Single-Dose Conditions.  
(Protocol 89-955) Study # 91

Investigator: [Signature]  
Study Site: [Signature]

Single Dose: X Multiple Dose: \_\_\_\_\_

Subjects: Normal X Patients \_\_\_\_\_ Young X Elderly \_\_\_\_\_  
Impaired: Renal \_\_\_\_\_ Hepatic \_\_\_\_\_ Other \_\_\_\_\_

Crossover 4-way Parallel \_\_\_\_\_ Washout 7 Days N= 24 ; M= 24 ; F= 0

Subject Healthy Adult Males  
Type:

Weight Mean= 164 Range= 141-190 lb

Age Mean= 27 Range= 18-37 yr

Subject  
Type:

Weight Mean= \_\_\_\_\_ Range= \_\_\_\_\_

Age Mean= \_\_\_\_\_ Range= \_\_\_\_\_

Treatment	Code	Dose	Dosage Form	Strength	Lot/Batch#	Size
Treatment	A	= 2 x 650mg acetaminophen in the fasted state	Acetaminophen SR Caplet	APAP 650mg/caplet	C-112-7D	103kg
Treatment	B	= 2 x 650mg acetaminophen in the fasted state	Acetaminophen SR Caplet	APAP 650mg/caplet	C-112-10C	990kg
Treatment	C	= 2 x 650mg acetaminophen in the fed state	Acetaminophen SR Caplet	APAP 650mg/caplet	C-112-10C	990kg
Treatment	D	= 1300mg acetaminophen in the fasted state	Extra-Strength <u>TYLENOL</u> Liquid	APAP 500mg/15mL	EMM096A	--†

†Production-scale batch.

Fasted A, B & D ; overnight fast and 4 hrs. post-dosing.  
Nonfast C Food Study Yes FDA High Fat Breakfast Yes

Biostudy 91 (continued):

Samples: Plasma 7 mL ; 0, 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hr

Urine NA ;

Feces NA ;

Assay Method:

(McNeil CPC Bioanalytical Method 2)

Assay Sensitivity: Quantification Limit 0.5 $\mu$ g/mL; Range 0.5-40 $\mu$ g/mL

Assay Accuracy: Mean Recoveries 87.0-96.7% (2 determinations of range)

Labeling Claims from Study (Study Conclusions):

1. The Clinical Formula (C-112-7D) and NDA Formula (C-112-10C) of Acetaminophen SR Caplets were bioequivalent.
2. Food delayed absorption, but did not affect the extent of acetaminophen absorption from Acetaminophen SR Caplets.
3. 1300mg acetaminophen was fully bioavailable (extent) from Acetaminophen SR Caplets relative to Extra-Strength TYLENOL<sup>®</sup> Liquid.

# Biostudy 91

Time (hr)	Mean Plasma Acetaminophen $\mu\text{g/mL}$ (S.D.)			
	C-112-7D (2 x 650mg, fasted)	C-112-10C (2 x 650mg, fasted)	C-112-10C (2 x 650mg, fed)	Extra-Strength TYLENOL® Liquid (1300mg, fasted)
0.0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.37 (1.81)
0.25	6.00 (4.14)	6.94 (5.51)	1.70 (0.82)	10.20 (5.97)
0.5	7.94 (3.92)	8.38 (3.63)	4.17 (3.92)	16.48 (5.17)
0.75	9.31 (3.20)	9.47 (3.04)	4.75 (4.11)	16.94 (4.57)
1.0	10.24 (3.08)	10.20 (2.46)	5.15 (3.90)	16.11 (3.87)
1.5	10.19 (3.08)	10.28 (2.30)	6.58 (4.06)	14.46 (3.36)
2.0	10.05 (2.75)	10.14 (2.50)	7.69 (3.46)	12.85 (3.22)
2.5	9.48 (2.70)	9.64 (2.69)	8.16 (3.07)	11.04 (3.10)
3.0	8.68 (2.63)	9.11 (2.72)	8.40 (3.21)	9.65 (2.95)
3.5	7.85 (2.58)	8.35 (2.76)	8.42 (2.99)	8.49 (2.83)
4.0	6.93 (2.42)	7.67 (2.60)	8.01 (2.80)	7.28 (2.63)
5.0	5.39 (2.02)	6.17 (2.26)	7.28 (2.60)	5.57 (2.25)
6.0	4.28 (1.75)	4.70 (1.96)	5.47 (2.18)	4.21 (1.89)
8.0	2.52 (1.19)	2.78 (1.35)	3.14 (1.51)	2.45 (1.25)
10.0	1.64 (0.81)	1.69 (0.81)	1.91 (1.02)	1.65 (0.83)
12.0	1.24 (0.56)	1.29 (0.57)	1.37 (0.71)	1.21 (0.55)
16.0	0.89 (0.28)	0.89 (0.23)	0.91 (0.35)	0.83 (0.29)
24.0	0.77 (0.20)	0.85 (0.42)	0.80 (0.20)	0.58 (0.03)

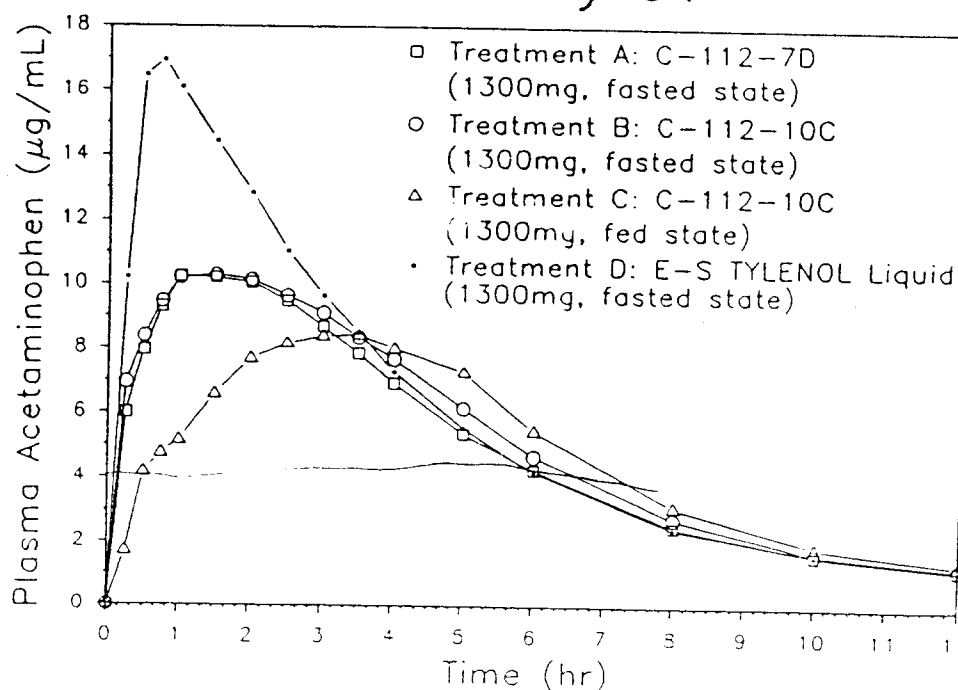
  

	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
C <sub>MAX</sub> ( $\mu\text{g/mL}$ )	11.59 (2.81)	11.94 (2.56)	10.08 (3.28)	18.45 (4.49)
T <sub>MAX</sub> (hr)	1.21 (0.78)	1.27 (0.96)	2.95 (1.34)	0.80 (0.47)
AUC <sub>INF</sub> ( $\mu\text{g} \cdot \text{hr/mL}$ )	66.15 (23.37)	70.53 (21.53)	63.47 (24.54)	78.44 (25.78)

*Why so much greater than previous study?*

*78/16.0*

## Biostudy 91



*00-0000 19*

**Table 1 (Revised 2/4/93): Pharmacokinetic Parameters — Clinical Formula vs NDA Formula**

Parameter	Mean ( $\pm$ S.D.)		90% Confidence Intervals (2 one-sided t-tests)	Pr >  T	Power	Percent <sup>1</sup> Detectable Difference
	C-112-7D (1300mg, fasted state)	C-112-10C (1300mg, fasted state)				
AUC ( $\mu\text{g} \cdot \text{hr/mL}$ )	62.14 (22.38)	66.15 (20.87)	-16.22 to 4.12	0.3246	0.8141	19.68
AUC <sub>INF</sub> ( $\mu\text{g} \cdot \text{hr/mL}$ )	66.15 (23.37)	70.53 (21.53)	-16.40 to 3.98	0.3128	0.8128	19.71
C <sub>MAX</sub> ( $\mu\text{g/mL}$ )	11.59 (2.81)	11.94 (2.56)	-13.23 to 7.40	0.6390	0.8022	19.95
T <sub>MAX</sub> (hr)	1.21 (0.78)	1.27 (0.96)	-36.34 to 26.51	0.7949	0.1289	60.78
K <sub>EL</sub> (hr <sup>-1</sup> )	0.234 (0.072)	0.214 (0.042)	-2.19 to 20.56	0.1826	0.7120	22.00
T <sub>1/2</sub> (hr)	3.29 (1.13)	3.38 (0.81)	-13.44 to 7.74	0.6553	0.7789	20.48

<sup>1</sup>Difference detectable between two means with a power of 80%.

**Table 2 (Revised 2/4/93): Pharmacokinetic Parameters — NDA Formula Fed vs Fasted**

Parameter	Mean ( $\pm$ S.D.)		90% Confidence Intervals (2 one-sided t-tests)	Pr >  T	Power	Percent <sup>1</sup> Detectable Difference
	C-112-10C (1300mg, fed state)	C-112-10C (1300mg, fasted state)				
AUC ( $\mu\text{g} \cdot \text{hr/mL}$ )	60.01 (23.33)	66.15 (20.87)	-19.45 to 0.89	0.1329	0.8141	19.68
AUC <sub>INF</sub> ( $\mu\text{g} \cdot \text{hr/mL}$ )	63.47 (24.54)	70.53 (21.53)	-20.20 to 0.18	0.1059	0.8128	19.71
C <sub>MAX</sub> ( $\mu\text{g/mL}$ )	10.08 (3.28)	11.94 (2.56)	-25.94 to -5.31	0.0139	0.8022	19.95
T <sub>MAX</sub> (hr)	2.95 (1.34)	1.27 (0.96)	100.54 to 163.39	0.0001	0.1289	60.78
K <sub>EL</sub> (hr <sup>-1</sup> )	0.235 (0.062)	0.214 (0.042)	-1.60 to 21.15	0.1562	0.7120	22.00
T <sub>1/2</sub> (hr)	3.18 (0.93)	3.38 (0.81)	-16.63 to 4.55	0.3446	0.7789	20.48

<sup>1</sup>Difference detectable between two means with a power of 80%.

**Table 3 (Revised 2/4/93): Pharmacokinetic Parameters from — NDA Formula vs Reference**

Parameter	Mean ( $\pm$ S.D.)		90% Confidence Intervals (2 one-sided t-tests)	Pr >  T	Power	Percent <sup>1</sup> Detectable Difference
	C-112-10C (1300mg, fasted state)	Extra Strength TYLENOL® Liquid (1300mg, fasted state)				
AUC ( $\mu\text{g} \cdot \text{hr/mL}$ )	66.15 (20.87)	75.15 (24.79)	-20.94 to -3.03	0.0289	0.9079	17.32
AUC <sub>INF</sub> ( $\mu\text{g} \cdot \text{hr/mL}$ )	70.53 (21.53)	78.44 (25.78)	-19.25 to -0.93	0.0706	0.8936	17.72
C <sub>MAX</sub> ( $\mu\text{g/mL}$ )	11.94 (2.56)	18.45 (4.49)	-41.96 to -28.61	0.0001	0.9951	12.91
T <sub>MAX</sub> (hr)	1.27 (0.96)	0.80 (0.47)	8.65 to 108.23	0.0545	0.0792	96.31
K <sub>EL</sub> (hr <sup>-1</sup> )	0.214 (0.042)	0.247 (0.066)	-23.39 to -3.73	0.0245	0.8423	19.02
T <sub>1/2</sub> (hr)	3.38 (0.81)	2.97 (0.70)	1.70 to 25.79	0.0612	0.6564	23.29

<sup>1</sup>Difference detectable between two means with a power of 80%.

Table 1: *ln*-Transformed Pharmacokinetic Parameters for Biostudy 91 - Clinical vs NDA Formulae

Parameter	Mean ( $\pm$ S.D., %C.V.)		Mean Ratio <sup>1</sup> (T/R %)	90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power (%)
	C-112-7D (1300mg, fasted)	C-112-10C (1300 mg, fasted)					
LAUC	4.071 (0.349, 8.6%)	4.143 (0.324, 7.8%)	107.5	97.5	to 118.5	0.2197	92
LAUCNF	4.134 (0.348, 8.4%)	4.210 (0.314, 7.5%)	107.9	97.7	to 119.2	0.2071	94
LCMAX	2.422 (0.248, 10.2%)	2.457 (0.219, 8.9%)	103.6	94.3	to 113.9	0.5274	95

<sup>1</sup>Mean Ratio = 100 \* exponent - reference for *ln*-transformed parameters.

Table 2: *ln*-Transformed Pharmacokinetic Parameters for Biostudy 91 - NDA Formula Fasted vs Fed

Parameter	Mean ( $\pm$ S.D., %C.V.)		Mean Ratio <sup>1</sup> (T/R %)	90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power (%)
	C-112-10C (1300mg, fed)	C-112-10C (1300mg, fasted)					
LAUC	4.032 (0.352, 8.7%)	4.143 (0.324, 7.8%)	89.5	81.2	to 98.6	0.0507	92
LAUCNF	4.089 (0.343, 8.5%)	4.210 (0.314, 7.5%)	88.6	80.2	to 97.8	0.0461	94
LCMAX	2.264 (0.306, 13.5%)	2.457 (0.219, 8.9%)	82.4	75.0	to 90.5	0.0010	95

<sup>1</sup>Mean Ratio = 100 \* exponent - reference for *ln*-transformed parameters.

Table 3: *ln*-Transformed Pharmacokinetic Parameters for Biostudy 91 - NDA Formula vs Reference

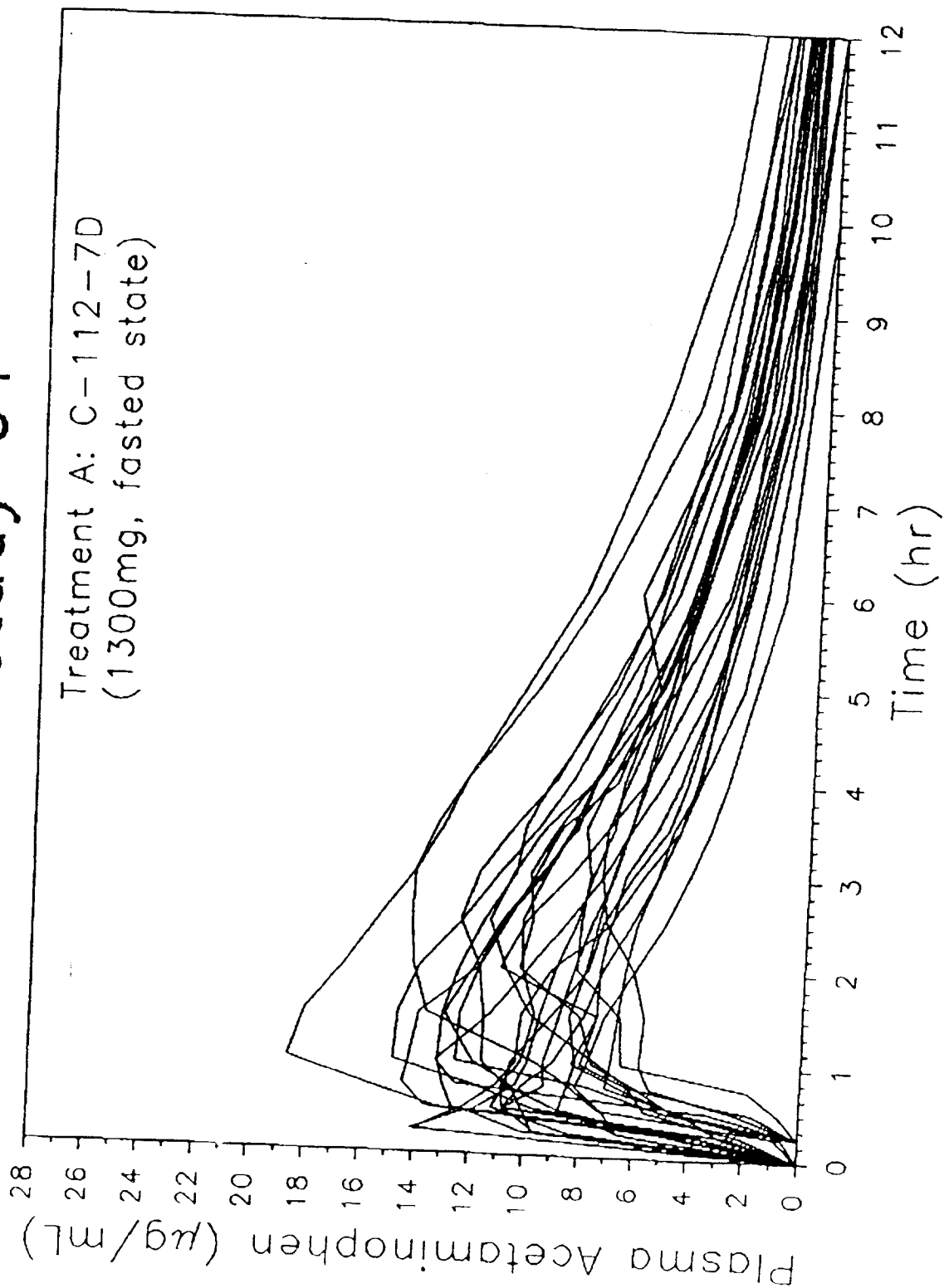
Parameter	Mean ( $\pm$ S.D., %C.V.)		Mean Ratio <sup>1</sup> (T/R %)	90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power (%)
	C-112-10C (1300mg, fasted)	ES-TYLENOL® Liquid (1300mg, fasted)					
LAUC	4.143 (0.324, 7.8%)	4.267 (0.335, 7.8%)	88.3	80.2	to 97.4	0.0373	92
LAUCNF	4.210 (0.314, 7.5%)	4.310 (0.334, 7.7%)	90.5	81.9	to 100.0	0.0989	94
LCMAX	2.457 (0.219, 8.9%)	2.884 (0.264, 9.2%)	55.2	59.4	to 71.7	0.0001	95

<sup>1</sup>Mean Ratio = 100 \* exponent - reference for *ln*-transformed parameters.



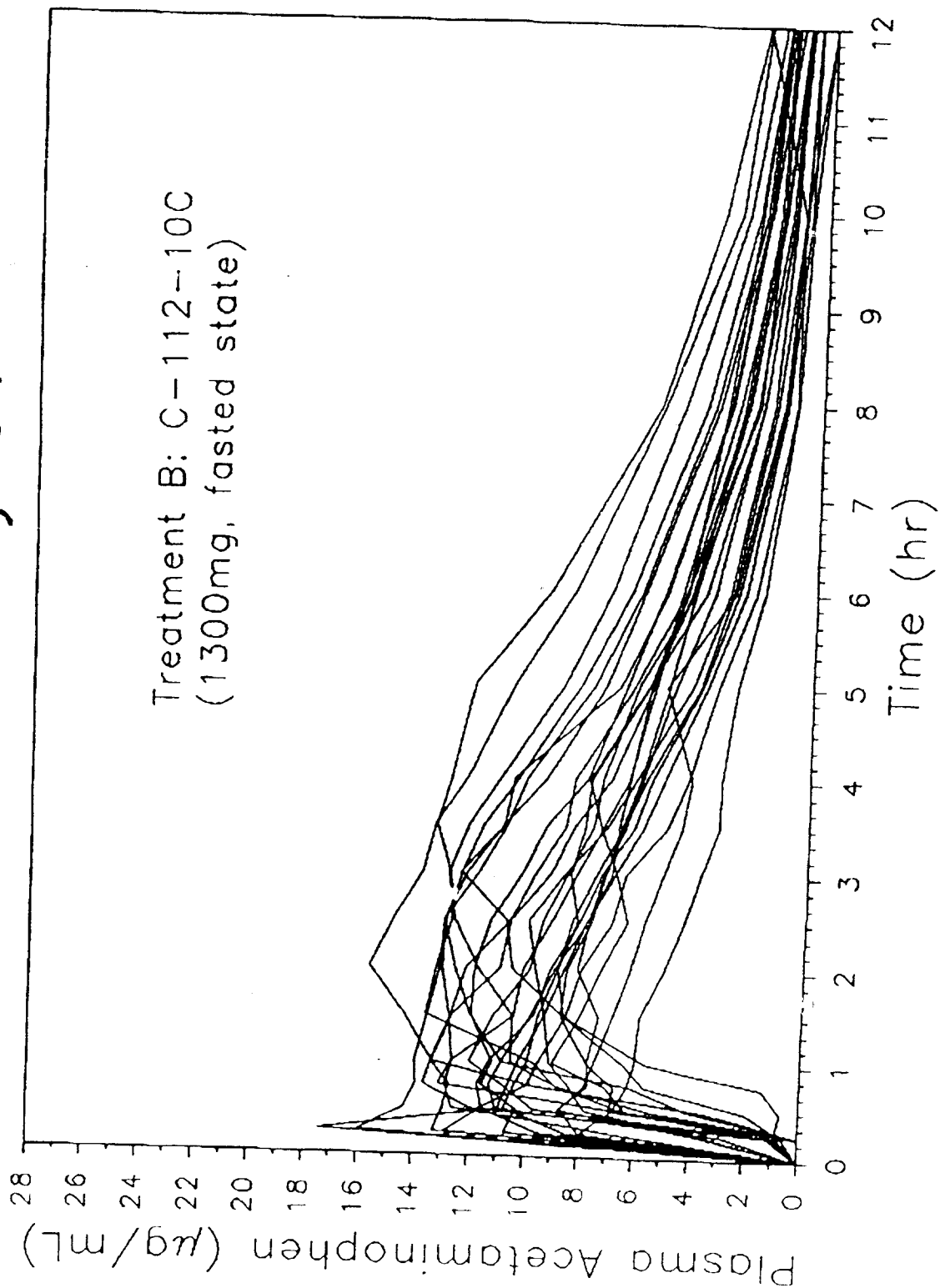
# Biostudy 91

Treatment A: C-112-7D  
(1300mg, fasted state)



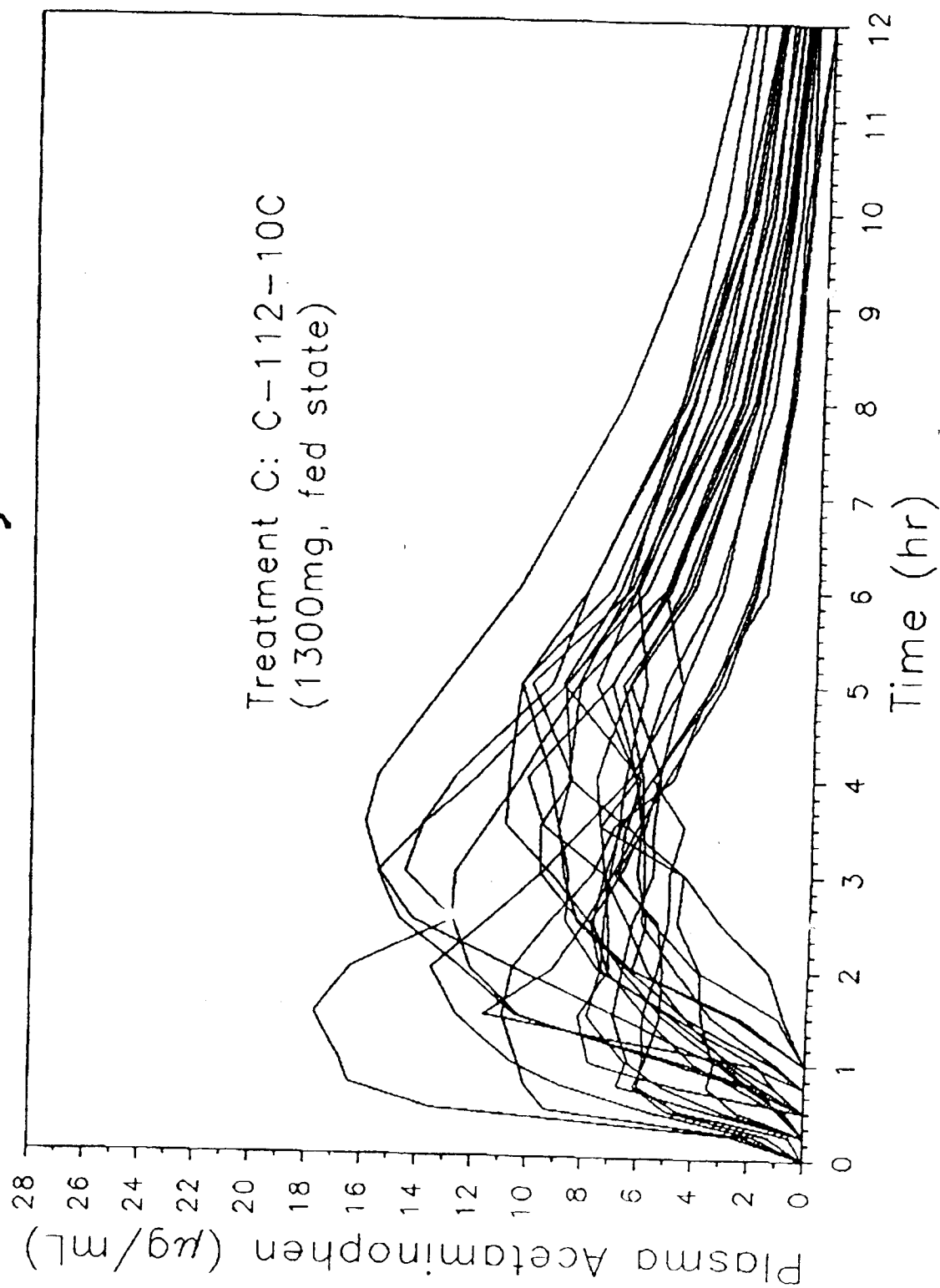
# Biostudy 91

Treatment B: C-112-10C  
(1300mg, fasted state)

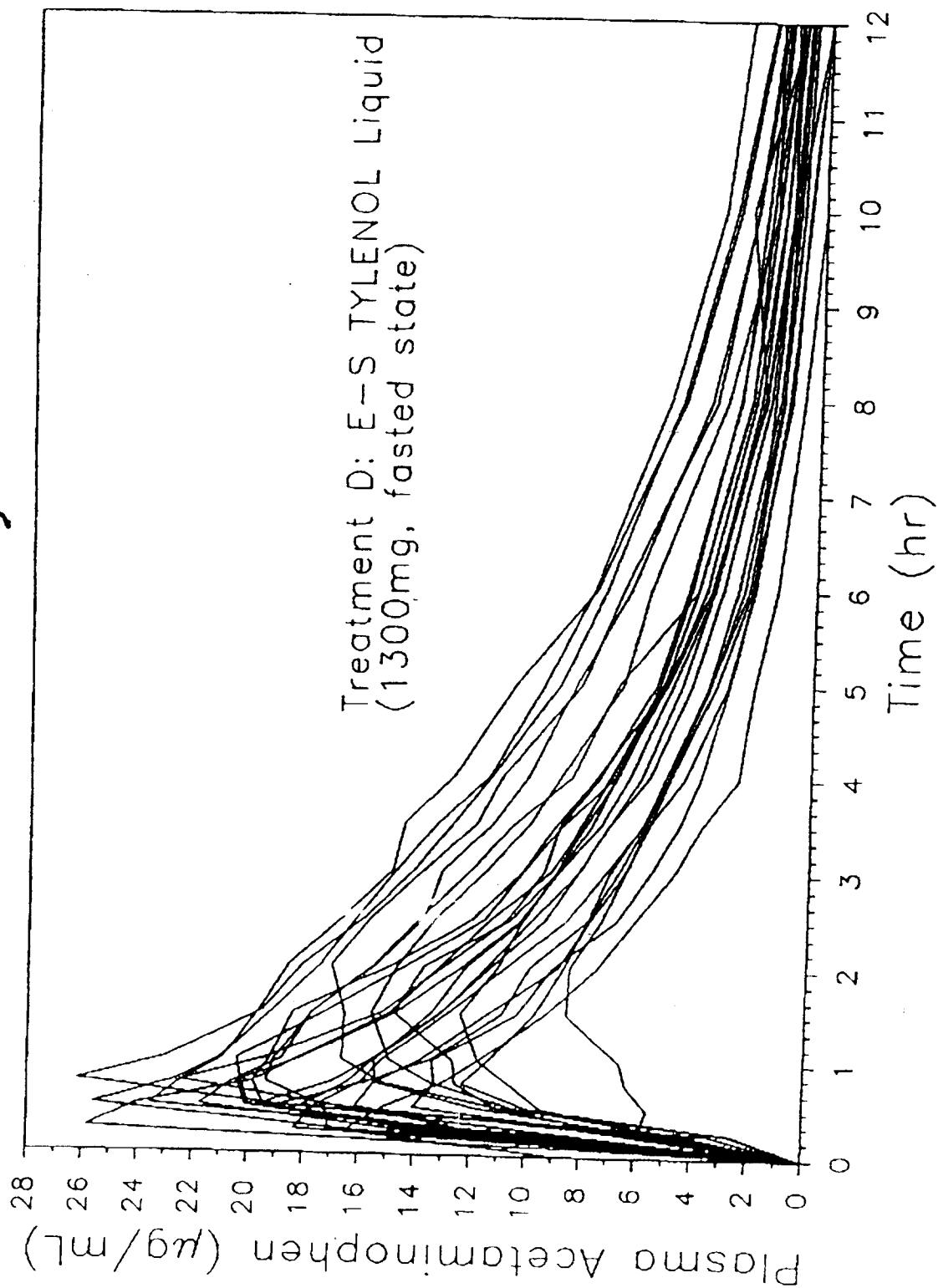


# Biostudy 91

Treatment C: C-112-10C  
(1300mg, fed state)



## Biostudy 91



NDA# 19-872/S-001 Submission Date: \_\_\_\_\_ Vol. \_\_\_\_\_

Study Type: A Comparison of a Sustained-Release Acetaminophen Caplet  
Formulation and a Conventional Tablet Formulation Under  
Multiple-Dose Conditions.  
(Protocol 89-956)

Study # 92

Investigator: \_\_\_\_\_

Study Site: \_\_\_\_\_

Single Dose: \_\_\_\_\_ Multiple Dose: X

Subjects: Normal X Patients \_\_\_\_\_ Young X Elderly \_\_\_\_\_  
Impaired: Renal \_\_\_\_\_ Hepatic \_\_\_\_\_ Other \_\_\_\_\_

Crossover 2-way Parallel \_\_\_\_\_ Washout 5 Days N= 24 ; M= 24 ; F= 0

Subject Healthy Adult Males  
Type: \_\_\_\_\_

Subject  
Type: \_\_\_\_\_

Weight Mean= 172 Range= 141-202 lb

Weight Mean= \_\_\_\_\_ Range= \_\_\_\_\_

Age Mean= 32 Range= 19-50 yr

Age Mean= \_\_\_\_\_ Range= \_\_\_\_\_

<u>Treatment</u>	<u>Code</u>	<u>Dose</u>	<u>Dosage Form</u>	<u>Strength</u>	<u>Lot/Batch#</u>	<u>Size</u>
Treatment	A	= 2 x 650mg acetaminophen every 8 hrs, total of 7 doses	Acetaminophen SR Caplet	APAP 650mg/caplet	C-112-10C	990kg
Treatment	B	= 2 x 500mg acetaminophen every 6 hrs, total of 9 doses	Extra- Strength TYLENOL® Tablet	APAP 500mg/tablet	FBA867	--†
Treatment		=				
Treatment		=				

†Production-scale batch.

Fasted A & B ; overnight fast and 4 hrs. post-dosing.

Nonfast \_\_\_\_\_ Food Study No FDA High Fat Breakfast \_\_\_\_\_

Biostudy 92 (continued):

Samples: Plasma 7 mL ; Treatment A: 0, 0.5, 1, 1.5, 2, 4, 6, 8, 8.5, 9, 10, 12, 16, 17, 24, 25, 32, 33, 40, 41, 48, 48.5, 49, 50, 52, 54, 56, 60, 64 and 72 hrs  
Treatment B: 0, 0.5, 1, 1.5, 2, 4, 6, 6.5, 7, 8, 10, 12, 12.5, 18, 18.5, 24, 24.5, 30, 30.5, 36, 36.5, 42, 42.5, 48, 48.5, 49, 50, 52, 54, 56, 60, 64 and 72 hrs  
Urine NA ;  
Feces NA ;

Assay Method:

(McNeil CPC Bioanalytical Method 2)

Assay Sensitivity: Quantification Limit 0.5µg/mL; Range 0.5-40µg/mL

Assay Accuracy: Mean Recoveries 87.0-96.7% (2 determinations of range)

Labeling Claims from Study (Study Conclusions):

1. Acetaminophen SR Caplets (NDA Formula C-112-10C) showed consistent pharmacokinetics over 7 doses, with a lack of dose-dumping.
2. The average plasma concentration at steady state for Acetaminophen SR Caplets was equivalent to that for the reference product.

# Biostudy 92

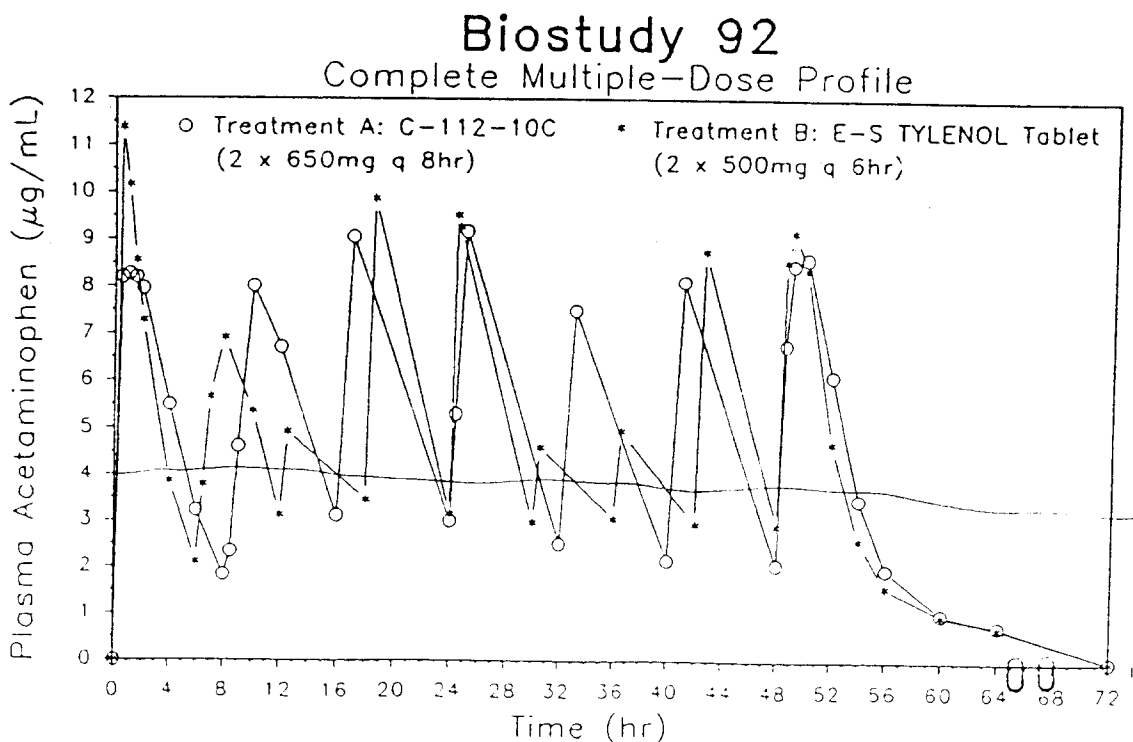
Mean Plasma Acetaminophen, $\mu\text{g/mL}$ (S.D.)			Mean Plasma Acetaminophen, $\mu\text{g/mL}$ (S.D.)		
Time (hr)	C-112-10C (2 x 650mg q 8hr, 7 doses)	E-S TYLENOL® Tablet (2 x 500mg q 6hr, 9 doses)	Time (hr)	C-112-10C (2 x 650mg q 8hr, 7 doses)	E-S TYLENOL® Tablet (2 x 500mg q 6hr, 9 doses)
0.0	0.00 (0.00)	0.00 (0.00)	25.0	9.19 (4.26)	NS
0.5	8.20 (3.96)	11.38 (4.28)	30.0	NS	2.97 (1.44)
1.0	8.27 (2.51)	10.16 (1.89)	30.5	NS	4.61 (2.92)
1.5	8.20 (1.71)	8.56 (1.94)	32.0	2.50 (1.24)	NS
2.0	7.96 (1.72)	7.28 (1.99)	33.0	7.51 (4.13)	NS
4.0	5.49 (1.84)	3.86 (1.53)	36.0	NS	3.06 (1.43)
6.0	3.22 (1.41)	2.10 (1.12)	36.5	NS	4.97 (3.11)
6.5	NS <sup>1</sup>	3.78 (2.42)	40.0	2.15 (1.01)	NS
7.0	NS	5.66 (3.97)	41.0	8.13 (3.36)	NS
8.0	1.83 (0.93)	6.92 (3.26)	42.0	NS	2.95 (1.22)
8.5	2.34 (1.35)	NS	42.5	NS	8.77 (4.86)
9.0	4.62 (3.41)	NS	48.0	2.06 (1.22)	2.91 (1.31)
10.0	8.02 (3.71)	5.36 (1.69)	48.5	6.78 (4.70)	8.56 (5.54)
12.0	6.71 (2.03)	3.12 (1.38)	49.0	8.48 (3.91)	9.18 (4.07)
12.5	NS	4.93 (2.33)	50.0	8.62 (2.74)	8.38 (2.84)
16.0	3.11 (1.65)	NS	52.0	6.12 (2.17)	4.70 (1.89)
17.0	9.07 (2.50)	NS	54.0	3.48 (1.65)	2.61 (1.26)
18.0	NS	3.46 (1.53)	56.0	1.97 (1.08)	1.58 (0.80)
18.5	NS	9.88 (6.07)	60.0	1.01 (0.45)	0.98 (0.38)
24.0 <sup>11</sup>	3.00 (1.57)	3.15 (1.67)	64.0	0.76 (0.17)	0.72 (0.14)
24.33 <sup>11</sup>	5.31 (3.44)	9.53 (6.93)	72.0	0.00 (0.00)	0.00 (0.00)
24.5	NS	9.29 (5.64)			

<sup>1</sup>NS = Not Sampled.

<sup>11</sup>Due to technician error, subjects dosed in Period 2 had 24-hour blood sample drawn 20 minutes after 24-hour dose. Plasma concentration listed as 24.33 hr.

	Mean (S.D.)	Mean (S.D.)
AUCtau ( $\mu\text{g} \cdot \text{hr/mL}$ )	44.36 (13.79)	47.41 (15.50) <sup>111</sup>
Avg Cp,SS ( $\mu\text{g/mL}$ )	5.54 (1.72)	5.93 (1.94) <sup>111</sup>
Cmin,SS ( $\mu\text{g/mL}$ )	2.22 (1.11)	2.11 (1.08) <sup>111</sup>
Fluctuation Index	1.49 (0.36)	1.44 (0.49)

<sup>111</sup>Reference data normalized for dose.



1300

1950

4000

20

Table 2 (Revised 2/4/93): Key Multiple-Dose Steady-State Parameters

Parameter	Mean (± S.D.)		90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power	Percent <sup>1</sup> Detectable Difference	
	C-112-10C (1300mg q 8hr)	Extra-Strength TYLENOL* (1000mg q 6hr)						
AUC <sub>T</sub> (μg · hr/mL)	44.36 (13.79)	36.47 (11.92)						
AUC <sub>T,N</sub> (μg · hr/mL)		47.41 (15.50)	-10.84	to	-2.04	0.0197	1.0000	7.51
AVG C <sub>p,ss</sub> (μg/mL)	5.54 (1.72)	6.08 (1.99)	-13.21	to	-4.36	0.0025	1.0000	7.56
AVG C <sub>p,ss,N</sub> (μg/mL)		5.93 (1.94)	-10.84	to	-2.04	0.0197	1.0000	7.51
AVG C <sub>MIN,ss</sub> (μg/mL)	2.22 (1.11)	2.97 (1.30)						
AVG C <sub>MIN,ss,N</sub> (μg/mL)		2.11 (1.08)	-2.74	to	13.37	0.2692	0.9827	13.75
FI <sup>2</sup>	1.49 (0.36)	1.44 (0.49)	-6.10	to	13.72	0.5160	0.9116	16.92

<sup>2</sup>Fluctuation Index not normalized.

<sup>1</sup>Difference detectable between two means with a power of 80%.

Table 3 (Revised 2/4/93): Other Pharmacokinetic Parameters

		Mean ( $\pm$ S.D.)							
Parameter		C-112-10C (1300mg q 8hr)	Extra-Strength TYLENOL® (1000mg q 6hr)	90% Confidence Intervals (2 one-sided t-tests)		Pr >  T	Power	Percent <sup>1</sup> Detectable Difference	
First Dose	AUC <sup>*</sup> ( $\mu\text{g} \cdot \text{hr/mL}$ )	41.53 (10.72)	33.97 (8.56)						
	AUC <sub>N</sub> <sup>*</sup> ( $\mu\text{g} \cdot \text{hr/mL}$ )		44.16 (11.13)	-12.20	to	0.26	0.1142	0.9995	10.64
*Calculated from 0 to 8 hr for SR Caplet, 0 to 6 hr for E-S TYLENOL®.									
First Dose	C <sub>MAX</sub> ( $\mu\text{g/mL}$ )	9.76 (2.26)	12.64 (2.71)						
	C <sub>MAX,N</sub> ( $\mu\text{g/mL}$ )		16.43 (3.53)	-47.68	to	-33.50	0.0001	0.9961	12.10
First Dose	T <sub>MAX</sub> (hr)	1.08 (0.87)	0.68 (0.32)	8.39	to	106.76	0.0569	0.1025	83.98
Last Dose	K <sub>a</sub> ( $\text{hr}^{-1}$ )	0.271 (0.071)	0.275 (0.078)	-7.14	to	4.25	0.6675	0.9999	9.72
	T <sub>1/2</sub> (hr)	2.73 (0.68)	2.73 (0.78)	-5.75	to	5.86	0.9873	0.9999	9.90

<sup>1</sup>Difference detectable between two means with a power of 80%.



Table 4: *ln*-Transformed Pharmacokinetic Parameters for Biostudy 92 - NDA Formula vs Reference

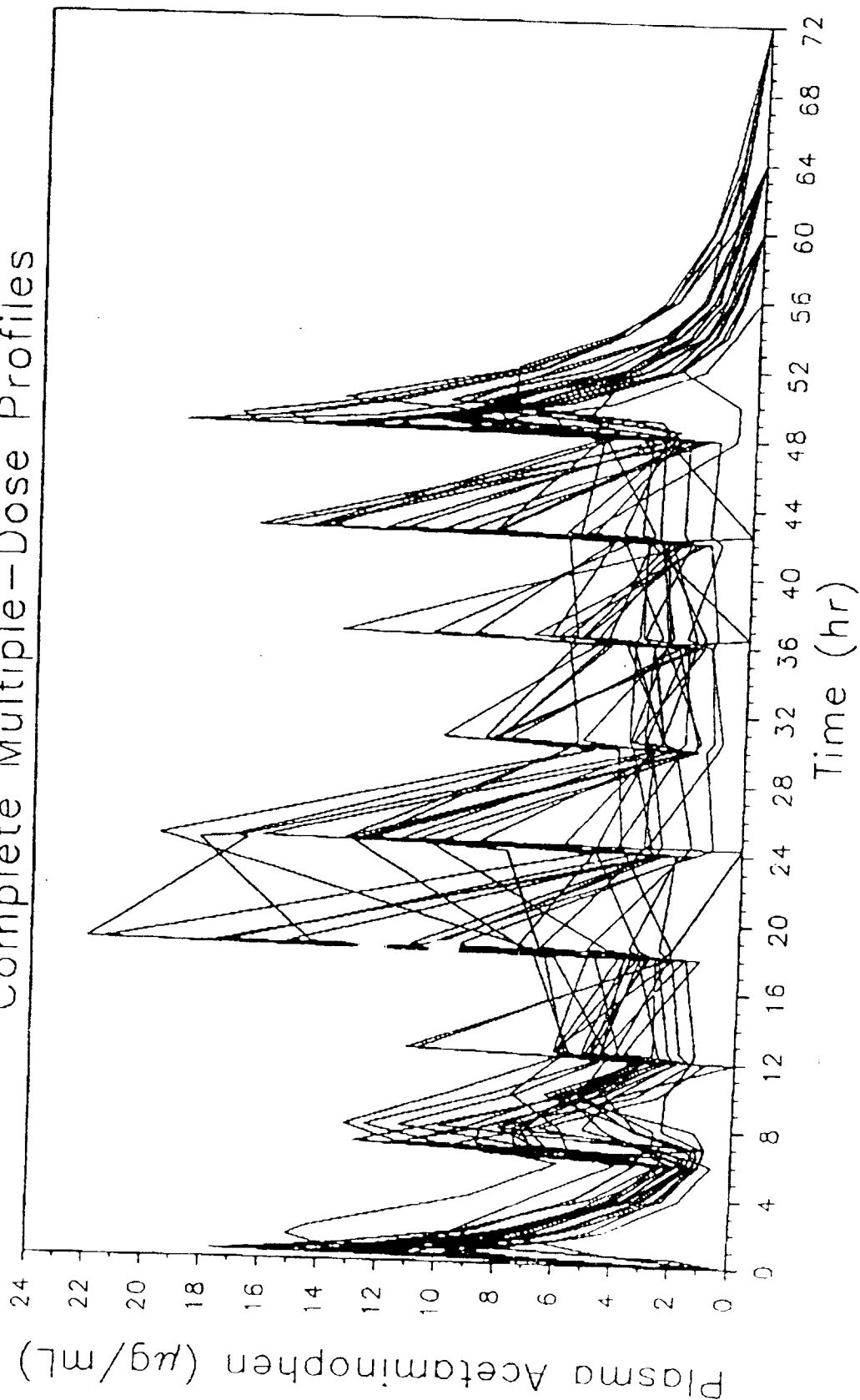
Parameter	Mean ( $\pm$ S.D.; %C.V.)		Mean Ratio <sup>1</sup> (T/R %)	90% Confidence Intervals (2 one-sided t-tests)			Pr >  T	Power (%)
	C-112-10C (1300mg q 8h)	ES-TYLENOL® (1000mg q 8h)						
LAUC <sub>T,N</sub>	3.748 (0.308, 8.2%)	3.795 (0.404, 10.7%)	95.4	89.1	to	102.2	0.2516	100
LAVG C <sub>0-8,N</sub>	1.668 (0.306, 18.3%)	1.715 (0.404, 23.6%)	95.4	89.1	to	102.2	0.2516	98
C <sub>MAX<sub>ss</sub></sub> <sup>1</sup> (µg/mL) (last dose)	10.03 (2.58, 25.7%)	11.44 (3.84, 33.5%)	(not applicable)	79.9	to	95.4	0.0123	99
LC <sub>MAX<sub>ss</sub></sub> <sup>1</sup> (last dose)	2.271 (0.279, 12.3%)	2.368 (0.416, 17.6%)	90.7	82.6	to	99.5	0.0845	94
LAVG C <sub>MIN<sub>ss,N</sub></sub>	0.686 (0.479, 69.8%)	0.608 (0.559, 92.0%)	108.1	98.2	to	119.0	0.1772	93
LAUC <sub>N</sub> (first dose)	3.690 (0.288, 7.8%)	3.761 (0.232, 6.2%)	93.1	85.7	to	101.3	0.1614	100
LC <sub>MAX<sub>N</sub></sub> (first dose)	2.249 (0.261, 11.6%)	2.776 (0.225, 8.1%)	59.0	53.5	to	65.1	0.0001	92

<sup>1</sup> Mean Ratio = 100 \* exponent - reference for *ln*-transformed parameters.

<sup>2</sup> Because of different doses and dosing intervals, maximum concentrations at steady-state should be normalized. However, the mathematical equation could not be simplified to allow for normalization.

# Biostudy 92

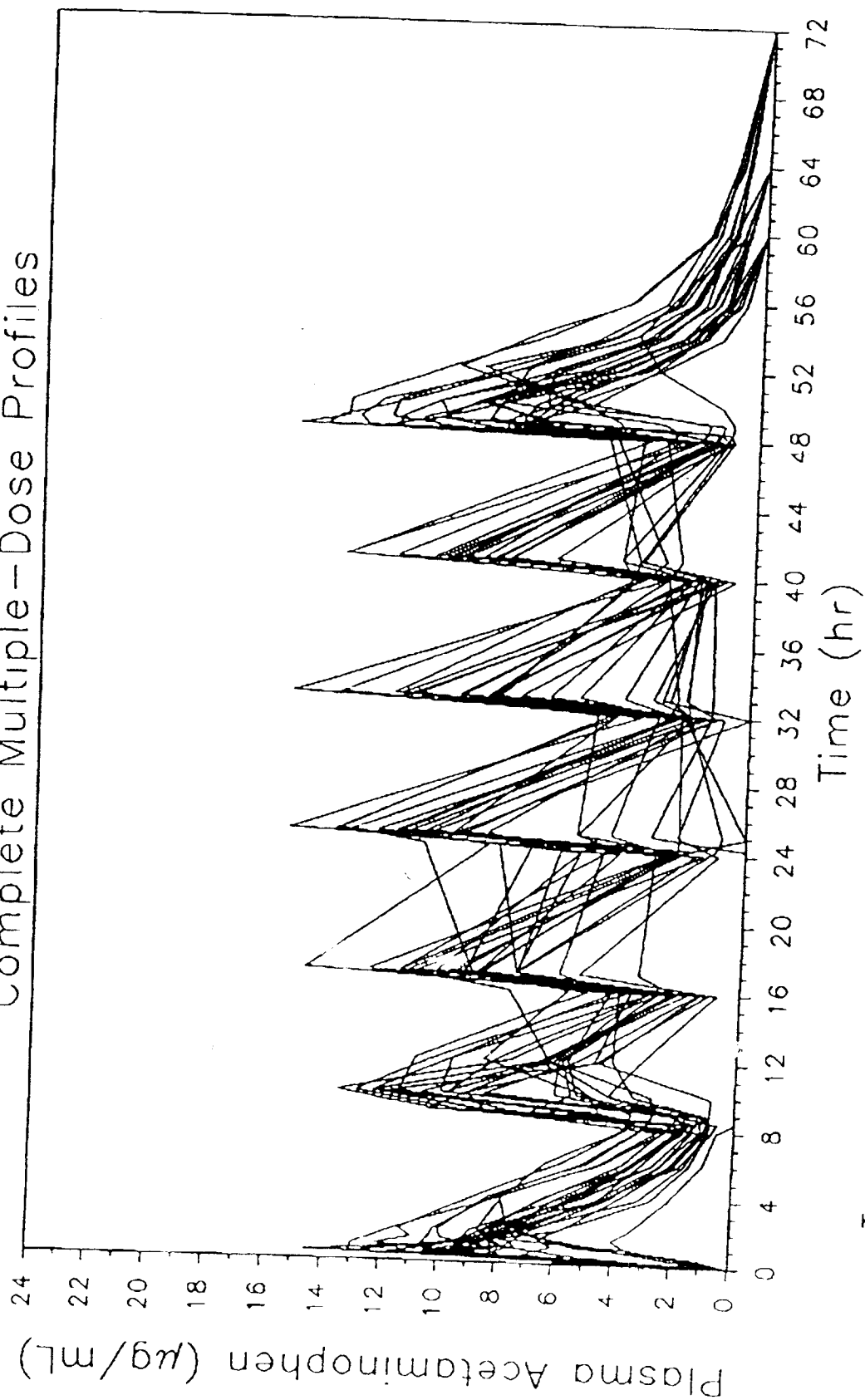
## Complete Multiple-Dose Profiles



Treatment B: E-S TYLENOL Tablet  
(2 x 500mg q 6hr)

# Biostudy 92

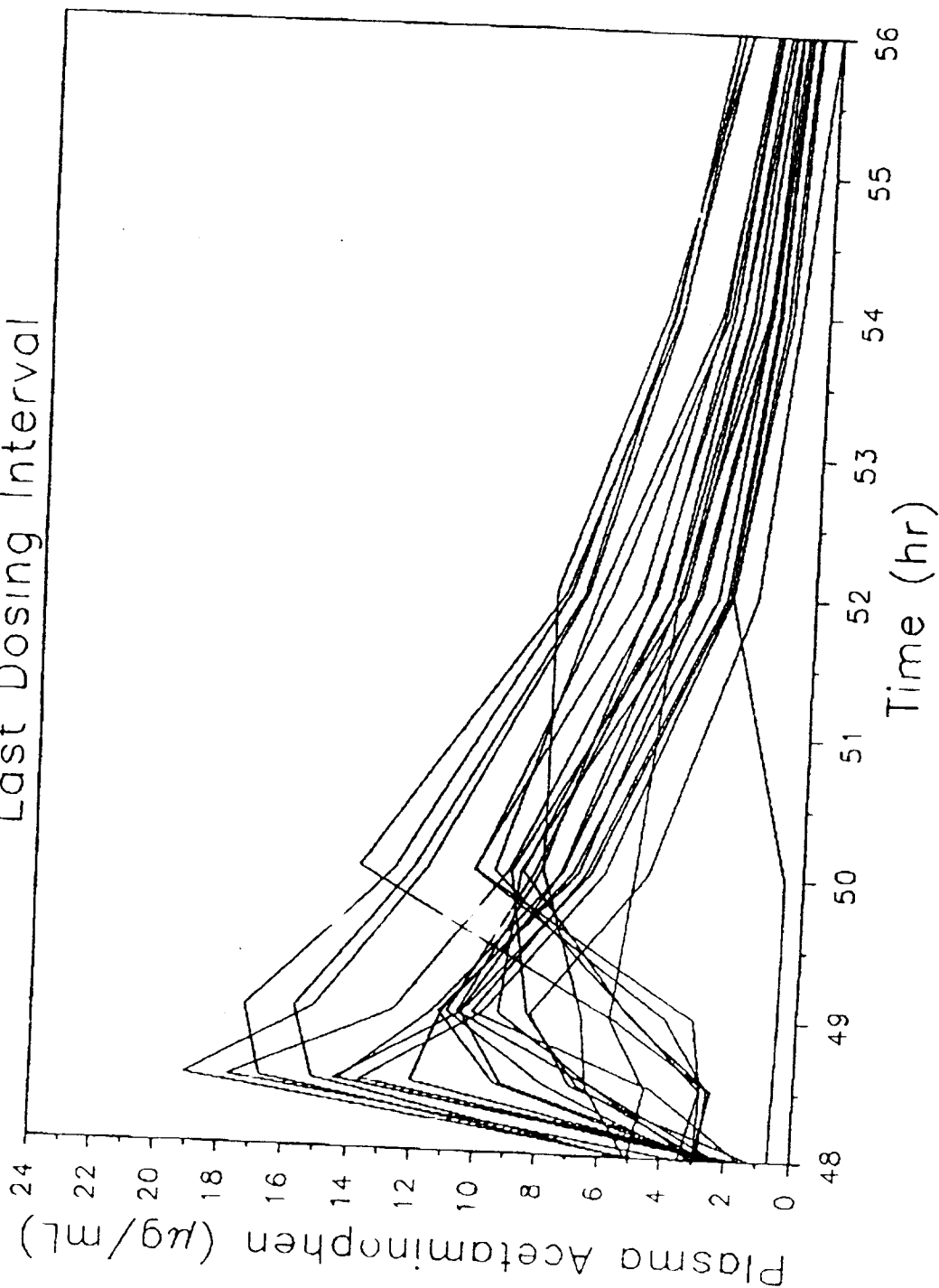
## Complete Multiple-Dose Profiles



Treatment A: C-112-10C  
(2 x 650mg q 8hr)

# Biostudy 92

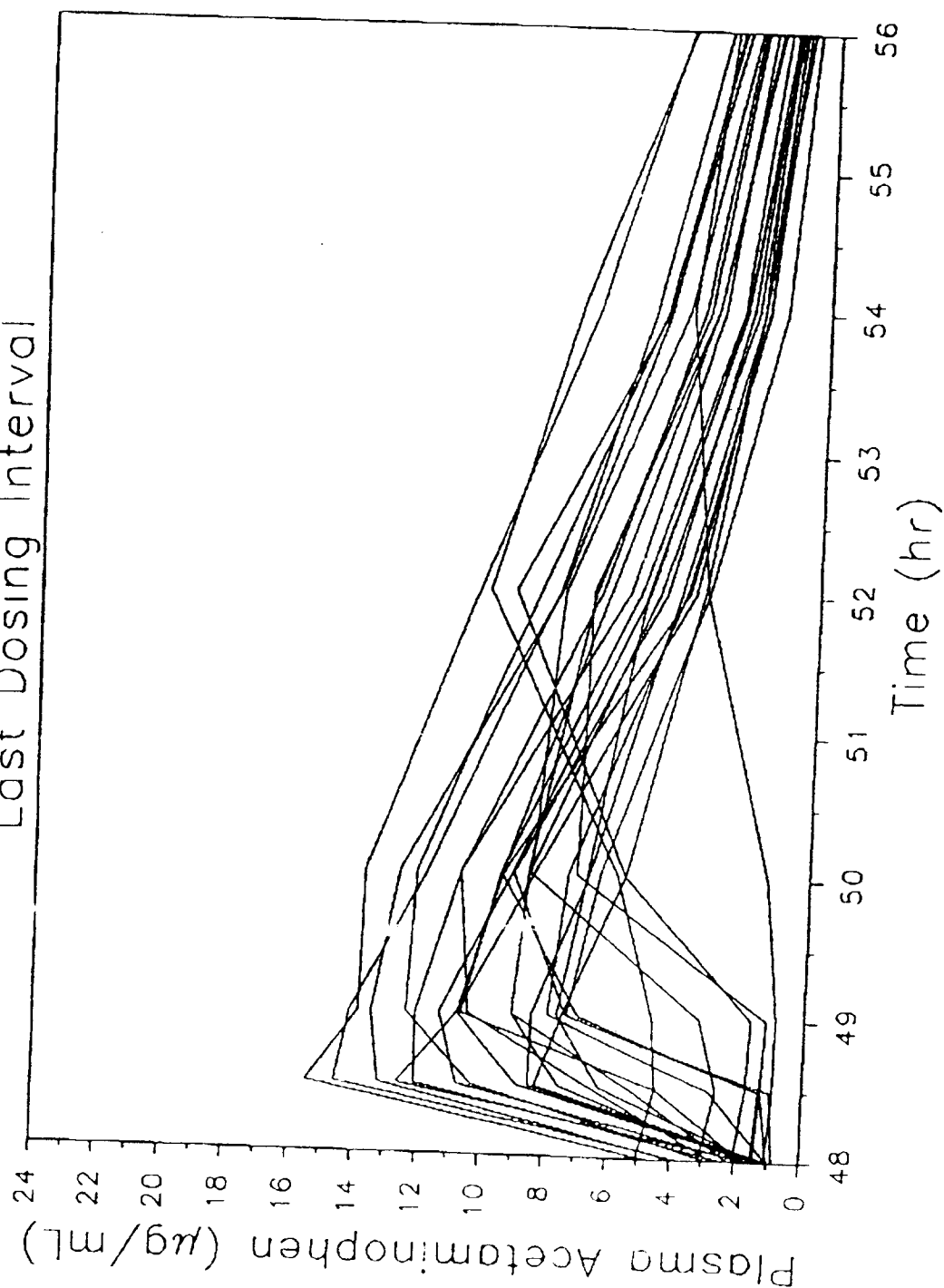
Last Dosing Interval



Treatment B: E-S TYLENOL Tablet  
(2 x 500mg q 6hr)

# Biostudy 92

Last Dosing Interval



Treatment A: C-112-10C  
(2 x 650 ng q 8hr)

## Appendix B, Supportive Trials

<b>Study 117</b>	NDA formulation vs. Regular Strength Tylenol Caplets									
	Single Dose	*	*	*	*	*	*	*	*	
										36

NDA# 19-872/S-001 Submission Date: \_\_\_\_\_ Vol. \_\_\_\_\_

Study Type: A Single-Dose Comparison of the Experimental Sustained-Release Acetaminophen Caplet (C-112-10C) with Regular-Strength TYLENOL® Caplets in the Fasted State.

(Protocol 92-225)

Study # 117

Investigator: \_\_\_\_\_

Study Site: \_\_\_\_\_

Single Dose: X

Multiple Dose: \_\_\_\_\_

Subjects: Normal X Patients \_\_\_\_\_ Young X Elderly \_\_\_\_\_  
Impaired: Renal \_\_\_\_\_ Hepatic \_\_\_\_\_ Other \_\_\_\_\_

Crossover 2-way Parallel \_\_\_\_\_ Washout 7 Days N= 24 ; M= 24 ; F= 0

Subject Type: Healthy Adult Males

Subject Type: \_\_\_\_\_

Weight Mean= 174 Range= 141-209 lb

Weight Mean= \_\_\_\_\_ Range= \_\_\_\_\_

Age Mean= 31 Range= 19-50 yr

Age Mean= \_\_\_\_\_ Range= \_\_\_\_\_

Treatment	Code	Dose	Dosage Form	Strength	Lot/Batch#	Size
Treatment	A	= 2 x 650mg acetaminophen in the fasted state	Acetaminophen SR Caplet	APAP 650mg/caplet	C-112-10C	990kg
Treatment	B	= 2 x 325mg acetaminophen at 0 and 4hr in the fasted state	Regular-Strength TYLENOL® Caplet	APAP 325mg/caplet	HPA590	---
Treatment		=				
Treatment		=				

<sup>†</sup>Production-scale batch.

Fasted A & B \_\_\_\_\_ ; overnight fast and 4 hrs. post-dosing.

Nonfast \_\_\_\_\_ Food Study No FDA High Fat Breakfast \_\_\_\_\_

Samples: Plasma 7 mL ; 0, 0.50, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16 and 24 hr

Urine NA ; \_\_\_\_\_  
Feces NA ; \_\_\_\_\_

Assay Method:

Assay Sensitivity: Quantification Limit 0.5µg/mL; Range 0.5-25µg/mL

Assay Accuracy: Mean Recoveries 91.8-99.8% (3 determinations of range)

Labeling Claims from Study (Study Conclusions):

1. One dose of 2 Acetaminophen SR Caplets 650mg (NDA Formula C-112-10C) is bioequivalent to two doses of 2 Regular-Strength ~~TYLENOL~~ Caplets 325mg, given 4 hours apart.

### Biostudy 117

Time (hr)	Mean Plasma Acetaminophen µg/mL (S.D.)	
	C-112-10C (2 x 650mg, fasted)	Regular-Strength TYLENOL® Caplets (2 x 325mg q 4hr, fasted)
0.0	0.00 (0.00)	0.00 (0.00)
0.5	7.08 (3.74)	6.77 (3.24)
1.0	9.45 (1.54)	7.22 (1.21)
1.5	9.56 (1.56)	8.17 (1.10)
2.0	9.40 (1.62)	6.28 (1.01)
3.0	8.38 (2.00)	3.91 (0.91)
4.0	8.89 (1.77)	2.97 (0.76)
4.5	8.16 (1.56)	8.64 (3.09)
5.0	5.56 (1.46)	9.03 (2.01)
5.5	4.88 (1.39)	8.08 (1.67)
6.0	4.33 (1.38)	7.10 (1.43)
7.0	3.27 (1.21)	5.19 (1.30)
8.0	2.54 (1.00)	3.99 (1.11)
12.0	1.11 (0.56)	1.47 (0.66)
16.0	0.40 (0.44)	0.66 (0.44)
24.0	0.00 (0.00)	0.00 (0.00)
	Mean (S.D.)	Mean (S.D.)
C <sub>MAX</sub> (µg/mL)	10.83 (1.67)	8.54 (1.52)
T <sub>MAX</sub> (hr)	1.23 (0.68)	0.79 (0.39)
AUC <sub>INF</sub> (µg · hr/mL)	63.01 (16.22)	63.30 (14.75)



# Biostudy 117

## C-112, SR-APAP Caplet 650mg

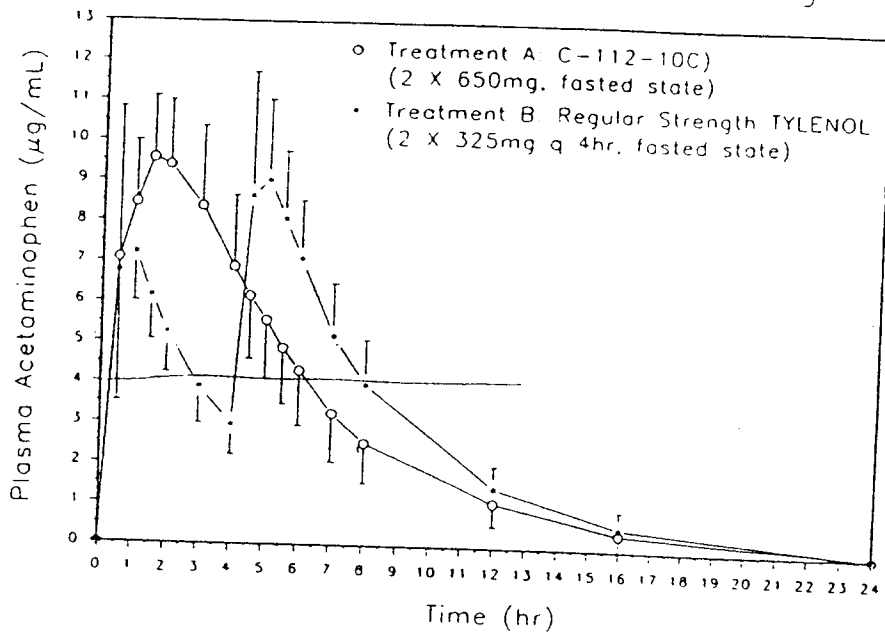


Table 5 - Summary of statistical analysis of Plasma Acetaminophen pharmacokinetic parameters comparing Treatments A and B

Parameter	Treatment Means		Pct Difference	PR> T	Power (I)	Confidence Intervals		Mean Ratio
	A	B				(90% Confidence)	(95% Confidence)	
C <sub>MAX1</sub>	10.832	8.538	26.87	0.0001*	99.24	119.6 - 134.2	118.1 - 135.7	
C <sub>MAX2</sub>	10.832	9.952	8.84	0.0228*	99.86	102.6 - 115.0	101.3 - 116.1	
T <sub>MAX1</sub>	1.229	0.792	55.26	0.0028*	20.11	127.1 - 161.4	121.3 - 189.1	
T <sub>MAX2</sub>	1.229	0.896	37.20	0.0486*	17.58	106.6 - 167.8	100.2 - 174.2	
AUC	59.258	59.892	-1.05	0.5925	99.99	95.6 - 102.3	94.9 - 103.0	
AUC-DNF	63.008	63.296	-0.45	0.8204	99.99	96.2 - 102.9	95.4 - 103.6	
KEL	0.225	0.258	-12.97	0.0003*	99.99	81.9 - 92.1	80.8 - 93.2	
HALF-LIFE	3.171	2.763	14.78	0.0001*	99.98	109.1 - 120.1	108.2 - 121.4	
L <sub>C</sub> MAX1	2.371	2.129		0.0001	99.81	119.4 - 135.9	117.8 - 137.7	127.4
L <sub>C</sub> MAX2	2.371	2.276		0.0174*	99.85	103.2 - 117.2	101.9 - 118.7	120.0
L <sub>AUC</sub>	4.050	4.065		0.4080	99.95	95.5 - 101.6	94.8 - 102.3	98.5
L <sub>AUC-DNF</sub>	4.112	4.121		0.5148	99.99	96.1 - 102.2	95.5 - 102.8	99.1
KA	2.028	0.699	190.12	0.0221*	4.73	199.5 - 380.7	177.7 - 402.5	
ABS-HALF	0.510	1.453	-64.92	0.0280*	1.80	2.4 - 57.8	-5.5 - 75.6	

Treatment A = 2 x Sustained-Release Acetaminophen Caplets (1300 mg) - test  
 Treatment B = 2 x Regular-Strength TYLENOL(R) Caplets q 4 hrs (1300 mg) - reference

Values for Treatments A and B are the least-square means (LSMEANS) from the ANOVA  
 L<sub>C</sub>MAX1, L<sub>C</sub>MAX2, L<sub>AUC</sub>, and L<sub>AUC-DNF</sub> are log-transformed parameters  
 \* = value was not calculated

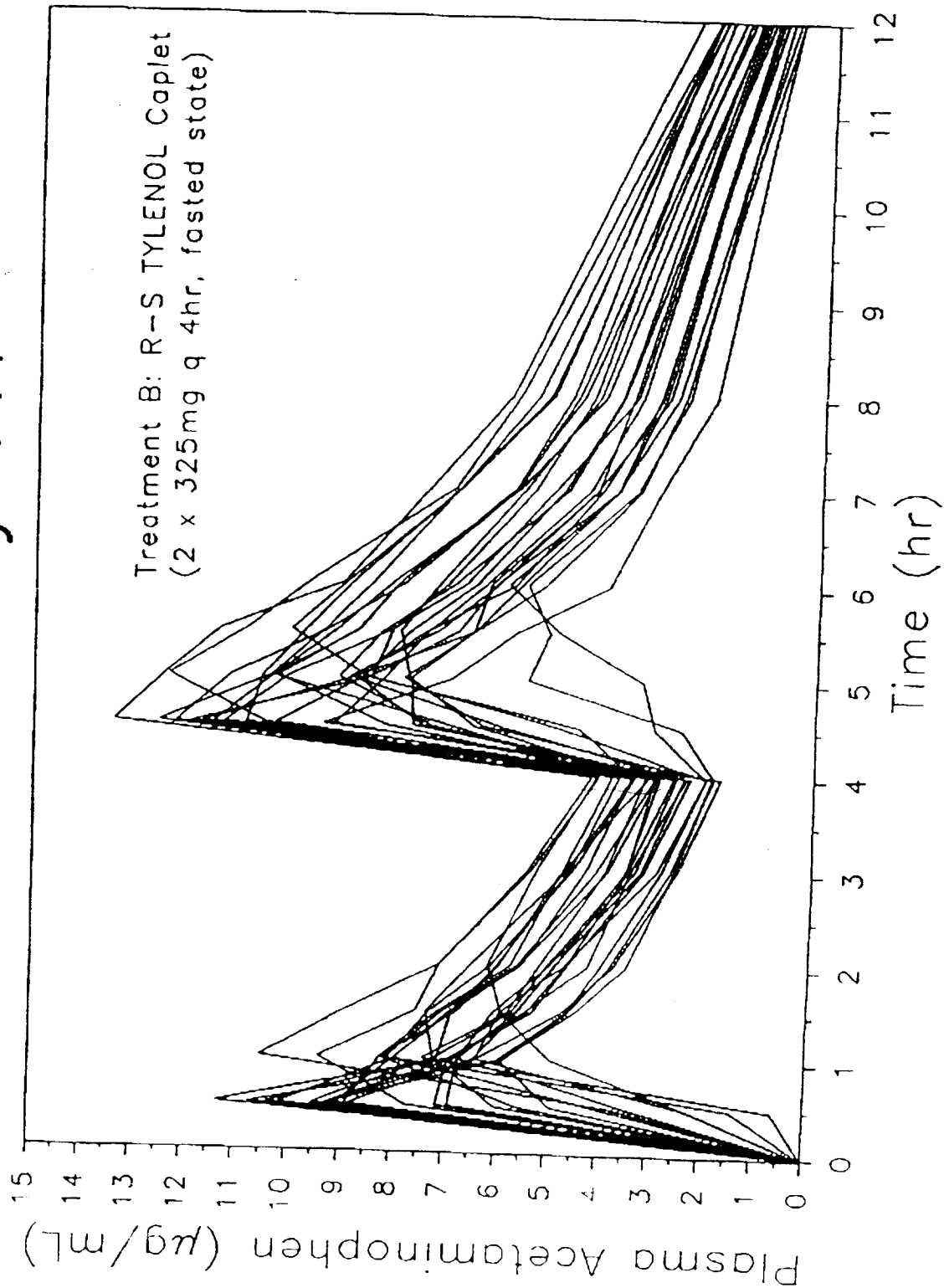
Pct Difference = difference between treatments (A - B) expressed as a percentage of Treatment B

PR>|T| = ANOVA test for significant differences between treatments  
 (\* difference is statistically significant; p<0.05)

Power = power (I) to detect 20% difference between treatments (95% confidence)

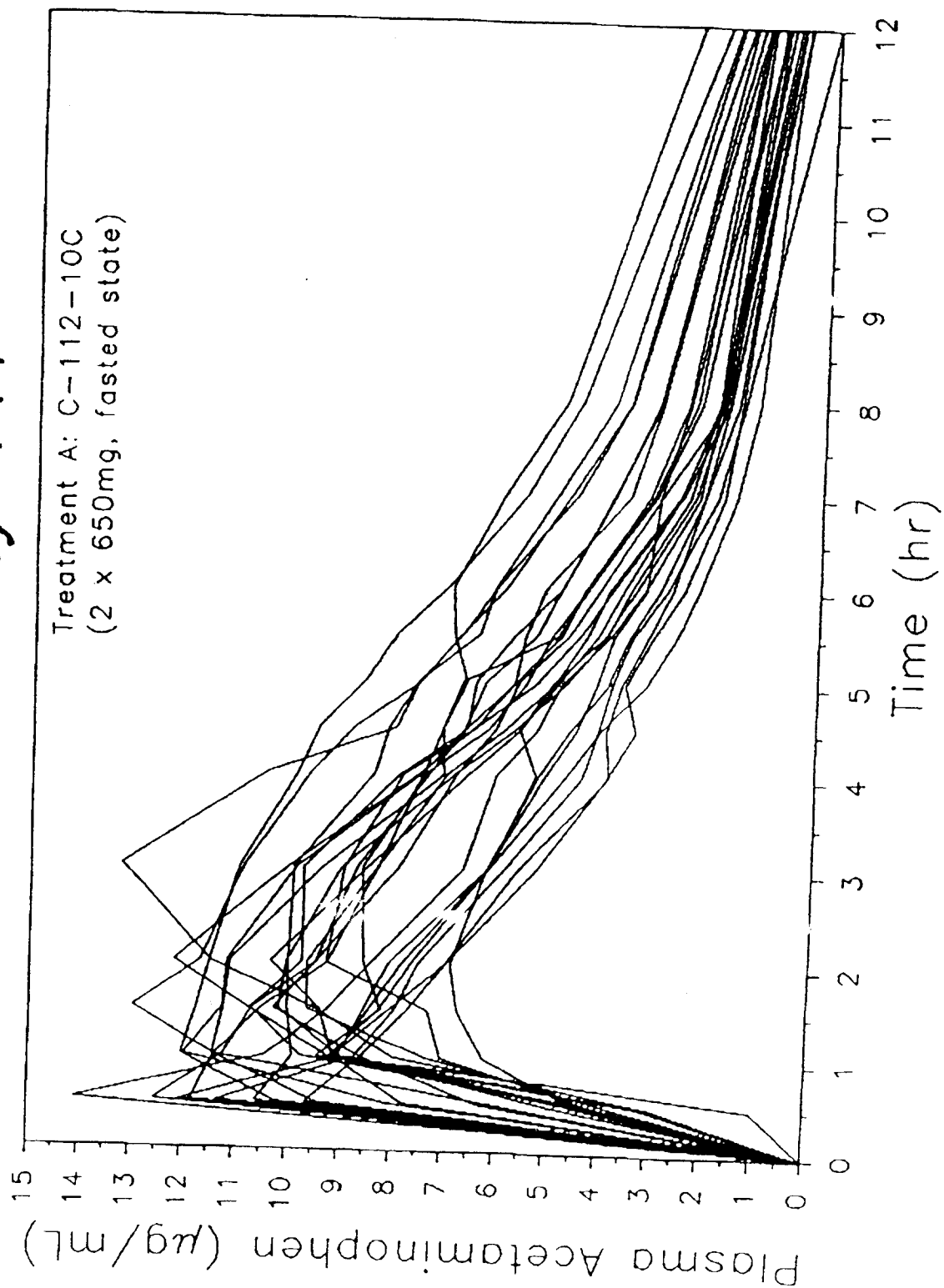
Mean Ratio = 100\*exp(test - reference) for log transformed parameters only

# Biostudy 117



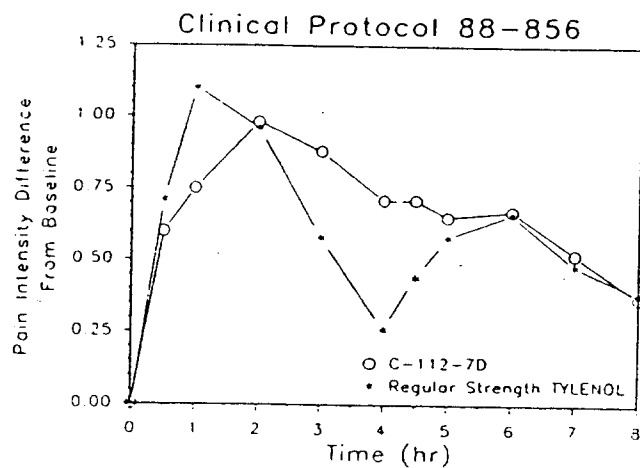
# Biostudy 117

Treatment A: C-112-10C  
(2 x 650mg, fasted state)

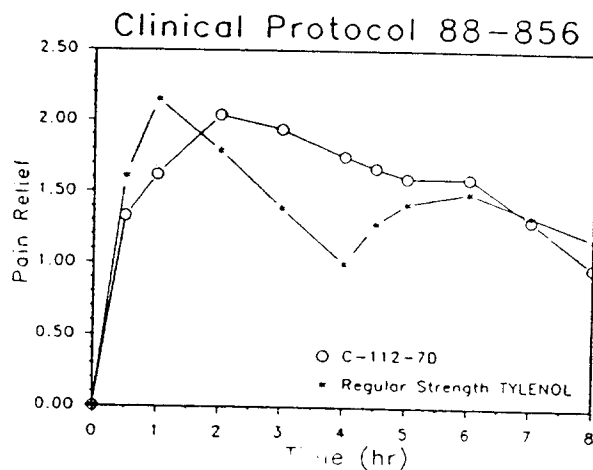


### Scheme A

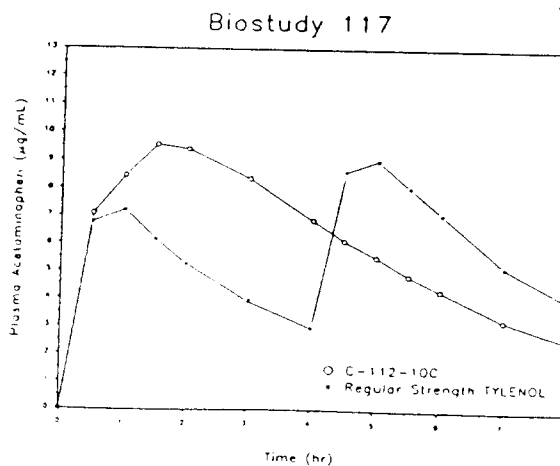
Graph 1



Graph 2

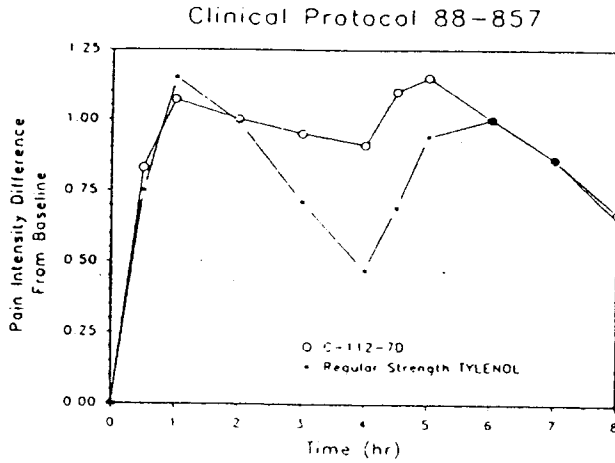


Graph 3

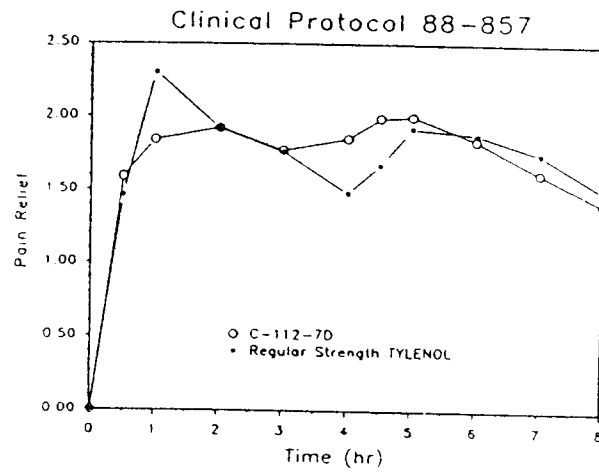


Scheme B

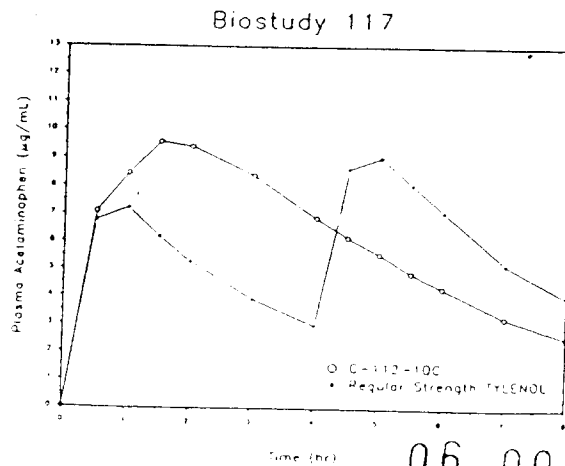
Graph 4



Graph 5



Graph 6





NDA: 19872  
PRODUCT: APAP SR CAPLETS (NOW EXTENDED RELIEF)  
SPONSOR: McNEIL CONSUMER PRODUCTS  
REVIEWER: E Douglas Kramer, MD  
DATE: January 26, 1994

ORIGINAL

SUMMARY OF MEDICAL REVIEW

JAN 26 1994

EFFICACY

This NDA contained 3 clinical studies in 3 pain models (Dental Pain, Episiotomy Pain, and Osteoarthritis). The dental and episiotomy pain studies compared single doses of SR APAP to 2 doses of RR APAP and placebo over 8 hours in 120 patients each. The dental pain study showed that both products had analgesic efficacy measured as pain intensity differences and pain relief scores. While 2 doses of RR APAP were generally comparable to single doses of SR APAP, RR APAP had a slightly faster onset and higher peak but a shorter duration of action when compared to SR APAP. These findings are typical of what would be expected in a comparison of sustained and regular release products. While the interpretation of the episiotomy study is confounded by a substantial placebo effect, the overall contour of the PID and pain relief curves is similar.

The OA study compared SR APAP (3900mg/day) and RR APAP (4000mg/day) for 30 days in 197 patients. No differences were noted between treatments by an analysis of variance. However, because the study did not have a placebo control, interpretation of the results depends on comparison of Q statistics and effect sizes results from other studies. Such a comparison reveals that this study has effect sizes for RR APAP that are consistent with previously successful studies. Therefore it seems reasonable to conclude that the ANOVA and Q statistics support the conclusion that the regimens tested are similar.

SAFETY

The adverse experiences reported in these studies are similar for both SR and RR APAP. Most of the adverse events were minor. In many instances they could not be distinguished from intercurrent illnesses.

LABELING

Dosage: Children 12 years of age and older: 2 caplets every 8 hours. No more than a total of 6 caplets in any 24 hour period.

Indications: Extended Relief Tylenol caplets act quickly to provide temporary relief up to 8 hours from minor aches and pains of arthritis, headaches, menstrual cramps, backaches, and from the discomfort of fever due to colds and flu.

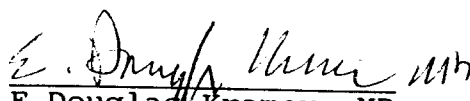
Other: The warnings and other parts of the label are currently standard.

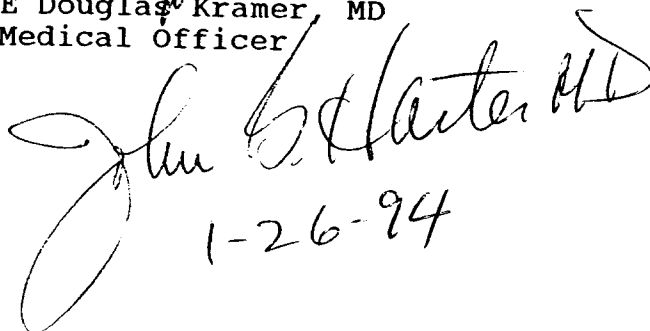
Issues:

1. An alcohol warning will need to be included in the labeling.
2. In several places in the labeling, the words quickly or fast are used to describe the onset of relief from this product. This should be modified to reflect the possibility of a slightly delayed onset of effect observed in the clinical studies for this product.

CONCLUSIONS:

1. This NDA is approvable.
2. The labeling issues above need to be addressed by the sponsor.

  
E Douglas Kramer, MD  
Medical Officer

  
1-26-94



DATE: January 25, 1994  
 NDA # 19872  
 SPONSOR: McNEIL Consumer Products  
 PRODUCT: APAP SR CAPLETS  
 STUDY# 87-746  
 Reviewer: E Douglas Kramer, MD

## APAP SR IN OA OF HIP OR KNEE

### SUMMARY

This study was a 9 center, entry washout, double blind comparison of APAP SR caplets vs APAP RR over 4 weeks. There was no placebo control. Patients had to have at least moderate pain, an exacerbation during washout, x-ray evidence of OA, a history of NSAID response, and pain which was exacerbated with motion and relieved with rest to be eligible. Basic efficacy measures including pain during the day, pain during the night, pain while standing, pain while walking, pain while retiring, pain while standing from a chair, and pain while climbing stairs were assessed after 1, 2 and 4 weeks of treatment. Of 197 patients enrolled, 39 did not meet all entry criteria. Because these patients generally had reasonable evidence of osteoarthritis, the sponsor was requested to analyse the results of this study in an ITT analysis with all patients enrolled. Patients in the 2 treatment groups were well matched at baseline. There were no consistent statistically significant differences between treatments by ANOVA. Q statistics ranged from 0.92 - 1.10 (QL, 0.65 - 0.77, effect sizes 0.82-0.99 for SR 0.78-0.97 for RR) for endpoints listed above. Changes from baseline for physician and patient global ratings could not be determined, as these ratings were not made at baseline.

In the absence of a placebo control, it is not possible to establish efficacy directly from this trial. However, the effect sizes of those variables that were measured at baseline are typical of those found in typical successful placebo controlled OA trials. Thus, it is likely that SR APAP is effective in the treatment of OA pain and that the finding of no statistically significant differences between RR and SR APAP is not merely due to chance.

### INTRODUCTION

This study was a 9 center, entry washout, double blind comparison of APAP SR caplets vs APAP RR over 4 weeks. There was no placebo control. Patients recieved either RR APAP 1000mg 4 times per day or SR APAP 1300mg 3 times per day and placebo once per day. They were evaluated at 1, 2 and 4 weeks of treatment.

## STUDY POPULATION

Inclusion and exclusion criteria are listed in table 1. The demographics of the intent to treat population are given in table 2.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Affected hip or knee (only 1 joint followed per patient)	Lactating or pregnant females
Pain on motion and weight bearing. At least moderate pain required	Active TB, hypertension, hepatic, renal, convulsive, malignant, hematological disease or alcohol abuse.
Pain, partially relieved by rest <sup>1</sup>	Significant GI disease or inability to tolerate po meds
Minimum of 3 mos of symptoms	Contra-indication to NSAIDS
positive x ray within 12 months	Hx of allergies or rheumatic diseases
hx of NSAID response	Persons taking possibly confounding meds (eg tranquilizers)
exacerbation during washout	Investigational drug in last 4 weeks, intra-articular steroids in 6 weeks, or anti-inflammatory/analgesic medication within 24 hours

Note that 35 patients who were randomized in the study did not meet the criterion of having pain that was both exacerbated with motion and relieved with rest.

Table 2: Demographics of OA patients (Intent To Treat Population)

Characteristic	APAP SR	APAP RR
N	96	95
Males	28	28
Females	68	67
Mean Age	64.7 (32 - 84)	65.5 (39 - 87)
Hip	16	16
Knee	80	80
Concomitant Meds	66%	65%
day pain	2.5 (0.06)	2.6 (0.06)
night pain	2.5 (0.05)	2.3 (0.07)
standing pain	2.2 (0.09)	2.3 (0.08)
walking pain	2.6 (0.07t)	2.6 (0.1)
ret pain	2.3 (0.09)	2.5 (0.1)
chair pain	2.5 (0.1)	2.6 (0.07)
stair pain	2.9 (0.08)	3.0 (0.08)

Patient participation rates are given in table 3

Table 3: Patient participation by week

DRUG	WEEK1	WEEK2	WEEK4
RR APAP	97	90	84
SR APAP	95	88	84

#### EFFICACY MEASURES AND STATISTICAL ANALYSIS

Efficacy measures used in this trial are listed in table 4. These observations were analysed in an intent to treat analysis with the last observation carried forward following dropout. Note that 35 patients who were randomized to treatment did not have pain that was exacerbated with motion and relieved with rest. It was elected to include these patients in the analysis because they had met other entry criteria. Differences between drugs were evaluated with an ANOVA containing terms for treatment, center, baseline pain and interactions by treatment as appropriate. Comparisons were made at 1, 2, and 4 weeks and at end of study. Q statistics were calculated for those variables which were measured at baseline.

Table 4: Efficacy Measures

Efficacy Measures	Unit of measure
Pain during day	0 - 4 scale
Pain during night	0 - 4 scale
Pain while walking	0 - 4 scale
Pain while retiring/arising	0 - 4 scale
Pain while standing from chair	0 - 4 scale
Pain while climbing stairs	0 - 4 scale
Pain relief during the day	none, a little, some, a lot, complete (0 - 4 scale)
Pain relief during the night	0 - 4 scale
Patient assess of analgesia	poor, fair, good, very good, excellent
Patient global assessment	poor, fair, good, very good, excellent (week 4 or end)
Phys eval of therapeutic resp	worse, none, minimal, moderate, marked
Phys overall eval of response	worse, none, minimal, moderate, marked (week 4 or end)
ROM:abduction, adduction, flexion, extension, ext & int rotation	degrees
Pain during abduction, adduction, flexion, extension, ext & int rotation	none, mild, moderate, moderately severe, severe (0 - 4 scale)
Duration of morning stiffness	minutes
Time to walk 50 feet	seconds

## RESULTS


Results of the ANOVA and Q statistics are summarized in table 4. No differences were found between treatments at 1, 2, or 4 week evaluations.

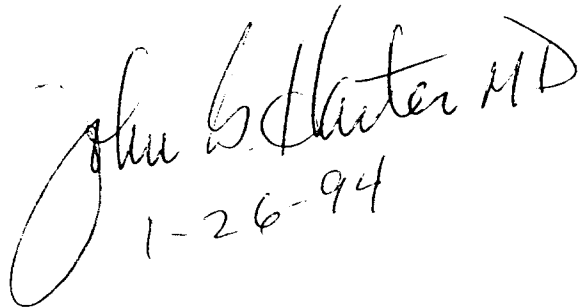
Table 4: ANOVA Results Summary

Efficacy Measure	Treatment Effect	Q statistic ratio/LL
Pain during day	NONE	0.93/0.65
Pain during night	NONE	1.00/0.73
Pain while walking	NONE	0.92/0.65
Pain while retiring/arising	NONE	0.97/0.67
Pain while standing from chair	NONE	1.04/0.77
Pain while climbing stairs	NONE	1.10/0.77
Pain relief during the day	NONE	NA
Pain relief during the night	NONE	NA
Patient assess of analgesia	NONE	NA
Patient global assessment	NONE	NA
Phys eval of therapeutic resp	NONE	NA
Phys overall eval of response	NONE	NA
Pain during abduction, adduction, flexion, extension, ext & int rotation	NONE	Range 1.1/0.81 to 0.56/0.12. 4 results not calculable

**CONCLUSIONS:**

1. This study provides indirect supportive evidence of the efficacy of SR APAP in osteoarthritis. In the absence of a placebo control, the conclusion that the effect sizes seen represent efficacy must be based on a historical comparison of other similar studies. However, such a conclusion seems reasonable.
2. This study provides indirect supportive evidence of the overall similarity of SR and RR APAP when used as the same total daily dose. The validity of the finding that SR and RR APAP are not statistically different depends critically on the conclusion that this trial demonstrated efficacy. Once again, in the absence of a placebo control, while such a conclusion may seem reasonable, it cannot come directly from the study itself.

  
E Douglas Kramer, MD  
Medical Officer

  
1-26-94

DATE: January 26, 1993  
NDA: 19872  
PRODUCT: APAP SR CAPLETS  
SPONSOR: MCNEIL  
STUDY #: 88-856  
REVIEWER: E Douglas Kramer, MD

## APAP SR IN POST OPERATIVE DENTAL PAIN

### SUMMARY

The study was an 8-hour, single-center, post-operative, double-blind, placebo-controlled dental pain study following 3rd molar extraction in 120 patients who experienced at least moderate pain. A single dose of APAP SR Caplets was compared to 2 doses of APAP RR caplets and 2 doses of placebo over 8 hours. Patients in each treatment group were well matched at baseline. Ratings of pain intensity, and pain relief, were made at 0, 0.5, 1, 2, 3, 4, 4.5, 5, 6, 7, and 8 hours, along with time to onset and time to rescue. Data was analysed by carrying forward the last observation prior to rescue or baseline, whichever was worse. Calculations were done by the sponsor were spot-checked. Results showed that both active drugs provided statistically significantly more pain relief compared to placebo for up to 6 hours (measured by PID and RELIEF scores). Notable differences were present between SR vs RR products in a manner consistent with a longer duration of action of the SR vs the RR product: 1. PID for SR was >placebo at 4 and 4.5 hours when RR was not. 2. Relief for SR was significantly > placebo at 3 and 4 hours while RR was not. In addition, there were trends in differences between SR and RR products that were typical of what would be expected in a comparison of SR and RR products. For example, RR APAP provided more rapid onset and higher peak of effect than SR APAP, but not significantly so.

This study provides substantial evidence of analgesic efficacy of SR APAP caplets. SR APAP is typical of a sustained release preparation in that a single dose has a longer duration of action than RR APAP and a slightly longer time to onset of effect compared to the RR preparation

### INTRODUCTION

The study was an 8-hour single-center, post-operative, double-blind, placebo-controlled, dental pain study following 3rd molar extraction of 1 - 3 teeth in 120 patients. Observations of pain intensity and pain relief were made at 0, 0.5, 1, 2, 3, 4, 4.5, 5, 6, 7, and 8 hours. The first hour of observations were made in the clinic followed by 7 hours of outpatient observation. Treatments are listed in table 1 and the demographics of the study population are listed in table 2.



table 1: Treatment Groups for dental pain study.

Treatment Group	Rx at time = 0 hr	Rx at time = 4 hr
APAP RR	650mg x 1 caplet placebo x 1	650mg x 1 caplet placebo x 1
APAP SR	650mg x 2 caplets	placebo x 2
Placebo	placebo x 2	placebo x 2

Table 2: Demographics of all patients enrolled (N=120)

characteristic	SR APAP	RR APAP	Placebo
N	40	40	40
% women	55%	57%	60%
% white	92%	85%	85%
mean age (sd) range	24.4 (6.3) (17 - 46)	24.3 (5.1) (16 - 37)	25.1 (5.1) 16 - 36
mean procedure time -- minutes(sd) range	7.5 (2.4) (5 - 13)	8.5 (3.4) (5 - 20)	9.2 (3.7) (3 - 20)
trauma (mild/mod/sev)	15/18/7	15/13/12	12/18/10
# extractions	1.8 (0.41) (1 - 2)	1.7 (0.46) (1 - 2)	1.9 (0.38) (1 - 3)
baseline pain (mod/mod- sev/sev)	27/13/0	27/13/0	23/15/2

#### EFFICACY MEASURES AND STATISTICAL ANALYSIS:

Data were analysed in an intent to treat fashion, carrying forward the last observation of patients who took rescue medication. Analgesic measures were analysed by an ANOVA at each time point. The model contained terms for treatment, initial pain and treatment by initial pain as appropriate. Patients with moderately severe and severe pain were pooled for this analysis. For times with a significant treatment effect, individual treatments were compared with Fisher's LSD. Median time to onset was analysed nonparametrically and by interpolation to the time when PRID=1. Duration of effect was analysed by the Kaplan Meier estimated survival function.

# RESULTS:

## 1. Populations for statistical analysis:

A total of 120 patients were enrolled. The six patients listed in table 3 were excluded from all or part of the efficacy analysis:

Table 3: Exclusions from the efficacy analysis

ID #	RX	Excluded Analyses	Reason	Onset/ rescue
35	Pla	Summary Measures, Time to Rescue, Onset, Global, Individual comparisons	Rescued @ 30min	N/Y
78	Pla	Summary measures, Time to rescue, Global, Individual comparisons	2nd dose @ 1.1 hr	N/Y
61	RR	Summary Measures, Individual comparisons	Slept from 4.5 - 8 hr	Y/N
73	RR	Summary Measures, Time to rescue, global	2nd dose @2.3 hr	Y/Y
24	SR	Summary Measures, Time to rescue, global, Individual comparisons	2nd dose @2hr; slept 2 -7 hr	Y/N
5	Pla	Global	no rating provided	Y/Y

## 2. Efficacy Summary

Endpoint	SR APAP	RR APAP	Placebo	Overall p
Median onset (min) stopwatch method (95% CL)	61.5 A (30 - 240)	43.5 A (30 - 240)	240 B (48 - 240)	0.0068
mean OPAR PRID method (95% CL)	16 AB (12 - 23)	14 A (11 - 20)	26 B (18 - 44)	
Duration(hr) (95% CL)	7.8 A (5 - 8+)	7.4 A (3.2 - 8+)	6.0 A (2.7 - 8+)	
MAXPID <sup>2</sup> (SEM)	1.2 (0.16)A	1.3 (0.16)A	0.7 (0.12)B	0.0003
MAXPAR (SEM)	2.6 (0.21)A	2.7 (0.22)A	1.5 (0.21)B	0.0002
SPID <sup>2</sup> (SEM)	4.5 (1.3) A	4.4 (1.2) A	0.5 (1.1)B	0.0080
TOTPAR (SEM)	12.6 (1.6)A	12.3 (1.7)A	6.9 (1.5)B	0.0195

Treatments with the same letter are not statistically different from each other.

<sup>2</sup> A significant interaction ( $p < 0.2$ ) was present for treatment by initial pain. Mean values in the table are for all patients. Results of pairwise comparisons are for patients with severe and moderately severe initial pain. Results for patients with moderate initial pain did not differ from placebo.

## 3. Analgesic Efficacy

### A. PID

Overall, there is a treatment effect for PID from 1 hour through 6 hours. Except at 4 hours, there is a significant interaction with the severity of baseline pain, and treatment effects that are seen in the overall population are due to patients with moderately severe and severe baseline pain and not to patients with moderate baseline pain. (FIGURE 1 - 3).

RR APAP differentiates from placebo at 1 hour - 3 hours. At 4 hours it is not distinguishable from placebo. RR APAP patients

experience less of an increase in PID following the second dose compared to the first and RR differentiates from placebo again at 5 and 6 hours.

SR APAP differentiates from placebo from 1 hour through 6 hours. At 5 hours, this difference is seen only in patients with moderately severe and severe initial pain.

Overall, RR and SR APAP are statistically different from each other at 4, 4.5, and 5 hours. As would be expected from a comparison of SR and RR formulations, SR is better than placebo at 4 and 4.5 hours, where RR is not; it is not different from placebo at 5 hours where RR is (after the second dose); and both treatments are different from placebo at 6 hours where the order of the treatments is again reversed with  $RR > SR$  (Figure 1). In addition, RR peaks slightly earlier and slightly higher than SR.

#### B. RELIEF

Overall, there is a treatment effect for relief from 1 hour through 4 hours that has no interaction with baseline pain.

RR APAP is significantly better than placebo at 1 and 2 hours while SR APAP is significantly better than placebo from 1 to 4 hours. (Figures 4 - 6)

RR and SR APAP are not statistically different from each other at any time during the study.

#### 4. Onset of relief

Time to onset of relief gave different results by different methods. The stopwatch method for onset of meaningful relief showed both active drugs with median times to onset significantly less than placebo. RR APAP was more rapid in onset than SR APAP, although not significantly so. As measured by the time when PRID reaches 1, RR APAP was significantly more rapid than placebo and SR APAP was not different from either RR APAP or from placebo. In addition, RR APAP tended to peak slightly earlier and higher than SR APAP in PID and RELIEF, but not significantly so.

#### 5. Duration of relief

As measured by the time when 50% of patients remedicated, neither active treatment was significantly different from placebo.

#### 6. Other measures

Both active drugs were significantly better than placebo for the summary measures TOTPAR, MAXPAR, and GLOBAL. SPID and MAXPID showed both active drugs to be significantly better than placebo for patients with moderately severe or severe pain. SR APAP was better than placebo for number of hours with pain 1/2 gone whereas RR APAP was not.

CONCLUSIONS:

1. This study provides substantial evidence of efficacy for SR APAP vs placebo in a dental pain model.
2. Differences between SR APAP and RR APAP are few and are small in magnitude where they exist. Differences that do appear between these products, most likely reflect real differences between regular and sustained release formulations in terms of onset, duration and peak of effect.

  
E Douglas Kramer, MD  
Medical Officer

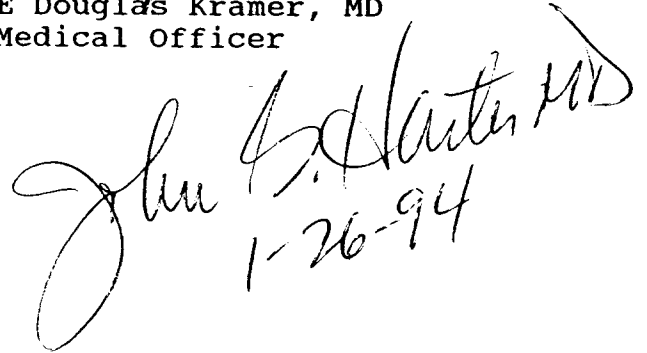
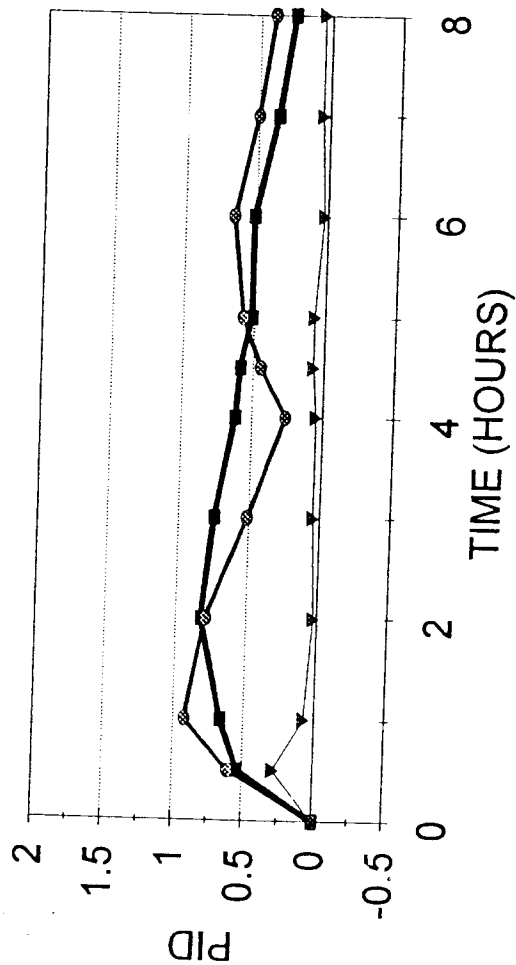
  
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FIGURE 1

# MEAN PID BY RX ELIGIBLE PATIENTS--DENTAL PAIN

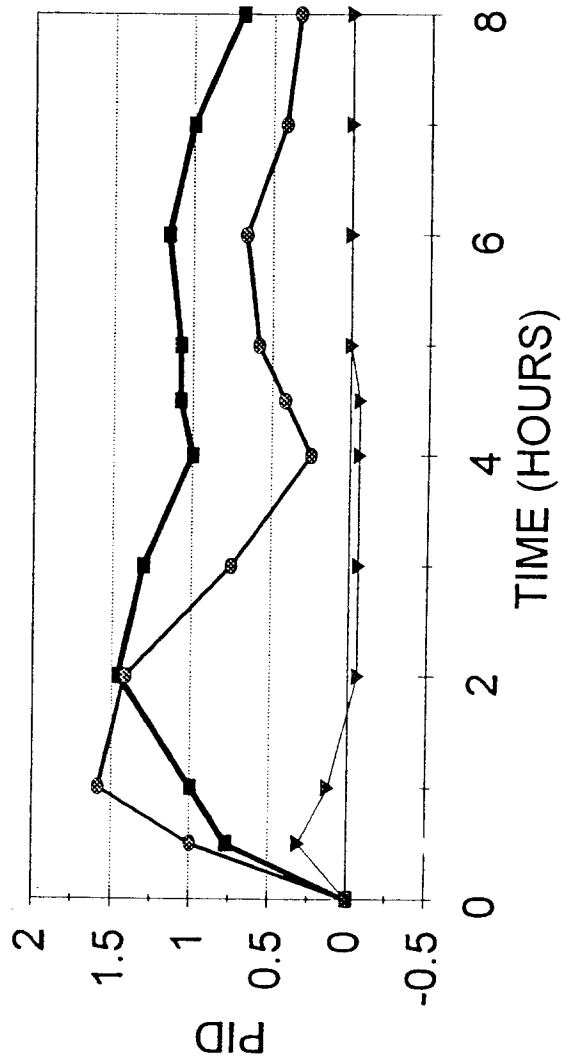


—■— SR    -○- RR    ▴ PLA

SR	0.54 (0.12)	0.67 (0.15)	0.82 (0.20)	0.74 (0.19)	0.62 (0.17)	0.59 (0.17)	0.51 (0.18)	0.51 (0.19)	0.36 (0.19)	0.26 (0.18)	0.13	0.34
RR	0.61 (0.14)	0.92 (0.19)	0.79 (0.19)	0.51 (0.16)	0.26 (0.15)	0.45 (0.17)	0.58 (0.19)	0.66 (0.20)	0.50 (0.19)	0.39 (0.19)	0.13	0.34
PLA	0.29 (0.10)	0.08 (0.13)	0.03 (0.14)	0.05 (0.15)	0.05 (0.15)	0.08 (0.16)	0.08 (0.16)	0.03 (0.16)	0.05 (0.16)	0.05 (0.16)	0.13	0.34
P	0.099	0.0001	0.0001	0.0023	0.0411	0.0287	0.0475	0.0211	0.05	0.05	0.13	0.34

FIGURE 2

# MEAN PID BY RX ELIGIBLE PATIENTS--DENTAL PAIN

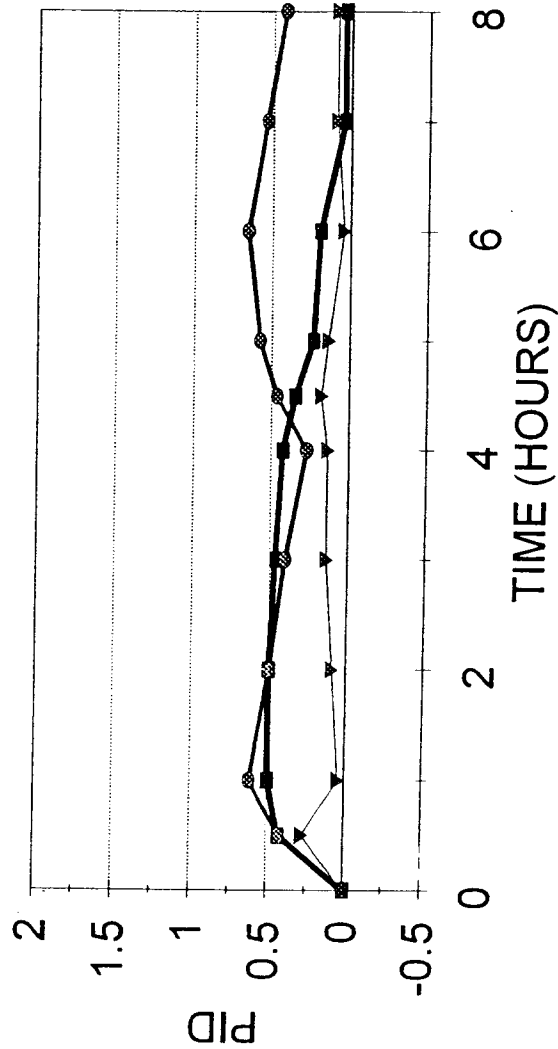


SEV-SR SEV-RR SEV-PLA

SEV SR	0.77 (0.20)	1.00 (0.30)	1.46 (0.35)	1.31 (0.38)	1.00 (0.32)	1.08 (0.33)	1.08 (0.33)	1.15 (0.36)	1.00 (0.34)	0.69 (0.33)
	13	11	8	8	8	8	8	8	7	5
	NA	A	A	NA	A	A	A	A	NA	NA
SEV RR	1.00 (0.25)	1.58 (0.36)	1.42 (0.38)	0.75 (0.35)	0.25 (0.28)	0.58 (0.38)	0.67 (0.38)	0.42 (0.29)	0.33 (0.28)	
	12	12	9	4	4	4	4	4	3	
	NA	A	A	NA	AB	AB	AB	NA	NA	
SEV PL	0.31 (0.15)	0.13 (0.22)	-0.06 (0.17)	-0.06 (0.19)	-0.06 (0.23)	0.00 (0.22)	0.00 (0.22)	0.00 (0.22)	0.00 (0.22)	
	16	10	6	5	5	5	4	2	2	
	NA	B	B	NA	B	B	B	NA	NA	
P	NA	0.0004	0.0001	0.0018	NA	0.014	0.0308	0.022	NA	NA

FIGURE 3

# MEAN PID BY RX ELIGIBLE PATIENTS--DENTAL PAIN



MOD-SR MOD-RR MOD-PLA

SR	0.42 (0.15)	0.50 (0.17)	0.50 (0.22)	0.46 (0.19)	0.42 (0.20)	0.35 (0.18)	0.23 (0.19)	0.19 (0.19)	0.04 (0.20)	0.04 (0.20)	0.04 (0.20)
	26	24	22	22	21	21	19	18	18	13	7
	NA	NS	NS	NS	NA	NS	NS	NS	NA	NA	7
RR	0.42 (0.16)	0.62 (0.19)	0.50 (0.19)	0.40 (0.17)	0.27 (0.19)	0.46 (0.21)	0.58 (0.22)	0.65 (0.23)	0.54 (0.25)	0.42 (0.25)	8
	26	26	23	21	19	19	18	17	16	13	8
	NA	NS	NS	NS	NA	NS	NS	NS	NA	NA	8
PLA	0.27 (0.13)	0.05 (0.17)	0.09 (0.21)	0.14 (0.21)	0.14 (0.21)	0.18 (0.21)	0.14 (0.23)	0.05 (0.23)	0.09 (0.24)	0.09 (0.24)	8
	22	22	20	18	16	16	16	15	13	12	8
	NA	NS	NS	NS	NA	NS	NS	NS	NA	NA	8
P	0.1006	0.312	0.508	0.6416	0.324	0.14	0.09	0.05	0.09	0.09	0.09
	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA



FIGURE 4

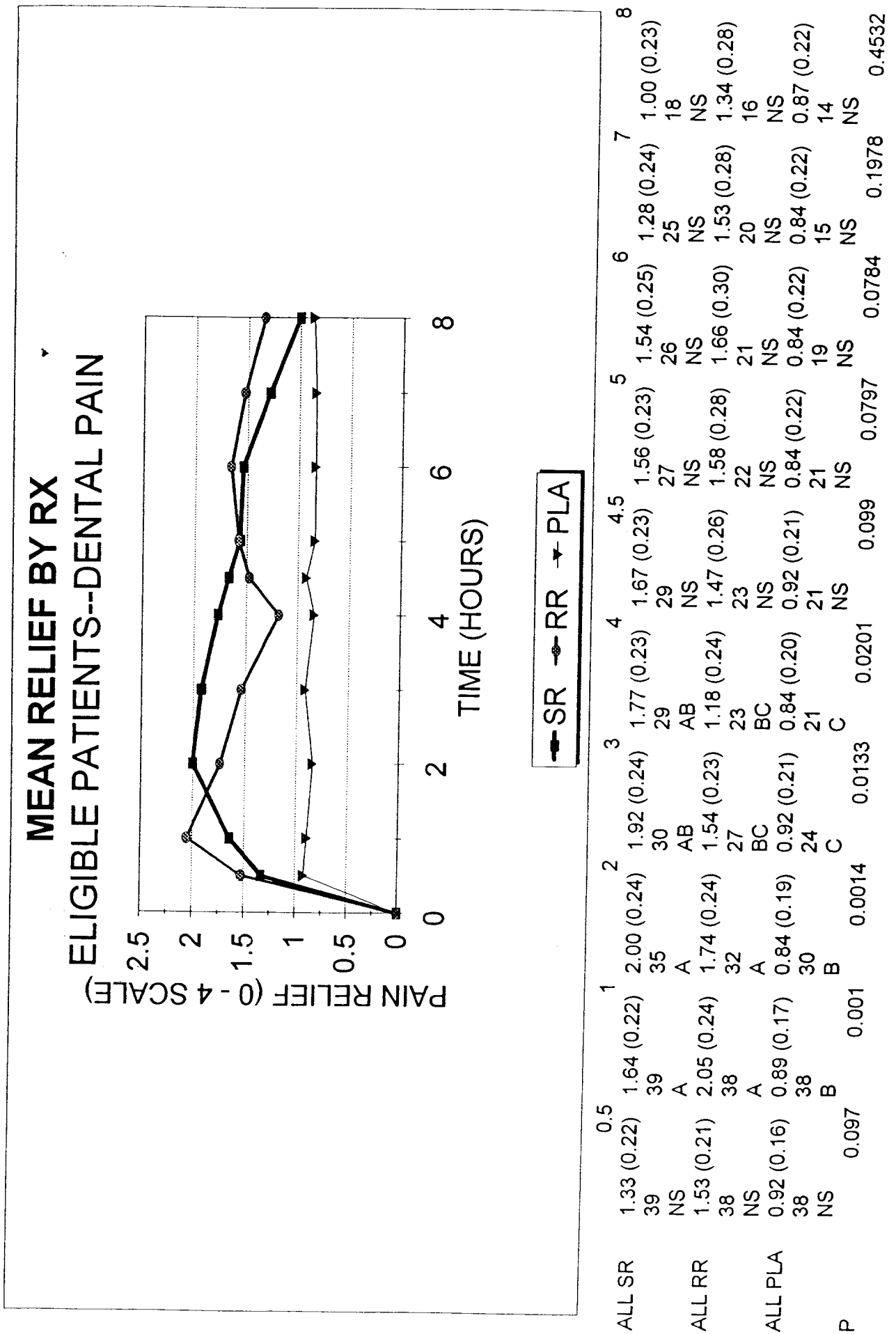
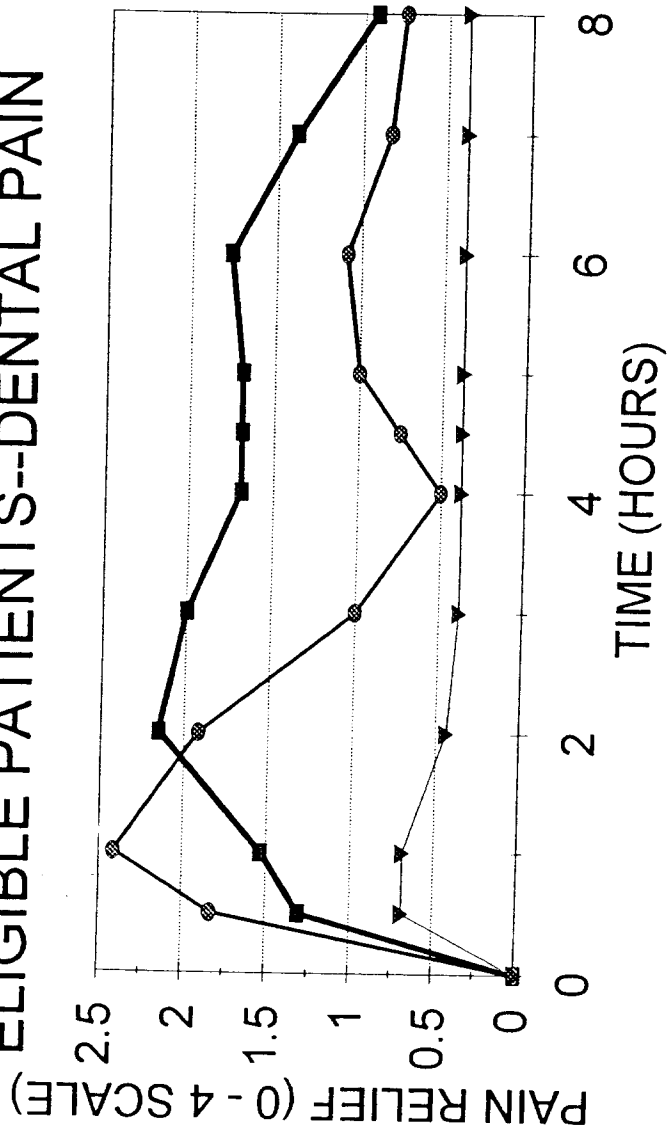


FIGURE 5

# MEAN RELIEF BY RX ELIGIBLE PATIENTS--DENTAL PAIN

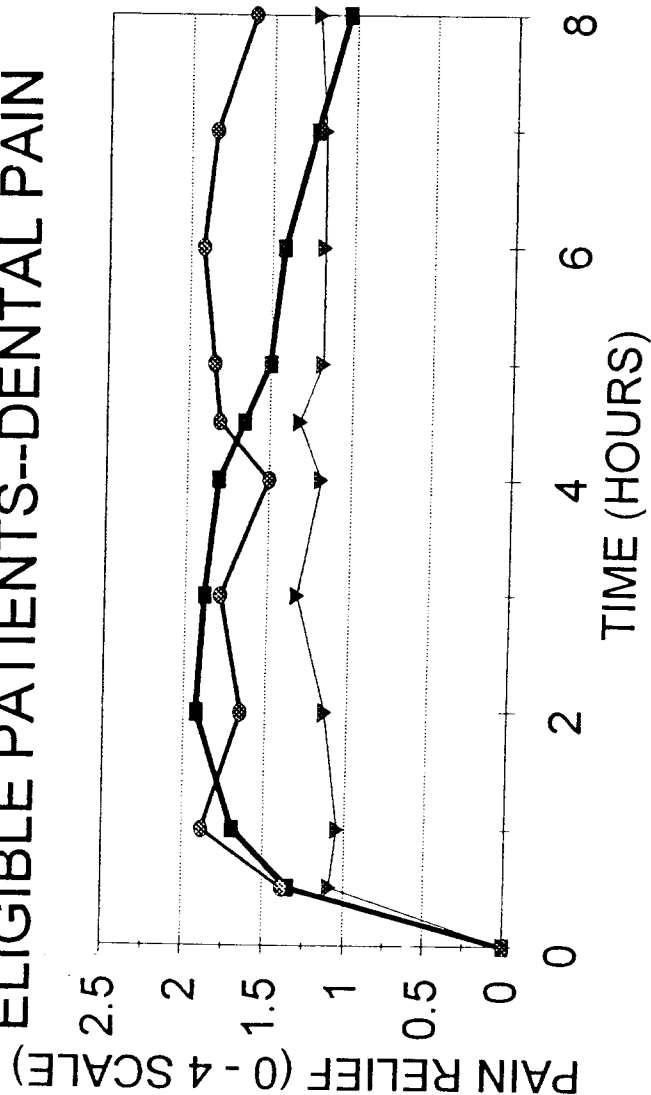


SEV-SR SEV-RR SEV-PLA

SEV SR	1.31 (0.33)	1.54 (0.39)	2.15 (0.42)	2.00 (0.48)	1.69 (0.41)	1.69 (0.41)	1.77 (0.44)	1.38 (0.45)	0.92 (0.42)
	13	13	11	8	8	8	8	7	5
SEV RR	1.83 (0.33)	2.42 (0.40)	1.92 (0.45)	1.00 (0.43)	0.50 (0.34)	0.75 (0.37)	1.08 (0.48)	0.83 (0.39)	0.75 (0.41)
	12	12	9	6	4	4	4	4	3
SEV PLA	0.69 (0.24)	0.69 (0.25)	0.44 (0.24)	0.38 (0.26)	0.38 (0.26)	0.38 (0.26)	0.38 (0.26)	0.38 (0.26)	0.38 (0.26)
	16	16	10	6	5	5	4	2	2

FIGURE 6

# MEAN RELIEF BY RX ELIGIBLE PATIENTS--DENTAL PAIN



MOD-SR    MOD-RR    MOD-PLA

MOD SR	1.35 (0.28)	1.69 (0.28)	1.88 (0.30)	1.81 (0.28)	1.65 (0.29)	1.50 (0.28)	1.42 (0.30)	1.23 (0.28)	1.04 (0.29)
	26	26	22	21	21	19	18	18	13
MOD RR	1.38 (0.27)	1.88 (0.30)	1.79 (0.27)	1.50 (0.29)	1.81 (0.32)	1.85 (0.34)	1.92 (0.37)	1.85 (0.36)	1.62 (0.36)
	26	26	21	19	19	18	17	16	13
MOD PLA	1.09 (0.21)	1.05 (0.22)	1.32 (0.28)	1.18 (0.28)	1.32 (0.30)	1.18 (0.32)	1.18 (0.32)	1.18 (0.32)	1.23 (0.31)
	22	22	18	16	16	16	15	13	12

DATE: January 26, 1993  
NDA: 19872  
PRODUCT: APAP SR Caplets  
SPONSOR: MCNEIL  
Study #: 88-857  
Reviewer: E Douglas Kramer, MD

## Tylenol SR Caplets in Episiotomy Pain

### SUMMARY

The study was an 8 hour 2-dose, 2-center, randomized, parallel comparison of APAP SR, APAP RR, and placebo in the treatment of pain following episiotomy in 123 patients. At least moderate pain was required at time of medication. Pain intensity and pain relief were measured at 0.5, 1, 2, 3, 4, 4.5, 6, 7 and 8 hours along with time to onset and time to remedication. For analysis, patients with moderately severe and severe initial pain were pooled and were analysed with ANOVA by initial pain and investigator using the last observation carried forward prior to rescue. The sponsors results were spot-checked. There was little separation between treatments in PID and RELIEF with both active drugs separating from placebo at only 4, 4.5 and 6 hours (PID) and at 4.5 - 7 hours (RELIEF). RR but not SR APAP differentiated from placebo in onset by stopwatch, while no treatments differed in terms of onset by PRID. Both active medications were superior to placebo in terms of summary analgesic measures (SPID and TOTPAR).

This study showed evidence of analgesic efficacy in only a few measures, with different measures of the same outcome (eg onset by stopwatch vs PRID) inconsistent. There are two possible reasons for this: First, patients with moderately severe and severe initial pain tended to do less well than patients with only moderate initial pain. Second, investigator Cooper's patients (N=75) often had substantial placebo responses, with mean placebo response at times being better than active drug. Investigator Mcquarrie's results, in contrast, gave results which were more internally consistent of what might be expected in an analgesic trial comparing RR and SR products.

Overall, this study provides some evidence of analgesic efficacy in both RR and SR APAP. The weaknesses in the evidence most likely result from substantial differences between investigators in the degree of placebo response.

### INTRODUCTION:

The study was an 8 hour 2-dose, 2-center, randomized, parallel comparison of APAP SR, APAP RR, and placebo in the treatment of pain following episiotomy in 123 patients. At least moderate pain was required at time of medication. Pain intensity and pain relief were measured at 0.5, 1, 2, 3, 4, 4.5, 5, 6, 7, and 8 hours. Medication was given at 0 and 4 hours as described in

table 1. Demographics for the study population are given in tables 2 and 3:

table 1: Treatment Groups for episiotomy study.

Treatment Group	Rx at time = 0 hr	Rx at time = 4 hr
APAP RR	650mg x 1 caplet placebo x 1	650mg x 1 caplet placebo x 1
APAP SR	650mg x 2 caplets	placebo x 2
Placebo	placebo x 2	placebo x 2

Table 2: Demographics of all patients enrolled by treatment group (N=123)

characteristic	SR APAP	RR APAP	Placebo
N	41	41	41
% white	88%	85%	88%
mean age (sd) range	26.6 (4.8) (15 - 40)	26.9 (6.1) (15 - 41)	26.9 (4.6) (20 - 36)
mean procedure time -- minutes(sd) range	142 (160) (4 - 550)	71 (83) (6 - 310)	133 (167) (8 - 645)
trauma (mild/mod/sev)	22/17/2	19/20/2	19/19/3
baseline pain (mod/mod- sev/sev)	36/5/0	31/9/1	29/11/1

There are no significant differences between treatment groups in any baseline measures.

Table 3: Demographics of all patients enrolled by investigator (N=123)

characteristic	Jay Cooper	McQuarrie	p value
N	75	48	
% white	81%	96%	0.034
mean age (sd) range	27.1 (5.6) (15 - 41)	26.4 (4.5) (18 - 36)	NS
mean procedure time -- minutes(sd) range	22 (15) (4 - 91)	219 (150) (23 - 645)	0.0001
trauma (mild/mod/sev)	54/18/3	6/38/4	0.001
baseline pain (mild/mod/sev)	57/16/2	39/9/0	NS

#### EFFICACY MEASURES AND STATISTICAL ANALYSIS:

Analgesic measures were analysed by an ANOVA at each time point. The worse of the last observation or baseline was carried forward following rescue. The model contained terms for treatment, center, initial pain, treatment by initial pain, and treatment by center as appropriate. For times with a significant treatment effect, individual treatments were compared with Fisher's LSD. Onset and duration of effect were analysed by survival techniques.

## RESULTS:

### 1. Patient populations

A total of 123 patients were enrolled in the study by 2 PI's and 5 subinvestigators. Patients excluded from the efficacy analysis are listed in the following table:

Table 3: Exclusions from the efficacy analysis

ID #	RX	Excluded Analyses	Reason	Onset/ rescue
32	RR	all	rescue at 0.6h	N/Y
126	SR	all	rescue at 0.6h	N/Y
53	RR	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	rescue at 2h for non epis pain	Y/Y
132	RR	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	rescue at 4.5h for non epis pain	Y/Y
73	RR	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	did not take 2nd dose	Y/Y
23	SR	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR, ONSET BY STOPWATCH	did not take 2nd dose	Y/N
74	PLA	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	2nd dose @ 3.4 h	Y/Y
83	PLA	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	2nd dose @ 3.3 h	Y/Y
102	PLA	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	2nd dose @ 2.0 h	Y/Y
86	RR	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	2nd dose @ 1.6 h	Y/Y
88	RR	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	2nd dose @ 2.8 h	Y/Y
98	SR	PID, PREL, PRID, SUMMARY MEAS, GLOBAL, TIME TO RESCUE, A-DURPAR	2nd dose @ 5 h	Y/N

57	SR	GLOBAL	No rating provided	Y/N
71	RR	GLOBAL	No rating provided	Y/N
9	PLA	ONSET BY STOPWATCH	No rating provided	N/N
15	PLA	ONSET BY STOPWATCH	No rating provided	N/Y
39	SR	ONSET BY STOPWATCH	No rating provided	N/N
47	RR	ONSET BY STOPWATCH	No rating provided	N/N

## 2. Efficacy Summary:

Endpoint	SR APAP	RR APAP	Placebo	rx p value
Median onset (min) stopwatch method(95% CL)	57 B (28 - 111)	32 A (24 - 50)	47 B (25 - 240)	0.0931 <sup>1</sup> 0.0196 <sup>2</sup>
mean OPAR PRID method (95% CL)	13.6 A (11 - 20)	13.8 A (11 - 18)	13.6 A (11 - 19)	
Duration(hr) (95% CL)	8+ A (7.5 - 8+)	8+ A (8+ - 8+)	5.6 A (3 - 8+)	0.0112 <sup>1</sup> 0.0104 <sup>2</sup>
SPID (SEM)	6.2 (0.9) A	7.0 (1.1) A	3.5 (1.1) B	
TOTPAR (SEM)	15.6 (1.5) A	16.8 (1.8) A	10.7 (1.5) B	

Treatments with the same letter are not statistically different from each other. Values without letters did not have an overall significant p value for treatment. <sup>1</sup>wilcoxon test of median time to remedication. <sup>2</sup>log rank test of median time to remedication.

Generally, investigator effects were common and highly significant, but significant interactions with treatment were few. Initial pain was commonly significant in the first dosing interval, but significant interactions with treatment were infrequent. Results for individual measures are reviewed below:

## 3. Analgesic efficacy

### A. PID

Overall, significant treatment effects for PID were found at 4, 4.5, and 6 hours. Both RR and SR APAP were significantly better than placebo but not different from each other at these times.



These differences were independent of investigator and the patient's level of initial pain. (Figure 1).

#### B. RELIEF

Significant treatment effects for RELIEF were found at 4.5 through 7 hours. Both RR and SR APAP were significantly better than placebo but not different from each other during this period. (Figure 2).

#### 4. Onset of relief

Neither active drug consistently outperformed placebo in time to onset of pain relief. As measured by the time after dosing when PRID reaches 1, all 3 treatments had an onset of relief of 13 - 14 minutes. As measured by the stopwatch method, RR APAP (median onset at 32 minutes) was better than placebo (median onset at 47 minutes) and SR APAP (median onset 57 minutes). SR APAP was not different from placebo.

#### 5. Duration of relief

Duration of relief as measured by median time to rescue is > 8 hours for both SR and RR APAP which is significantly longer than placebo at 5.5 hours. This is reflected in the number of patients who did not remedicate in 8 hours (SR=66%, RR=69%, and placebo=39%).

#### 6. Other Measures

For MAXPID, investigator McQuarrie's patients had a significant treatment effect for both active drugs. MAXPAR was marginally significant ( $p=0.056$ ), also with both active drugs > placebo. SPID also showed both active treatments > placebo. Treatment effects were observed for PRID from 4 - 6 hours, with both active drugs being > placebo from 4.5 - 6 hours. At 4 hours this effect was due solely to McQuarrie's SR APAP patients.

#### CONCLUSIONS:

1. This study provides little evidence of the efficacy of SR APAP.
2. It is difficult to determine the magnitude of any differences between RR and SR products in this study, but they appear to be similar to the Dental Pain study.

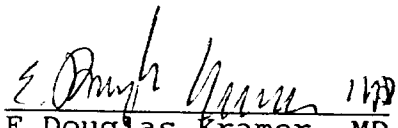
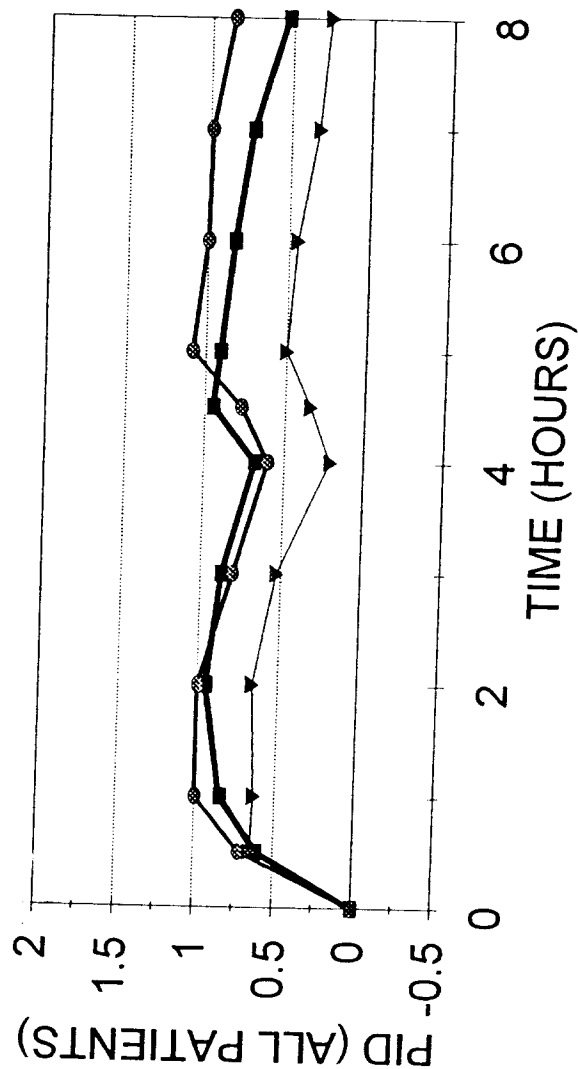
  
E Douglas Kramer, MD  
Medical Officer

Figure 1

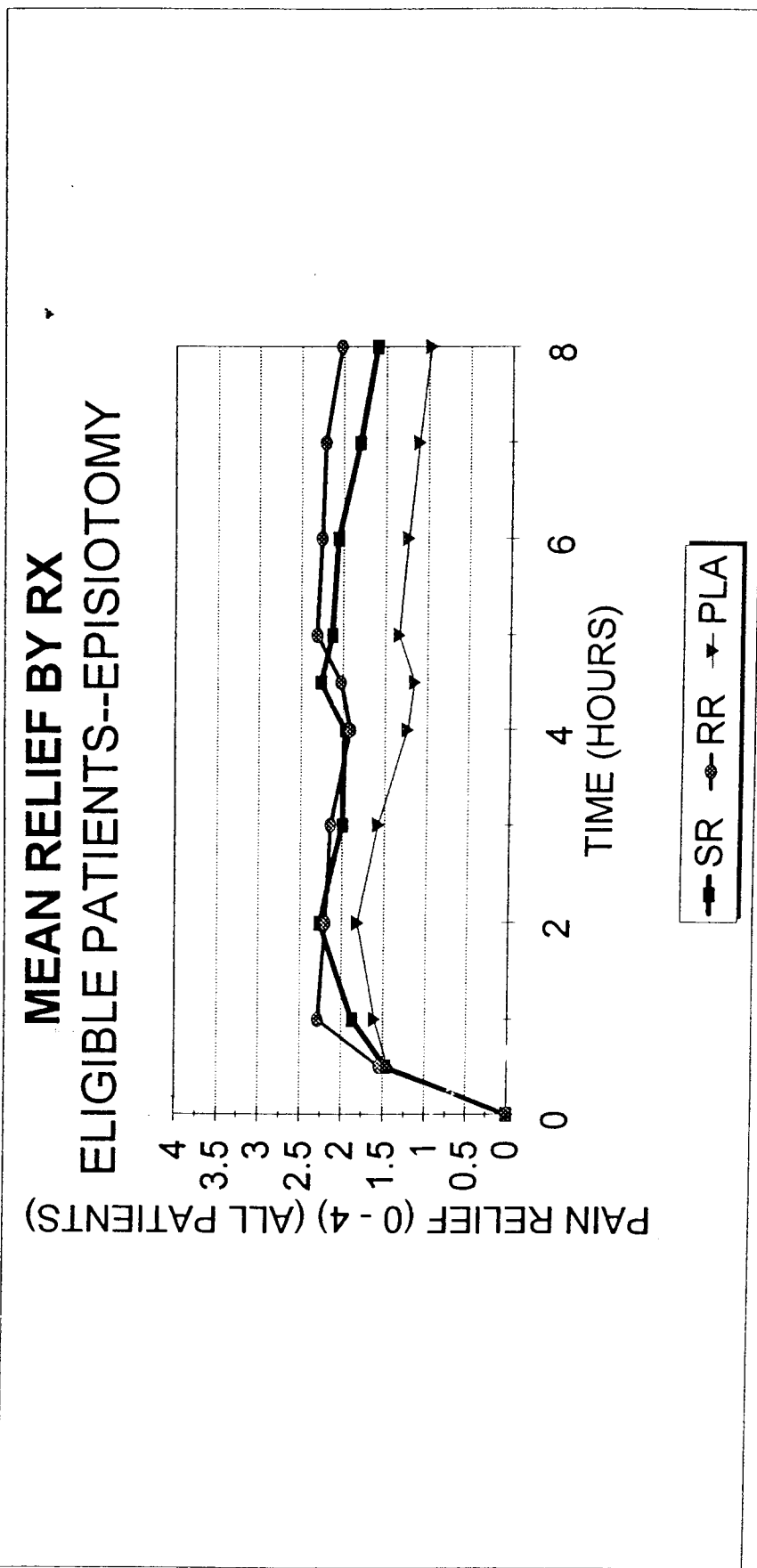
# MEAN PID BY RX ELIGIBLE PATIENTS--EPISIOTOMY



SR RR PLA

	1	2	3	4	4.5	5	6	7	8
SR	0.61 (0.02) 38 NS	0.84 (0.02) 36 NS	0.95 (0.02) 36 NS	0.87 (0.02) 35 NS	0.68 (0.02) 33 A	0.91 (0.03) 33 NS	0.83 (0.03) 30 A	0.73 (0.03) 27 NS	0.53 (0.03) 25 NS
RR	0.71 (0.02) 35 NS	1.00 (0.02) 32 NS	1.00 (0.03) 32 NS	0.80 (0.03) 28 NS	0.60 (0.03) 26 A	1.09 (0.03) 26 NS	1.00 (0.03) 26 A	0.99 (0.03) 26 NS	0.86 (0.03) 24 NS
PLA	0.64 (0.02) 38 NS	0.63 (0.02) 38 NS	0.66 (0.02) 30 NS	0.53 (0.03) 26 NS	0.21 (0.03) 24 B	0.34 (0.03) 23 B	0.50 (0.03) 23 NS	0.45 (0.03) 18 B	0.32 (0.03) 16 NS
P	0.730	0.055	0.090	0.430	0.027	0.004	0.084	0.031	0.103
									0.201

Figure 2



SR	0.5	1	2	3	4	4.5	5	6	7	8
	1.47 (0.04)	1.87 (0.04)	2.26 (0.04)	2.00 (0.04)	1.97 (0.04)	2.26 (0.04)	2.13 (0.04)	2.06 (0.04)	1.81 (0.04)	1.61 (0.04)
	38	38	36	35	33	33	33	30	27	25
	NS	NS	NS	NS	NS	A	A	A	A	NS
RR	1.54 (0.03)	2.29 (0.03)	2.20 (0.04)	2.14 (0.04)	1.91 (0.04)	2.03 (0.04)	2.31 (0.04)	2.26 (0.05)	2.21 (0.05)	2.03 (0.05)
	35	35	32	28	26	26	26	26	26	24
	NS	NS	NS	NS	NS	A	A	A	A	NS
PLA	1.45 (0.03)	1.61 (0.03)	1.82 (0.04)	1.58 (0.04)	1.24 (0.04)	1.16 (0.03)	1.34 (0.04)	1.24 (0.04)	1.11 (0.04)	0.97 (0.04)
	38	38	30	26	24	23	23	18	16	15
	NS	NS	NS	NS	NS	B	B	B	B	NS
P	0.878	0.066	0.383	0.207	0.056	0.001	0.007	0.006	0.005	0.086

DATE: January 25, 1994  
NDA: 19872  
SPONSOR: McNeil Consumer Products  
PRODUCT: APAP SR CAPLETS  
REVIEWER: E Douglas Kramer, MD  
SAFETY REVIEW

This review concerns safety data from the OA, Dental pain and Episiotomy studies in this NDA.

#### OA Study.

This study compared 3900mg SR APAP to 4000mg RR APAP daily for 1 month. Adverse experiences reported were generally minor and comparable for both drugs studied. It is difficult to ascribe them to the drug rather than intercurrent illness in a long term study. Adverse experiences are summarized in table 1.

Table 1: Adverse experiences

	SR APAP	RR APAP
Total Patients	96	96
Total patients with AE's	40	33
Total AE's reported	74	83
Digestive AE <sup>1</sup>	36	33
Whole Body AE	14	19
Cardiovascular AE	5	5
MILD severity	35	30
MODERATE severity	23	19
SEVERE severity	2	0
Not Related to Rx	14	34
Remote Related to Rx	1	0
Poss Related to Rx	28	19
Probable Related to Rx	0	0
Definite Related to Rx	2	3

<sup>1</sup> GI AE's included Nausea, diarrhea, constipation, dyspepsia and vomiting. For SR there were 12, 5, 4, 5 and 0 cases and for RR there were 6, 8, 0, 9, and 1 cases respectively of these complaints.

Many of the adverse experiences reported were either in the context of possibly related symptoms (eg fatigue, fever and diarrhea) or were potentially explicable on the basis of the subject's history (eg neck pain in a patient with OA of the cervical spine).

Six SR patients and 3 RR patients withdrew from the study because of adverse experiences. In only 1 instance (nausea in an APAP SR patient) was this felt to be definitely related to the study drug.

#### Dental pain and Episiotomy Studies

These studies were 2 dose 8-hour studies comparing SR APAP, RR APAP and placebo. The rates of adverse experience were comparable for RR APAP, SR APAP and placebo in these studies as shown in tables 2 and 3.

Table 2: Dental Pain AE's

	RR	SR	PLACEBO
Total patients	40	40	40
Total AE	7	5	6
AE Drop-outs	none	none	none
Max AE Severity	mild	mild	mild
Drug relation	unknown	poss-unknown	unknown

Table 3: Episiotomy Pain AE's

	RR	SR	PLACEBO
Total patients	41	41	41
Total AE	1	3	0
AE Drop-outs	none	none	NA
Max AE Severity	moderate	moderate	NA
Drug relation	Unknown	Remote-unknown	NA

#### SUMMARY:

The safety data from these studies reveals, for the most part, minor complaints, many of which are possibly not related to the study drug or which are potentially explicable as part of other conditions (eg intercurrent infections).

CONCLUSIONS:

1. Overall, the safety profile of the SR and RR forms of APAP is similar.

  
E Douglas Kramer, MD  
Medical Officer

