IN THE COURT OF APPEALS FOR THE STATE OF MISSISSIPPI

KRYSTAL MARIE TESTON **APPELLANT**

VS. **Case#2007-TS-00353-COA**

STATE OF MISSISSIPPI

APPEAL FROM THE CIRCUIT COURT OF HARRISON COUNTY, MISSISSIPPI
SECOND JUDICIAL DISTRICT

BRIEF OF THE APPELLANT KRYSTAL MARIE TESTON

(ORAL ARGUMENT REQUESTED)

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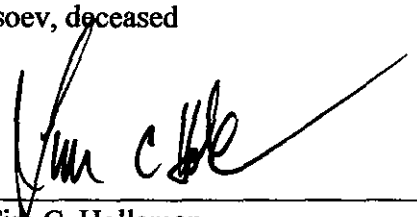
CERTIFICATE OF INTERESTED PARTIES

The undersigned counsel of record certifies that the following listed persons have an interest in the outcome of this case. These representations are made in order that the Justices of the Supreme Court and/or the Judges of the Court of Appeals may evaluate possible disqualification or recusal.

1. Cono Caranna, District Attorney;
2. Mark Ward, Assistant District Attorney;
3. Beth McFayden, Assistant District Attorney;
4. Krystal Teston, Appellant;
5. Tim C. Holleman, Attorney for the Appellant;
6. Michael Boyce Holleman, Attorney for the Appellant;
7. David and Rebecca Miller, parents of Lindsay Miller, deceased, and Josh Miller;
8. Josh Miller, passenger in SUV;
9. Nicole Thurman, passenger in SUV
10. David Finch, father of Elizabeth Finch, deceased;
11. Svetlana Sisoev, parent of Maksim Sisoev, deceased



Tim C. Holleman,
Attorney for the Appellant,
Krystal Marie Teston

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I. STATEMENT OF THE ISSUES

A. The trial court should have sustained Teston's motion for a JNOV or alternatively, the verdict is so contrary to the overwhelming weight of the evidence that to allow it to stand would sanction an unconscionable injustice.

B. The trial court erred in allowing the State's expert, Barbieri, to give his opinion of the levels of hydrocodone in Teston's bloodstream at the time of the accident and that she was impaired by hydrocodone at the time of the accident.

1. Barbieri provided an opinion that Teston was impaired at the time of the accident based on an inaccurate and incomplete hypothetical.

2. Barbieri's opinions of the hydrocodone blood levels that would be present in Teston's blood stream at the time of the accident, based on the hydrocodone blood levels shown to exist three hours later, and at that level Teston was impaired should not have been admitted under M.R.E. 702.

3. The expert's opinions should have been excluded under MRE 401, 402 and 403.

C. The Court erred in excluding and prohibiting mention of the statement of Krystal Teston that was recorded by the Biloxi Police Department following the accident and/or prohibiting cross-examination of Officer Brantley or other witnesses regarding the statement.

D. The trial court erred in reversing its ruling, in limine, prohibiting evidence of the defendant being charged with driving with suspended license) and erred in doing so after voir dire and selection of the jury.

E. The trial court erred in allowing the State to proceed to trial on count v-viii of the indictment requiring the defendant to defend said charges.

F. The trial court erred in failing to instruct the jury as to the correct burden of proof in this case, the evidence being entirely circumstantial.

G. The State improperly commented in opening statement and in closing argument on Teston's failure to testify.

H. Defendant's sentence of 15 years on each count for a total of 60 years to run consecutively with 30 years suspended was grossly disproportionate to the crime.

I. The court erred in permitting the introduction of blood drawn in violation of section 63-11-8, MCA, 1972.

II. STATEMENT OF THE CASE

A. NATURE OF THE CASE

On September 10, 2004, three young college students, Lindsey Miller, Elizabeth Finch and Maksim Sisoev, were killed in a tragic single-car accident on Interstate 10 in Biloxi, Mississippi. Another passenger, Josh Miller, the brother of Lindsey, was severely injured. This was a non-contact accident in which Lindsey Miller, the driver of the SUV occupied by the victims, lost control of the SUV, which then rolled over and collided with a concrete barricade on Interstate 10. The accident occurred when the driver of a black Honda attempted to change lanes into the SUV's lane.

Teston's convictions under 63-11-30(5) MCA for causing these unfortunate deaths and injuries, rest not on evidence, but in large measure on the emotions of a Jury that experienced graphic descriptions of the accident and victims, including one victim described for the Jury as flopping on the pavement like a dead fish, "bleeding out of every hole in her head". (R. Vol. II. p.616) This result was aided by erroneous evidentiary rulings and other substantial errors detailed in this brief.

B. COURSE OF PROCEEDINGS AND DISPOSITION BELOW

Teston was indicted on eight counts of causing the accident while impaired, two for each death and injury. The indictment alleged impairment by "other substance", Hydrocodone (Counts I-IV) and impairment by other substances, substance unspecified, (Counts V-VIII). (R. E. p. 11-15; R. Vol. I p. 12-16). Prior to trial, Teston filed Motions, *in limine* and to Suppress, challenging, *inter alia*, the blood evidence, proposed expert testimony (R. E. 45-51; R. Vol. I p. 90-96) and the indictment (R. E. 16-21; R. Vol. I p. 18-19). The trial court denied the Motion to Suppress. (R. Vol. IV. pp. 252-255) and allowed the trial to proceed on the eight count Indictment.

On January 18, 2007, after a 3-day trial, Teston was convicted of four (4) counts (Counts I-IV) of driving under the influence of other substances to wit: hydrocodone, her prescribed medication, causing death or injury. The trial court sentenced Teston to 15 years on each count to run "consecutively" for a total of 60 years, with 30 years suspended.

C. STATEMENT OF RELEVANT FACTS

The only two witnesses who testified to the accident itself were Stacey Ross and Nicole Thurman, a passenger in the SUV. Stacey Ross testified that she was driving east on Interstate 10 in the middle lane, of the three lane interstate. (R. Vol. V. pp. 445:11-14). The weather was clear and it was still daylight at approximately 7 pm. Traffic was more heavy than light. (R. Vol. V. p. 444:3). A Buick was traveling next to her in the left lane. (R. Vol. V. p. 446:2) The SUV was behind her in the center lane. (R. Vol. V. p. 446:5). Ross did not directly see the events leading up to and including the accident. She made her observations through the rear view mirrors of her car. (R. Vol. VI. p. 464:5-12). A black Honda approached behind a Buick in the left lane very rapidly. (R. Vol. V. p. 446:21). The black Honda began tailgating the Buick to try to get the Buick to move over. (R. Vol. VI. p. 478:1). The black Honda would drop back a little ways then go up on the Buick's bumper again. (R. Vol. VI. p. 477:14-23). According to Ross, the driver of the black Honda was behaving "aggressively". (R. Vol. V. p. 447:3). The black Honda would approach the Buick in the passing lane, and then drop back. The Buick never moved over. (R. Vol. V. p. 447, R. Vol. VI. p.478-479). While "aggressive", the black Honda was in control the entire time. Ross did not see the driver or the passenger of the black Honda. (R. Vol. V. p. 449:2-4).

Ross decided to speed up to allow passage around the Buick in the center lane. (R. Vol. V. p. 448:1). When she did, the black Honda attempted to change to the center lane, to follow Ross around the Buick. Briefly, the black Honda entered the center lane into the path of the SUV, causing

it to swerve and lose control. (R. Vol. V. p. 448). The Honda immediately returned to the left lane. (R. Vol. V. p. 450:9; R. Vol. V. p. 466:23-26).

Importantly, according to Ross, when the driver of the black Honda moved back into left lane, the black Honda did not lose control. (R. Vol. VI. p. 466:29; 467:15-18). Following the accident, the Honda came to a safe a safe stop, (R. Vol. VI. p. 467:17-28), in the middle of the lane. (R. Vol. VI. p. 468:5-8). Ross brought her vehicle to a stop to the right of the black Honda on the shoulder of I-10. (R. Vol. VI. p. 468:22-24). Ross observed the Honda make a U-turn. (R. Vol. VI. p. 468:22-24; 469:7) and proceed a quarter of a mile, back to the accident scene. (R. Vol. VI. p. 469:16; 473:19) The driver parked perfectly parallel to the shoulder of the road. (R. Vol. VI. p. 472:6; Exhibits D-1 through D-5). During this time, Ross could not see what was going on inside the black Honda. (R. Vol. VI. p. 474:2). Ross did not see Teston driving the black Honda. (R. Vol. VI. p. 474:5). Through her rearview mirror, Ross saw a female get of out of the driver's side of the black Honda. (R. Vol. VI. p. 452:11). She could not identify Teston as that female. (R. Vol. VI. p. 452:22). Ross described the female from the black Honda as hysterical, upset and crying uncontrollably, when she exited the car. (R. Vol. VI. p. 475:12-17).

Nicole Thurman was in the SUV, in the front passenger seat. (R. Vol. VII. p. 609:28). Lindsey Miller was driving. (R. Vol. VII. p. 609:22). They were traveling in the center lane, maintaining a speed probably around 70-75 miles an hour. They saw a car come "flying out of nowhere" and zoomed up right on the tail end of the car in the left lane right ahead of them. Thurman said to the others "that's a cute car". It was a black Honda Accord or a Civic. It had a Florida tag and they were thinking: "Oh, Florida, that's nice. Maybe we should go to Florida next for our next trip". Then all of a sudden like the black Honda comes "flying into their lane". Lindsay swerved, but there was a car to the right, then she tried to just get back in their lane, but she lost

control and they smashed into the concrete barrier in the center of I-10. (R. Vol. VII. p. 612:25-29 to 614:12).

Thurman describe the manner the black Honda moved into their lane of travel as "[i]t was crazy, frantic, reckless. It was spastic the way it just jerked from here to there". (R. Vol. VII. p. 619:7). After the accident and after seeing her "friends", she claimed that Teston came over to her acting "crazy" trying to hug and touch her, kept saying come here, I'm sorry, it's okay, it's going to be okay, it's going to be okay, you're going to be okay, I'm sorry, I'm sorry. Ms Thurman was angry at Teston because she assumed that was who had caused the accident. (R. Vol. VII. p. 620). She further testified that Teston was spilling over her words and some of the words didn't make sense together. (R. Vol. VII. p. 621). Thurman's testimony was consistent with Ross' testimony that the female who exited the black Honda was hysterical, upset and crying uncontrollably. (R. Vol. VI. p. 475).

Teston was arrested for driving with a suspended driver's license (at approx. 8:53 pm[1]) for failure to pay some traffic tickets. After her arrest, Teston asked Officer Brantley to get her medicines out of her car. He then discovered Lorecet (hydrocodone) in her vehicle. He asked her, "Have you taken any of these today?" She answered, "Two". (R. Vol. VI. p. 524:3-4). Incredibly, he did not ask her "when" today she had taken them, i.e., before or after the accident. (R. Vol. VI. p. 539). This is particularly troublesome in light of his initial observations that she was not impaired, was left unsupervised and when he returned to Teston, she was obviously impaired. Later[2] Brantley asked her if she would consent to a blood test. She agreed and allegedly stated that immediately

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[1] (R. Vol. VI. p. 522).

after the accident, she took a Xanax and a Goody's to calm down. (R. Vol. VI. p. 540). Brantley admitted he did not know whether she was adding to the Lorecet she had already told him about. Neither of these alleged statements was recorded[3]. These two unrecorded statements were made approximately 2 hours **after the accident** and while Teston admittedly was under the influence of hydrocodone[4]. At that time, Teston was "mumbling" and "confused" (emphasis added). (R. Vol. VI. p. 538:7-12; 539:11; 544:14).

Krystal Teston consented to a blood test, which showed she had 110 ng/ml of hydrocodone in her blood, three (3) hours (at 10:09 pm) **after the accident** (at 7:09 pm). Less than one (1) hour after the blood test, Brantley and another investigator (who did not testify) took a recorded statement from Teston and specifically asked her "when" she took her prescription medicine. Teston explained that **after the accident** she had taken 1½ Lorecet and then another ½ Lorcet, then a Xanax and a "Goodies PM". (R. Vol. VI. p. 559-566 – proffer; Exhibit 1-Transcript of Recorded Statement of Teston - p. 14 lns 25 to p. 15 lns 1-7). The Court erroneously excluded this recorded statement of the Teston. The Court refused to allow cross-examination of Brantley to impeach the officer about his observations of impairment or his failure to video Teston while they were in the interview room where the recorded statement was taken. (R. Vol. V. pp. 406-415). The State "misled" the jury into believing that Teston had taken two (2) Lorecet "today" before the accident based upon initial poor questioning by a trained DUI Enforcement Officer.

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[2] "When" he asked this was disputed. His report written that night stated he took her to the station and asked her to consent to blood test and that's when the second statement was made, however at trial he claimed he did so at the scene. (R. Vol. VI. p. 541).

[3] Portions of the only recorded statement of Teston were improperly excluded by the Court where Teston explained: after the accident, she took one and a half (Lorcet), and a half a more...and a Tylenol PM or Goodies and half a Xanax. (See R. Vol. VI. p. 559-566 – proffer; Exhibit 1-Transcript of Recorded Statement of Teston - p. 14 lns 25 to p. 15 lns 1-7).

The State was required to prove that **at the time** (7:09 pm) **of the accident**, Teston was operating a motor vehicle while "under the influence of any other substance which has impaired such person's ability to operate a motor vehicle". Section 63-11-30(1) (b) and (5), Mississippi Code of 1972 as amended. The evidence in this case not only failed to prove guilt, but the testimony of the State's trained DUI Enforcement Officer established that Teston was *not* impaired **at the time of the accident**. Teston seeks not just reversal, but also an acquittal in this Court on all counts. *Headrick v. State*, supra.

The trial court erroneously allowed the State's expert toxicologist, Dr. Barbieri, to give opinions of Teston's blood levels and impairment based on inaccurate and materially incomplete hypothetical questions and unreliable scientific data and methods.

Nevertheless, on cross-examination, Barbieri admitted the trained DUI enforcement officer's observations of Teston upon arrival at the scene of the accident (approximately 23 minutes after the accident) indicated no impairment "at that time". (R. Vol. VII. p. 672). He further admitted the same DUI enforcement officer's later observations of Teston, that she had slurred speech, confusion, mumbling, etc. indicated impairment "at that time". (R. Vol. VII. p. 672). He also agreed that it was obvious that something had "obviously" changed between the trained DUI officer's first observations of Teston and the second observations of Teston. (R. Vol. VII. p. 673). Furthermore, Barbieri's calculation of Teston hydrocodone blood level at the time of the accident still placed her below Barbieri's own threshold for impairment.

Although the State was allowed to introduce the results of a blood sample test, the only conclusion supported by the evidence is that Teston took her medications after the accident, which

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[4] See footnote 3 above.

she had in her possession, while she was left unsupervised by a trained DUI Enforcement Officer. *See, Ashley v. State*, 538 So.2d 1181, 1184-85 (Miss. 1989).

Dr. Robert Ryan testified as an expert for Teston. Dr. Ryan, a Board Certified Toxicologist, who has practiced in toxicology and pharmacology since 1982, has been involved in the development of 100-150 new prescription drugs. (R. Vol. VII. p. 692-693). Contrary to Barbieri, Ryan has been involved in hundreds of studies the effect of multiple dosing of drugs. (R. Vol. VII. p. 693, 694). Ryan explained that multiple dosing of a drug affects the pharmacokinetics (how the drug behaves in the body) dramatically. (R. Vol. VII. p. 694) For these reasons, Ryan testified that extrapolating Teston blood level using the single dose study of five men, relied on by Barbieri, was not scientifically valid. (R. Vol. VII. p. 702).

In cases involving multiple doses of hydrocodone, Ryan explained, "the drug doesn't get metabolized or degraded in the body as quickly, because the things that are used to degrade that drug have been depleted." (R. Vol. VII. p. 699-670). Ryan testified that in his opinion based on a reasonable degree of medical certainty, Teston's hydrocodone levels could have resulted from the combination of two 10 mg doses of hydrocodone after the accident. (R. Vol. VII. p. 700).

III. SUMMARY OF THE ARGUMENTS

There was no evidence presented by the State that Teston's ability to operate a motor vehicle was impaired **at the time of the accident** by "hydrocodone" or any other substance. The State's witnesses themselves demonstrated that **at the time of the accident** Teston was not impaired. Mrs. Ross' testified that while the black Honda was being driven "aggressively", it was in complete control, brought itself to a safe stop after the accident, turned around, drove over to and on the shoulder safely back to the accident scene and parked perfectly parallel on the shoulder. A trained DUI enforcement had close contact and substantial interaction with Teston within approximately 23

minutes after the accident. At that point, Teston showed no signs of impairment. He left Teston unsupervised for an undetermined amount of time. He later came back to her and for the first time noticed signs of impairment which signs were not present at his first contact. The State's own expert admitted such was consistent with not being impaired **at the time of the accident** and something changed between the contacts. The lack of evidence in this case is even more compelling than in *Headrick v. State*, 637 So.2d 834 (Miss. 1994) in which the Mississippi Supreme Court reversed and rendered a similar conviction. The trial court should have sustained the Motion for an acquittal (J.N.O.V) or alternatively granted a new trial on the ground that the verdict was against the overwhelming weight of the evidence.

The Court erred in allowing the State's expert to give opinions of Teston's hydrocodone blood level at the time of the accident, based on a single blood sample taken three hours after the accident and to opine that Teston was impaired at the time of the accident[5]. The Court erred in allowing the State's expert to give opinions, over Teston's objections, based upon hypothetical questions that did not encompass and clearly omitted material and undisputed material facts

The State was allowed to mislead the Jury by introducing incomplete statements of Teston. The Court erred in excluding portions of the only recorded statement Teston in which she explained when she took her prescription Lorecet and how many. Rule 106, *Mississippi Rules of Evidence* (MRE), specifically authorizes the introduction of "other...recorded statements" under the rule of completeness and Rule 611(a)(1) permits presenting evidence so as to make the interrogation and presentation effective for the ascertainment of the truth. Even without Rules 106 and 611, MRE,

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[5] Such opinion is legally insufficient where the State's own witness, a trained DUI Enforcement Officer, saw no evidence of impairment within minutes after the accident, left Teston unsupervised, then returned noticing signs of impairment for the first time.

Teston should have been allowed to cross-examine Officer Brantley with the later recorded statement in his presence and in which he participated to impeach on his recollection of the first oral statement and vagueness of his question.

The Court erred in reversing its Order based on a confessed motion, *in limine*, allowing the State to introduce evidence of Teston being arrested on suspended driver's license on the night of the accident. This evidence was neither relevant, nor material to any fact and any relevancy was outweighed by its prejudicial effect. The Court erred in reversing its ruling excluding said evidence after voir dire selection of the jury and opening statements, which prevented Teston from exploring whether any jurors would have been prejudiced by such evidence or addressing such in opening statement to the selected jurors.

The Court erred in not dismissing Counts V to VIII of the Indictment, which charged the Appellant twice for each death or injury for "other substances", requiring the Appellant to defend the additional Counts, even though the State conceded that no substances, other than hydrocodone, were found in Teston's blood. The Court erred in not sustaining Appellant's Motion to Suppress the blood evidence taken three (3) hours after the accident in question in violation of Section 63-11-8, MCA, 1972 and after the Appellant was left unsupervised for an extended period of time

The evidence presented by the State was entirely circumstantial, and the Court erred in not instructing the jury that State burden was to prove guilt beyond a reasonable doubt and to the exclusion of every reasonable hypothesis consistent with innocence.

The Court's consecutive sentence of 15 years for each count for a total of 60 years, with 30 years suspended was grossly disproportionate to the crime and facts of this case.

The State's argument in opening statement that "She [Teston] can't come here now and say, oops, and we're all sorry about the dead kids. That's just not how it works" and more egregiously in rebuttal closing argument: "She [Appellant] can't come here with a straight face and tell you I lied for whatever kind, sweet reason counsel opposite might have you believe", were clearly direct comments on Teston's failure to testify and require reversal.

The Appellants convictions should be reversed and rendered as in *Headrick v. State, infra,* or alternatively, reversed and remanded for new trial.

IV. ARGUMENT

A. THE TRIAL COURT SHOULD HAVE SUSTAINED TESTON'S MOTION FOR A JNOV OR, ALTERNATIVELY THE VERDICT IS SO CONTRARY TO THE OVERWHELMING WEIGHT OF THE EVIDENCE THAT TO ALLOW IT TO STAND WOULD SANCTION AN UNCONSCIONABLE INJUSTICE.

Following these convictions, Teston requested that the trial court grant a JNOV or, alternatively a new trial on the ground that the verdict was against the overwhelming weight of the evidence.

> The standard of review for denial of a directed verdict and a judgment notwithstanding the verdict are identical. *Sperry-New Holland v. Prestage*, 617 So.2d 248, 252 (Miss. 1993). Under that standard, this Court considers all of the evidence in the light most favorable to the State and gives the State the benefit of all favorable inferences that may reasonably be drawn from the evidence. If the facts so considered point so overwhelmingly in favor of the appellant that reasonable men could not have arrived at a guilty verdict, this Court is required to reverse and render. On the other hand, if there is substantial evidence in support of the verdict of such quality and weight that reasonable and fair-minded jurors in the exercise of impartial judgment might have reached different conclusions, this Court is required to affirm. *American Fire Protection, Inc. v. Lewis*, 653 So.2d 1387, 1391 (Miss. 1995)
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> In determining whether a jury verdict is against the overwhelming weight of the evidence, this Court must accept as true the evidence which supports the verdict. A new trial is the proper remedy in those instances where the verdict is so contrary to the overwhelming weight of the evidence that to allow it to stand would sanction an unconscionable injustice. *Baker v. State*, 802 So.2d 77, 81 (Miss. 2001).

Seeling v. State, 844 So.2d 439 (Miss. 2003).

Not only does the evidence in this case fail to support these convictions, it absolves Teston of "guilt". The fact witnesses called by the State established that while the Honda was driving aggressively in an attempt to get the driver of a Buick blocking the passing lane to move over, the Honda's speed was the same as the vehicles surround it, just before and after the accident, Honda was in control and brought itself to a complete and safe stop in its lane of travel. The Honda was able to turn around and return to the scene on the shoulder of the road and park parallel to the road on its shoulder. Teston was the only witness that attempted to render aid, and was by all accounts was understandably hysterical and crying uncontrollably. The evidence supplied by the only police officer to testify, Officer Brantley, irrefutably established that Teston was not impaired when he arrived on the scene approximately 23 minutes following the accident.

1. DUI OFFICER BRANTLEY

Brantley, a trained DUI Enforcement Officer, arrived on the scene at approximately 7:32 pm, 23 minutes after the accident. The first witness he talked to was Krystal Teston. Brantley was 1 to 3 feet from Teston. He asked her several questions and she had no problem responding or answering. He asked her for her driver's license and watched her walk to her car, get her purse out of the car, and retrieve her license, walk back to him, hand him driver's license and he gave her a form to fill out. Teston exhibited no signs of impairment at that time. (R. Vol. VI. pp. 535-536).

This evidence of lack of impairment nearest the time of the accident could not have been stronger. This Court has affirmed exclusion of evidence of a positive test for marijuana and a marijuana cigarette found in a decedent, when the last person who saw the decedent before the accident testified the decedent was not impaired in any form or fashion. *Accu-Fab v. Ladner*, 778

So.2d 766, 771-72 (Miss. 2001). In this case, a trained DUI Enforcement Officer also saw no evidence of impairment in Teston within minutes of the accident.

Brantley then left Teston unsupervised for an undetermined amount of time to continue his investigation. Later, when he returned to Teston, her demeanor was noticeably different because she now had "slurred speech, mumbling, confused, dilated and glassy eyes". (R. Vol. VI. pp. 538:7-12; 539:11; 544:14). This was clearly different from the first (7:32 pm) time he talked to her. (R. Vol. VI. at p. 538:8-12). He still did not arrest her for driving under the influence at that time, despite her earlier admission that she had been driving her vehicle.[6] Earlier (7:32 pm) he had seen nothing to indicate Teston was impaired. (R. Vol. VI. pp. 544-545). Something had noticeably changed between the first time he saw her and the second. (R. Vol. VI. pp. 538:7-12; 539:11; 544:14).

Eventually, Teston was arrested for driving with a suspended driver's license (8:53 pm) She asked Officer Brantley to get her medicines out of her car. He then discovered the Lorecet in her vehicle. He then asked her: Have you taken any of these today? She allegedly answered, "Two". (R. Vol. VI. p. 524:3-4). He did not ask her "when" today she had taken them and admitted that "today" included after the accident. (R. Vol. VI. p. 539). Later[7] he asked her if she would consent to a blood test. She agreed and allegedly stated that immediately after the accident, she took half a Xanax and a Goody's to calm down. Neither of these alleged statements was recorded[8]. These unrecorded oral statements were also made while Teston admittedly was under the influence of

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[6] Of course, in the meantime he had not observed her driving her vehicle while impaired and she was not impaired when he first observed her and she admitted driving "her vehicle"

[7] "When" exactly he asked was disputed. His report done the night of the accident stated he took her to the station and asked her to consent, however, at trial he claimed he did so at the scene of the accident.

[8] Portions of the only recorded statement of Teston were improperly excluded by the Court where Teston explained: after the accident, she took one and a half (Lorcet), and a half a more...and a Tylenol PM or Goodies and half a Xanax. (R. Vol. VI. p. 559-566 – proffer; Exhibit 1-Transcript of Recorded Statement of Teston - p. 14 lns 25 to p. 15 lns 1-7)

hydrocodone and by Brantley's own admission had: "slurred speech, mumbling, confused, dilated and glassy eyes" (emphasis added). Other officers[9] (See Exhibit D-1 through 5; R. Vol. VI. p. 550) had contact with Teston after the accident and yet Brantley was the only officer called to testify for the State. Krystal Teston consented to a blood test, which showed she had 110 ng/ml of hydrocodone in her blood, three (3) hours (at 10:09 pm) after this accident (at 7:09 pm).

2. STACEY ROSS

Stacey Ross testified that she was traveling east on Interstate 10 in the middle lane, of the three lane interstate. (R. Vol. V. p. 445:11; 445:14). The weather was clear and it was still daylight at approximately 7 pm. Traffic was more heavy than light. (R. Vol. V. p. 444:3). A Buick was traveling next to her in the left lane. (R. Vol. V. p. 446:2) An SUV was behind her in the center lane. (R. Vol. V. p. 446:5). Mrs. Ross did not directly see the events leading up to and including the accident but actually made her observations through her the rear view mirrors of her car. (R. Vol. VI. p. 464:5-12). A black Honda approached behind a Buick in the left lane very rapidly. (R. Vol. V. p. 446:21). The black Honda began tailgating the Buick to trying to get the driver of the Buick to move over. (R. Vol. VI. p. 478:1). The black Honda would go back a little ways then go up on the Buick's bumper again. (R. Vol. VI. p. 477:14-23). The black Honda was behaving "aggressively". (R. Vol. V. p. 447:3). This lasted several minutes. The black Honda would go back and forth and the Buick never moved over. (R. Vol. V. p. 447-479). While aggressive, the black Honda was in control the entire time. The black Honda did all of this in its lane and didn't venture out of its lane. (R. Vol. VI. p. 479:3-18). Mrs. Ross did not see the driver or the passenger of the black Honda. (R. Vol. V. p. 449:2; 449:4). Mrs. Ross decided to speed up. (R. Vol. V. p. 448:1). When she did, the

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[9] Officer Cvitanovich, also a trained DUI officer (R. Vol. VI. p. 548), was seen in photographs talking with Teston. (R. Vol. VI. p. 550).

black Honda attempted to change behind her to the center lane, into the path of the SUV also behind her. When the driver of the Honda realized that there was someone in the center lane, it immediately returned to the left lane. (R. Vol. V. p. 450:9; R. Vol. VI. p. 466:23-26). When it moved back into its lane, the black Honda did not run off the road or hit the barrier. (R. Vol. VI. pp. 466:29; 467:15-18). The Honda brought itself to a safe stop. (R. Vol. VI. p. 467:17-28). The Honda stopped generally in the middle of the lane. (R. Vol. VI. p. 468:5-8). Mrs. Ross was to the right of the black Honda on the shoulder. (R. Vol. VI. p. 468:22. 468:24). Ross saw the Honda turn around and make a U-turn. (R. Vol. VI. pp. 468:22-24; 469:7). The black Honda drove, a quarter of a mile, back to the accident scene and parked on the shoulder of the road. (R. Vol. VI. pp. 469:16; 473:19). The black Honda parked parallel to the shoulder of the road. (R. Vol. VI. p. 472:6; Exhibit D-1 through D-5). During this time, Ross could not see what was going on inside the black Honda. (R. Vol. VI. p. 474:2). Ross did not see Teston driving the black Honda. (R. Vol. VI. p. 474:5). Through her rearview mirrors, Ross saw a female get of out of the driver's side of the black Honda. (R. Vol. VI. p. 452:11). She could not identify Teston as that female. (R. Vol. VI. p. 452:22). Ross described the female as hysterical, upset and crying uncontrollably. (R. Vol. VI. p. 475:12-17).

3. NICOLE THURMAN, SUV PASSENGER

Nicole Thurman was in the SUV, located in the front passenger seat. (R. Vol. VII. p. 609:28). Lindsey Miller was driving. (R. Vol. VII. p. 609:22). They were traveling in the center lane, maintaining a speed probably around 70-75 miles an hour. All of a sudden, they saw a car come flying out of nowhere and zoomed up right on the tail end of the car in the left lane right ahead of them. Thurman said to the others "that's a cute car". It was a black Honda Accord or a Civic. It had a Florida tag and they were thinking: "oh, Florida, that's nice. Maybe we should go to Florida next for our next trip". Then all of a sudden, the black Honda comes flying into their lane. Lindsay

swerved, but there was a car to the right, then she tried to just get back in their lane, but she lost control and they smashed into the concrete barrier in the center of I-10. (R. Vol. VII. pp. 612:25-29 to 614:12). Thurman describe the manner the black Honda was being driven as "It was crazy, frantic, reckless. It was spastic the way it just jerked from here to there". (R. Vol. VII. p. 619:7). Thurman testified that after the accident:

> a girl comes like crazy up to me and just like is screaming and like saying all this stuff, and like some of made it sense, some of it didn't. She was just saying, oh, baby, baby come here....came straight over to me, looked a mess, had a big white tee shirt on really baggy, short dark hair, I want to say black pants, very thin, looked sickly. Tried to hug me. Tried to touch me. Kept on saying, oh, baby, come here, I'm sorry, it's okay, it's going to be okay, it's going to be okay, you're going to be okay, I'm sorry, I'm sorry, come here. And I was angry, and I assumed that was who had hit us or caused the accident....Because no one was else was acting that way.
>
> (R. Vol. VII. p. 619:28).
>
> She was saying things over and over and over again and spilling over her words, and, you know, some of the words didn't make sense together.
>
> (R. Vol. VII. p. 621:21).

Ross also confirmed the female that exited the black Honda was "upset" and "hysterical". (R. Vol. VII. p. 474). The State's expert admitted that Teston's actions as described by Thurman were "absolutely" consistent with simply having witnessed a horrific accident such as in this case and being upset. (R. Vol. VII. p. 673).

4. THE STATE'S TOXICOLOGIST, BARBIERI

The State's expert, Barbieri, testified on cross-examination:

> Q. Assuming that a trained police officer, we started talking about this and I didn't get to it, trained in DUI enforcement approached an individual, had a conversation one to two feet away from them, did not notice any slurred speech, did not notice any sleepiness, did not notice any lethargicness, did not notice any type of confusion, asked her questions and got responses, asked her to walk to her vehicle and get her driver's license and got out, and noticed no evidence of impairment, do you agree that that would be indication that that person was not impaired?

A. I would agree that would be indications of not impairment at that time.

Q. And if that person, that police officer, that trained police officer comes back to that individual some 40 to 45 minutes later, maybe an hour, and at that time he notices slurred speech, confusion, mumbling, things of that nature that indicate -- do you agree that that would indicate impairment at that time?

A. It sounds that would indicate impairment at that time.

Q. Would you also agree that it indicates that maybe something has changed between the first time that he talked to her, talked to somebody, that individual, until the second time he talked with her?

A. I think it's obvious that something has changed.

(R. Vol. VII. pp. 672-673).

Furthermore, even Barbieri's attempted retrograde extrapolation of Teston's hydrocodone blood levels at the time of the accident, based on the blood sample taken three hours later, placed Teston's blood levels below that level established by Barbieri as the threshold for impairment. (See R. Vol. IV p. 175:7-11).

The evidence in this case, taken in the light most favorable to the State, requires this Court to reverse and render the verdicts and convictions of Krystal Marie Teston. The State did not and could not establish the element of Krystal Marie Teston impairment **at the time of the accident** from any "other substance". The State had to prove that Teston took hydrocodone before the accident and was impaired **at the time of the accident.** The State failed to do so. *Headrick v. State*, 637 So.2d 834 (Miss. 1994); *Wilkerson v. State*, 731 So.2d 1173 (Miss. 1998).

In fact, the State's evidence, including the testimony of a trained DUI enforcement officer established that Teston was not impaired at the time of the accident. While both Ross and Thurman establish that the driver of the a black Honda drove in a perhaps fast and aggressively manner, both establish that the driver maintained control of the vehicle. The State's own expert conceded based upon the evidence Teston was not impaired at the time Brantley first encountered her, was impaired

when he returned to her and something obviously occurred when she was left unsupervised for a period of time. This evidence was undisputed.

The State bears the burden of proving a Defendant's guilt by overcoming the presumption of innocence. This burden is upon the State to prove the defendant's guilt through evidence that satisfies each element of the charged crime. *McVeay v. State*, 355 So.2d 1389 (Miss. 1978).. The burden of proving each element of an offense always remains with the prosecution and never shifts from the State to the Defendant. *Heidel v. State*, 587 So.2d 835 (Miss. 1991); *Brown v. State*, 556 So.2d 338 (Miss. 1990). Operation of a vehicle while under the influence of any other substance which has impaired such person's ability to operate a motor vehicle **at the time of the accident**, as prohibited by Miss. Code Ann. §63-11-30(1)(b) (2004), is the essential element which at trial the State has the burden of proving beyond a reasonable doubt. There was absolutely no evidence advanced at the trial from which the jury could have reasonably concluded that Teston was legally impaired **at the time of the accident**, therefore, the State failed to prove the element of impairment **at the time of the accident**. There was no admission by Teston and there was no conflicting evidence regarding the impairment of Teston at the time of, or prior to, the accident causing these deaths and injuries. The only evidence closest to the accident showed no impairment by a trained DUI Enforcement officer. There clearly was insufficient evidence presented at trial upon which the jury could have found the existence of the threshold element of impairment **at the time of the accident**. "Before a conviction of any crime may stand, there must be in the record evidence to establish each element of the crime." *Fisher v. State*, 481 So.2d 203, 211 (Miss. 1985). The record in this case does not contain sufficient evidence from which a rational juror could have found the existence of the element of "impairment" of Teston by other substances **at the time of the accident** beyond a reasonable doubt, therefore the jury's verdicts were against the overwhelming weight of the

evidence and the judgment of the Trial Court and the imposition of punishment must be reversed and this Court should rendered verdicts of acquittal. *Headrick v. State*, supra.

B. THE TRIAL COURT ERRED IN ALLOWING THE STATE'S EXPERT, BARBIERI, TO GIVE HIS OPINION OF THE LEVELS OF HYDROCODONE IN TESTON'S BLOODSTREAM AT THE TIME OF THE ACCIDENT AND THAT SHE WAS IMPAIRED BY HYDROCODONE AT THE TIME OF THE ACCIDENT

If these convictions rest at all on any testimony, they rest on the testimony of the expert Barbieri, a toxicologist called by the State. Over Teston's objections, both before[10] and during trial, the Court allowed Barbieri to extrapolate from the blood concentrations of hydrocodone in Teston's blood three hours after the accident to arrive at a blood level **at the time of the accident** and to opine that Teston was impaired by hydrocodone **at the time of the accident.** For the reasons that follow, the court committed error by allowing this testimony.

Because there was no evidence that Teston was impaired **at the time of the accident**, and, in fact, evidence by the State witnesses to the contrary, there is no doubt that Barbieri's testimony heavily influenced Teston's jury.

> Juries are often in awe of expert witnesses because, when the expert witness is qualified by the court, they hear impressive lists of honors, education and experience. An expert witness has more experience and knowledge in a certain area than the average person. See M.R.E. 702. Therefore, juries usually place greater weight on the testimony of an expert witness than that of a lay witness. *See generally Simmons v. State*, 722 So.2d 666, 673 (Miss. 1998); *see also United States v. Benson*, 941 F.2d 598, 604 (7th Cir. 1999) (an expert's "stamp of approval" on a particular witness's testimony [or theory of the case] may unduly influence the jury).
>
> *Edmonds v. State*, 955 So.2d 787, 792 (Miss. 2007).

Particular care should be undertaken by the Courts to insure that, in a case brimming with emotions and sympathies for the tragic loss of three beautiful persons and the injury to another, all

graphically described for the jury, the verdict is not the product of speculation, conjecture and sympathy. This includes shielding the jury from being unduly influenced by "opinions" of an "expert" on the ultimate question of fact that are not scientifically reliable and are little more than speculation by an expert.[11]

Rule 702 of the *Mississippi Rules of Evidence* (Amended 2003) provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

This Court has adopted the federal standard laid out by the United States Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S. Ct. 2786, 125 L. Ed. 2d 469 (1993), and it progeny. *Mississippi Transportation Comm'n v. McLemore*, 863 So.2d 31, 36 (Miss. 2003).

1. BARBIERI PROVIDED AN OPINION THAT TESTON WAS IMPAIRED AT THE TIME OF THE ACCIDENT BASED ON AN INACCURATE AND INCOMPLETE HYPOTHETICAL

An expert may give an opinion based on a hypothetical question.[12] It has long been the law of this State that the hypothetical question posed to an expert "must be so framed as to fairly reflect facts either admitted or proved, otherwise the testimony drawn out by them can have no real value,

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[10] Teston filed a pre-trial motion challenging the blood evidence and expert opinions under M.R.E. 401, et seq. and 702, including a *Daubert* challenge, which was heard on June 9, 2006. R. Vol. III 124-150 to R, Vol. IV. 151-187).

[11] "The party offering the testimony must show that the expert based his opinion not on opinions or speculation, but rather on scientific methods and procedures." *Mississippi Transportation Comm'n v. McLemore*, 863 So.2d 31, 36 (Miss. 2003).

[12] Barbieri was not present for any testimony. His opinions are based entirely on the hypothetical question supplied by the State.

but may do much harm in the decision of the case". *Cates v. State*, 171 Miss. 106, 157 So. 95 (1934). While this rule of law predates MRE 702, it is embodied in that part of the rule that requires that the opinion be based on sufficient facts or data and on our court's requirement that it be relevant. *Jones v. State*, 918 So.2d 1220, 1226-1228 (Miss. 2005).

While the State may provide facts in a hypothetical question consistent with its theory of the case, *Magnolia Hospital v. Moore*, 320 So.2d 793, 798 (Miss. 1975), it cannot elicit an opinion based on assumed facts unsupported by the evidence. *Washington v. Greenville Manufacturing and Machine Works*, 223 So.2d 642, 644 (Miss. 1969). Furthermore, the State must include in its hypothetical all undisputed facts that are material to the question posed. *Magnolia Hospital v. Moore,* supra at p. 799.; *See also, Strickland v. M.H. McMath Gin, Inc.*, 457 So.2d 925, 928 (Miss. 1984).

A). THE HYPOTHETICAL

The State posed the following hypothetical to Barbieri:

Q. Again, Dr. Barbieri, I'm going to pose a hypothetical to you based on facts that are in the evidence. Okay?

A. Yes.

Q. First, we must assume the evidence is that the wreck occurred approximately at seven o'clock p.m.

A. Yes.

Q. Also, we know from the evidence that the blood was drawn approximately three hours later. And we know that it was 110 nanograms at that time, correct?

A. Yes.

Q. If we add to that hypothetical that the defendant at the time or immediately prior to the wreck was driving very erratically; that immediately after the wreck she walked across oncoming traffic; she had difficulty immediately, immediate at the scene acting properly and putting words together; that some 50, 55 minutes later at the scene when an officer had an opportunity to have an extended visit with the defendant, she still had slurred

speech, she was still disoriented, she was still confused, had difficulty speaking, had difficulty putting words together; based on that hypothetical, in your opinion, was the defendant impaired at the time of the wreck?

(R. Vol. VII. pp. 648-649).

Over Teston's objections[13], Barbieri was allowed to give the following opinion:

A. All the signs and symptoms that you described are consistent with a drug such as hydrocodone. And based upon the fact that a level of 110 was found three hours after, it would be my opinion that she was impaired with hydrocodone at that time.

In a follow-up question, the State added to this hypothetical the assumption that Teston took two (2) pills after the accident. Barbieri opined that her blood level would be 100 ng/ml **at the time of the accident** and that she would be impaired. (R. Vol. VII. pp. 675-76).

B). THE OMISSION OF MATERIAL UNDISPUTED FACTS

The hypothetical posed to Barbieri misstated or omitted undisputed, material facts, all of which came from the State's witnesses. Most compelling are the omissions, which include:

(1) that just prior to the accident, the black Honda had been driving aggressively, trying to get a Buick, ahead of it, in the passing lane to allow it to pass;

(2) that the black Honda maintained control of itself in the left lane of travel, never leaving its lane of travel for a period of minutes before the accident. It moved up and back several times trying to get the Buick to allow it to pass;

(3) that when the witness, Ross, who was traveling in the center lane and had observed Black Honda driving for several minutes; sped up the Black Honda attempted to move into the center lane to pass;

(4) when black Honda realized it was too close to the SUV, traveling behind Ross, it then corrected back to the left lane, maintaining control of the vehicle. The black Honda did not hit the concrete barrier or cross the line on the left side of the road;

(5) the black Honda came to a controlled and safe stop in the center lane of travel, within a quarter mile;

(6) that black Honda then turned around and traveled on the shoulder of the road to the

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[13] The court held a hearing outside the presence of the jury and overruled Teston's objections to the hypothetical question on the grounds that it did not encompass all of the facts. (R. Vol. VII. pp. 644-648).

scene of the accident, parking parallel to the roadway;

(7) that Teston crossed the roadway to assist Ms. Thurman, that she was hysterical, crying, repeating herself and spilling her words; (not slurring her speech) [on cross examination the State's expert agreed that this was also consistent with just being upset R. Vol. VII. p. 673];

(8) that Teston remained at the scene by her vehicle after help arrived and was approached by Officer Brantley, a trained DUI/drug enforcement officer at approximately 7:32 pm, who had an opportunity to observe Teston closely. During this encounter, Brantley had a conversation with Teston, determined that she was a witness to the accident; asked her for her driver's license, observed her walk to and from her car to retrieve her license, handed her driver's license to him and gave her a form to fill out. In this encounter, Teston did not exhibit any signs of impairment, including slurred speech, sleepiness, mumbling, confusion or sedation;

(9) that Brantley left her unsupervised for a period of time and when he returned to Teston and this time readily observed that her speech was slurred, she was mumbling, seemed confused, had dilated and glassy eyes and in his opinion, impaired. He testified this was different from the first time he talked to her;

All of these undisputed facts were material to the opinion solicited from Barbieri. In fact, Barbieri established the materiality of many of these facts on cross-examination, with Barbieri admitted that many were inconsistent with impairment Importantly, Barbieri admitted that assuming the undisputed facts established by Brantley were true, Teston was **not impaired** just following the accident, but was impaired by the time of Brantley's second encounter. Barbieri testified that obviously that something had changed in the interim, i.e., she had taken her medication after the accident. (R. Vol. VII. pp. 672-73).

Barbieri also admitted on cross-examination that hydrocodone causes pinpoint pupils, an effect that is not absent even in people who have a tolerance to the drug. The fact that Teston's' pupils were not yet pinpointed at the time of Brantley's second encounter with Teston confirms that she had only recently ingested the medicine. (R. Vol. IV. p. 659:8-14).

C). THE MISREPRESENTATION OF UNDISPUTED FACTS

Furthermore, some of the facts stated in the hypothetical are false or misleading. No witness describes Teston and driving "very erratically"[14]. Other than when she attempted to change lanes to follow Ross and maneuver around the Buick blocking the left lane, Teston maintained a steady course in her lane of travel. After noticing the SUV, she was able to recover and maintain complete control of her vehicle.[15]

The State misled Barbieri by stating that after the accident Teston had "difficulty immediately, immediate at the scene acting properly and putting words together; that some 50, 55 minutes later at the scene when an officer had an opportunity to have an extended visit with the defendant, she still had slurred speech, she was still disoriented, she was still confused, had difficulty speaking, had difficulty putting words together." There is no reference point for what "acting properly" means in this context. Teston was the only one of the State's witnesses that actually tried to help the victims. While Teston was hysterical and crying and "spilling over her words", it is false to suggest to the witness that she was immediately after the accident, confused, disoriented, having difficulty speaking or putting her words together, or exhibiting slurred speech. Her conduct before the accident, immediately following and Brantley trained observations within minutes of the accident belie this factual assumption.

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[14] It is clear from the record that "erratic driving" scenario was a creature of the State. R. Vol. III p. 138-139. The State had no testimony to support this characterization. At the conclusion of Ross's testimony, Ross having described only aggressive, but purposeful behavior by Teston, in an obviously canned Q&A, the ADA asked Ms. Ross, Q. If you were asked to describe the black Honda's driving, what word will you use? A: Aggressive, erratic. (R. Vol. VI. pp. 459-460). The court should look to the actual description of Teston's driving by Ross and Thurman, not a canned answer meant to satisfy only an expert's requirement.

[15] Cambridge Online Dictionary defines "erratic" as "irregular, uncertain or without organization in movement or behavior". Merriam Webster's Dictionary defines "erratic" as "having no fixed course: wandering <an *erratic* comet>". Neither of these two definitions describe what any witness described in the testimony.

D). ADMISSION OF THE OPINION BASED ON INACCURATE ASSUMPTION CAUSED SUBSTANTIAL PREJUDICE

The failure to include the undisputed material facts and the inclusion of misleading facts rendered Barbieri's opinions based on the hypothetical irrelevant under M.R.E. 401, highly prejudicial under M.R.E. 403 and not based on sufficient facts or data as required by M.R.E. 702. The error caused substantial prejudice to Teston requiring reversal.

2. BARBIERI'S OPINIONS OF THE HYDROCODONE BLOOD LEVELS THAT WOULD BE PRESENT IN TESTON'S BLOOD STREAM AT THE TIME OF THE ACCIDENT, BASED ON THE HYDROCODONE BLOOD LEVELS SHOWN TO EXIST THREE HOURS LATER, AND AT THAT LEVEL TESTON WAS IMPAIRED SHOULD NOT HAVE BEEN ADMITTED UNDER M.R.E. 702.

In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 589, 593-94, 597, 113 S.Ct. 2786, 125 L. Ed. 2d 469 (1993), the Supreme Court charged trial judges with a gatekeeper function to exclude unreliable expert testimony. The trial court should ensure that the evidence is reliable and relevant. The Supreme Court articulated five factors that could be used in making a reliability determination, while emphasizing that the analysis should be flexible: (1) whether the theory can be and has been tested; (2) whether the theory has been subjected to peer review and publication; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling its operation; and (5) whether it has achieved general acceptance in the relevant community. *Id.*. at 593-94.

In *Kumho Tire Co. Ltd. v. Carmichael*, 526 U.S. 137, 119 S.Ct. 1167, 1171, 143 L. Ed. 2d 238 (1991), the Court held that neither *Daubert* nor the federal rules of evidence requires a court to admit opinion evidence that is connected to existing data only by the ipse dixit of the expert." Kumho Tire, 526 U.S. at 157 (finding no abuse of discretion in rejecting opinion of expert) (internal citation and quotation marks omitted) (emphasis added). *Daubert* and *Kumho Tire Co.*, as well as

MRE 702 and this Court's decisions, require that expert opinion evidence be connected to existing data by something more than a chain of dubious inferences that amount to an expert's assertion that "it is so because I say it is so."

While the list of factors set out in *Daubert* are not all-inclusive, they do provide a framework for a court performing this important gate keeping function. *Edmonds v. State*, 955 So.2d 787, 791 (Miss. 2007). The party offering the expert's testimony must show that the expert has based his testimony on the methods and procedures of science, not merely his subjective beliefs or unsupported speculation. *Miss. Transp. Comm'n v. McLemore*, 863 So.2d 31, 36 (Miss. 2003).

A) THERE IS NO CREDIBLE, SCIENTIFIC BASIS FOR RETROGRADE EXTRAPOLATION OF HYDROCODONE BLOOD LEVELS TO A PERIOD THREE HOURS BEFORE THE BLOOD SAMPLE WAS DRAWN

While retrograde extrapolation of blood alcohol (BAC) levels by experts has been allowed[16], it has not been without criticism.[17] More importantly, retrograde extrapolation of BAC levels, where it is appropriate, is based on numerous studies over many years by the leading scientists in the field.[18] However, the State's own expert admitted there are no scientific studies supporting retrograde extrapolation of hydrocodone[19] and not a single reported decision approving or even discussing it has been found.

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[16] *Smith v. State*, 942 So. 2d 308 (Miss. Ct. App. 2006)(introduction of BAC taken four hours after the accident and extrapolation testimony allowed, unchallenged, where defendant was closely observed and did not ingest any alcohol in the interim).

[17] *Mata v. State*, 46 S.W.3d 902, 904 (Tex. Crim. App. 2001)(disallowing retrograde extrapolation testimony in BAC case, where expert did not know the relevant factors regarding the defendant, such as weight, time of last drink, etc.). *Mata* contains an exhaustive examination of the science and reliability of retrograde extrapolation in alcohol cases; see also *Smith v. State*, 942 So. 2d 308 (Miss. Ct. App. 2006).

[18] *Id.*.

[19] Barbieri, *Daubert* Hearing, (R. Vol. III. p. 126)

I. THE BARNHART SINGLE-DOSE STUDY OF FIVE MEN

Barbieri based his opinion almost exclusively on one published report from 1977 that does not even deal with the subject of retrograde extrapolation of hydrocodone serum levels, referred to as the Barnhart report in the testimony.[20] Interestingly, the authors reported, "little is known about pharmacokinetic or metabolic characteristics of this drug in spite of its widespread usage".[21] The authors conducted the test on dogs and five male human subjects of various weights.

Barnhart was a single 10-mg oral dose study and consisted of measuring the blood levels on the five human subjects at different intervals. The reported results of the test showed that in these five subjects, this single dose of hydrocodone produced a peak levels concentrations ranging from 18 to 32 ng/ml[22] with an average time to reach peak levels of 1.3 +/- .03 hours.[23]

The Barnhart report does not represent a scientifically reliable method or basis for retrograde extrapolation of hydrocodone levels based on a single sample. The study was not conducted for that purpose. Excluding the dogs, it was based on only five people, all males, of various weights. More importantly, it does not even begin to address such issues as gender, weight, food consumption, tolerance and particularly multiple dosing, which was indisputably involved in this case.

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[20] J. W. Barnhart and W. J. Caldwell, Gas Chromatographic of Hydrocodone in Serum, 30 Journal of Chromatography 243-249 (1977) Appendix A.

[21] *Id.* at 243.

[22] Barbieri used inconsistent peak levels in his reports and his testimony. 32 ng/ml, (R. Vol. III. P. 136, R. Vol. IV. p. 165, R. Vol. VII. p. 661); 30 ng/ml (R. Vol. IV. p.157); 20 ng/ml (R. Vol. III. p.127); 24 ng/ml (R. Vol. III. p. 128); 25 ng/ml (R. Vol. VII. p. 642).

[23] *Id.*. at 249.

II. THE EFFECTS OF MULTIPLE DOSING: BARBIERI CONCEDED INSUFFICIENT DATA

Barbieri falsely applied the data from the Barnhart study to reach his conclusions. Barbieri assumed that the blood levels reached with a single dose of hydrocodone could be simply multiplied by the number of doses taken or assumed to reach a blood level as a starting point for his extrapolation testimony. Barbieri failed to consider the effects of multiple or sequential dosing on the blood levels. Barbieri incorrectly assumed, without any scientific support, that the effects of multiple dosing would be linear. (R. Vol. IV. pp. 171-172; R. Vol. VII p. 702). Importantly, Barbieri conceded on cross-examination that he could not give an opinion on the blood levels if Teston took 20 mg of Lorecet (two pills) because there were no studies or data on a 20 mg dosage. (R. Vol. VII p. 670:-71)

Dr. Robert Ryan, a Board Certified Toxicologist, who has practiced in toxicology and pharmacology since 1982, has been involved in the development of 100-150 new prescription drugs. (R. Vol. VII. pp. 692-693) Ryan has been involved in hundreds of studies the effect of multiple dosing of drugs. (R. Vol. VII. pp. 693, 694). Ryan explained that multiple dosing of a drug affects the pharmacokinetics (how the drug behaves in the body) dramatically. (R. Vol. VII p. 694) For these reasons, Ryan testified that extrapolating Teston blood level using the single dose study of five men (the Barnhart study) was not scientifically valid. (R. Vol. VII. p. 702)

In cases involving multiple doses of hydrocodone, Ryan explained, "the drug doesn't get metabolized or degraded in the body as quickly, because the things that are used to degrade that drug have been depleted." (R. Vol. VII. pp. 669-670). Citing the Knoll report[24] as an example, one subject measured a peak level of hydrocodone of 27 based on a 10 mg dose. When that same subject

was given a 15 mg dose, the peak level was measured at 68, more than double the levels, with an increase of only ½ in dosage. (R. Vol. VII. pp. 699-670).[25]

Ryan testified that in his opinion based on a reasonable degree of medical certainty, Teston's hydrocodone levels could have resulted from the combination of two 10 mg doses of hydrocodone after the accident. (R. Vol. VII. pp. 700).

Barbieri admitted that the Barnhart study might not hold true for females (R. Vol. IV. p. 152, R. Vol. VII. p. 661). Further, he testified that one would have to account for the weight of individual in determining blood levels (R. Vol. IV. p. 152, R. Vol. VII. p. 661), which he did not do in this case. (R. Vol. IV. p. 153). Barbieri admitted the Barnhart report, on which he relied, did not consider the effects of the sequence of dosage or multiple dosing on the peak concentration levels, all of which he admitted would have an effect. (R. Vol. VII. p. 670).

In this case, there is no evidence that Barbieri's opinions were either "based upon sufficient facts or data" or "the product of reliable principles and methods". *Miss. R. Evid.* 702; Giannaris *v. Giannaris*, 2007 Miss. LEXIS 399, 21-22 (Miss. 2007). The State failed to establish the relevance of the Barnhart data to support their expert's conclusions.

B) THERE IS NO CREDIBLE, SCIENTIFIC BASIS FOR CONCLUDING THAT TESTON WAS IMPAIRED BY HYDROCODONE AT THE TIME OF THE ACCIDENT

In the *Daubert* hearing, Barbieri testified that he uses 100 ng/ml as the level at which someone is impaired. Barbieri cited only antidotal evidence to support this conclusion:

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[24] Knoll Pharmaceuticals, Vicoprofen Tablets, Clinical Pharmacology, Rev. NDA, submission date April 26, 1996, Appendix B.

[25] Barbieri was aware of the *Knoll* study, Barbieri could not say whether the effects shown in that study would apply to a total dosage of 20 mg because there are *no studies or data* addressing that scenario. (R. Vol. VII. pp. 670-71)

> There's a statement by a toxicologist that I typically use where he reported on two driving cases where an individual had in their blood, this again was whole blood, 130 nanograms and 190 nanograms of hydrocodone and they were judged to be erratic drivers at that point. *so typically I use the value of somewhere around 100 nanograms for impairment* as we' re defining it today for hydrocodone induced effects. But that's just a ballpark number of course. (R. Vol. IV. pp. 174-75)

An expert opinion supported only by antidotal reports, which on their face are distinguishable from the facts at hand, are wholly insufficient to support admissibility of Barbieri's opinion. *See, Rec. Devs. of Phoenix v. City of Phoenix*, 220 F. Supp. 2d 1054, 1060-1061 (D. Ariz. 2002); *Skipper v. Sears Roebuck & Co.*, 1996 U.S. Dist. LEXIS 20726 (D. La. 1996); *Goodyear Tire & Rubber Co. v. Thompson*, 11 S.W.3d 575, 582 (Ky. 2000).

Barbieri testified that the test conducted on Teston's blood had an error rate of 10% (R. Vol. III. p. 150), which the State stipulated to at trial. (R. Vol. VII. p. 691) Furthermore, as body weight and metabolism has an effect on concentrations, tolerance of a particular subject would be a factor in determining what level of hydrocodone would produce impairment.

I. BARBIERI'S IMPAIRMENT THRESHOLD IS NOTHING MORE THAN THE *IPSE DIXIT* OF THE EXPERT

An expert's opinion must be connected to existing data by something more than a chain of dubious inferences that amount to an expert's assertion that "it is so because I say it is so". Barbieri cited no scientific studies, reports or other data to support his opinion that hydrocodone induces impairment at the level of 100 ng/ml. His sole basis was two antidotal cases involving erratic driving at much higher levels. Barbieri simply picked a number out of thin air without any scientific basis. See e.g., *Smith v. State*, 942 So.2d 308 (Miss. Ct. App. 2006) [retrograde extrapolation of alcohol "based upon world's leading **alcohol** blood testing scientists consider the method reliable and widely use the method to estimate BAC"].

Courts have allowed experts to give opinions of impairment based on blood levels in cases involving alcohol[26]or some drugs.[27] However, in those instances the scientific studies and data supporting both impairment and extrapolation were voluminous.

> Furthermore, unlike alcohol, where studies have been able to establish a direct measurement and correlation between the amount of alcohol in the system and the extent of impairment, with drugs there have been insufficient studies (and it may not be possible to do sufficient studies) to establish a comparable correlation between drug levels and impairment.

United States v. Everett, 972 F. Supp. 1313, 1317-1318 (D. Nev. 1997).

In this case, involving a prescription medication, Barbieri could not support his opinions with any reliable and relevant scientific data. Barbieri's opinions amount to nothing more than speculation and conjecture and should not have been allowed.

II. THE MARGIN OF ERROR PLACED BARBIERI'S CALCULATION BELOW HIS THRESHOLD LEVEL FOR IMPAIRMENT

Asked to assume that Teston took two 10 mg hydrocodone doses after the accident, Barbieri, using his faulty extrapolation method, opined that Teston's blood level would be 100 ng/ml **at the time of the accident**. Barbieri arrived at this number by using 25 ng/ml per dose (as opposed to the 32 g/ml he testified to at the Daubert hearing) and subtracting 50 from 110 ng/ml, leaving 60 ng/ml, which he opined would place her at 100 ng/ml **at the time of the accident**.

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[26] The cases and studies involving alcohol are too voluminous to cite. *See, Mata v. State*, 46 S.W.3d 902; 2001 Tex. Crim. App. 2001); *Smith v. State*, 942 So. 2d 308 (Miss. Ct. App. 2006)

[27] While not as extensive as alcohol there is abundant scientific data concerning the impairment from marijuana. *See, e.g., Bocanegra v. Vicmar Servs.*, 320 F.3d 581, 589 (5th Cir. 2003) (extensive studies cited regarding impairment from marijuana); *Mitchell v. Mt. Hood Meadows Or., Ltd. P'ship*, 195 Ore. App. 431, 442-443 (Or. Ct. App. 2004) (expert testified that the correlation between impairment and cannabinoid levels in urine samples has been the subject of published studies and those studies have been subject to peer review).

Barbieri's calculations failed to account for the 10% margin of error in the test results, as he testified in the *Daubert* hearing, a number the State stipulated to at trial. (R. Vol. VII. p. 691) This correction would place Teston's blood levels below 100 ng/ml, his threshold for impairment.

III. "THERE'S JUST ONE CAVEAT...THE DOSAGE HISTORY" -BARBIERI

In the *Daubert* hearing, the Trial Court examined Barbieri about whether he could give an opinion as to Teston's impairment three (3) hours before the blood was drawn. Barbieri responded, "With no other Caveats, I would say yes. **And that caveat would be in terms of dosage history, in terms of taking the drug.**" (R. Vol. III p. 142).

The State faced an impossible burden in this case. In this one statement, the hole in the State's case is exposed. Barbieri would need to know when and how much medicine Teston took in order to give opinions about her impairment **at the time of the accident**. The State could not and did not supply this critical information.

Failing to insure that Teston did not take her prescribed medications after the accident, the State took refuge behind Teston's incomplete statement that she had taken two pills "today". Using retrograde extrapolation and subtracting these two pills, asking Barbieri to assume they were taken after the accident, Barbieri then arrives at a blood level of 100 ng/ml **at the time of the accident.**[28] Using Barbieri's error factor of 10%, even this calculation places Teston below Barbieri's threshold for impairment **at the time of the accident.**

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[28] Both experts testified that if Teston took no medications after the accident, then her blood levels would be lethal **at the time of the accident.** (R. Vol. VII pp. 655 and 698).

The State's problem is that their case depends on Teston taking at least four 10 mg pills during the day, not just two.[29] The State's case rest on an expert's testimony that Teston had to take more than two pills, four at a minimum, if all were taken after the accident and more if some were taken before the accident. Proving Teston's statement, given at a time when the State contends she was impaired, is false does not relieve the State of its heavy burden to prove by reliable expert testimony when she took the additional pills or that the only combinations of dosage possible would result in impairment **at the time of the accident**.

There are innumerable combinations that could result in the hydrocodone levels found in Teston's blood three hours after the accident. She could have taken two or three[30] after the accident, which combined with a therapeutic blood level **at the time of the accident**, would place her below the impairment threshold **at the time of the accident**. The point is that having anchored its case to more than two pills, the State had to eliminate by a reasonable degree of scientific certainty all combinations which would result in a hydrocodone level of less than 100 ng/ml **at the time of the accident**. This they could not and did not do.

Barbieri's caveat is that before he could give a opinion on impairment, he would need to know the dosage history. The State's evidence did not supply this critical information.

Because the State did not test Teston immediately after the accident or secure her so that she could not take any medications, the State could not support a retrograde extrapolation, assuming there is scientific reliability in Barbieri's methods. See, *Hedrick v. State*, 637 So.2d 834, 838-839

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[29] This scenario involved Teston taken four pills 1.5 hours before the blood sample was drawn. Under the State's theory, Teston would have had to take more than four pills in some unknown combination to be impaired **at the time of the accident**.

[30] What if in Teston's "confused" state, Teston mistakenly took another Lorcet rather than a Xanax she told Brantley she thought she took although the blood test showed no Xanax.

(Miss. 1994)(results from test given 3 hours after fatal accident insufficient where defendant consumed gin in the intervening 3 hours); *Smith v. State*, 942 So.2d 308 (Miss. Ct. App. 2006) (test given 4 hours after the accident with no intervening consumption of alcohol – retrograde extrapolation allowed). The State was unable to provide sufficient evidence from which Barbieri could give an opinion of the levels of medication in Teston's blood stream or her impairment **at the time of the accident.**

3. THE EXPERT'S OPINIONS SHOULD HAVE BEEN EXCLUDED UNDER MRE 401, 402, AND 403

Assuming compliance with MRE 702, the opinions should have been excluded under M.R.E. 401 *et seq*. By excluding material, undisputed facts from the hypothetical, the opinions offered by Barbieri were neither relevant nor material. Furthermore, the value of Barbieri's opinions was substantially outweighed by the prejudice they caused. The opinions confused the jury, encouraging jurors to speculate on Teston's impairment. The testimony should have been excluded under M.R.E. 401, 402 and 403.

C. THE COURT ERRED IN EXCLUDING AND PROHIBITING MENTION OF THE STATEMENT OF KRYSTAL TESTON THAT WAS RECORDED BY THE BILOXI POLICE DEPARTMENT FOLLOWING THE ACCIDENT AND/OR PROHIBITING CROSS EXAMINATION OF OFFICER BRANTLEY OR OTHER WITNESSES REGARDING THE STATEMENT.

The Trial Court admitted three (3)[31] out of four (4) statements of Teston and excluded the only recorded statement, wherein Teston explained the medicines she took after the accident. The Court prohibited counsel from referencing the recorded statement or cross-examining Brantley about the statement.

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[31] Two unrecorded oral statements and one written statement (State's Exhibit 5, R. Vol. VI. p. 511).

1. THE INCOMPLETE STATEMENTS

After Brantley placed Teston in his vehicle, she asked Brantley to "get her medication out of her vehicle". After Brantley retrieved Teston's medication, he asked Teston, "Have you taken any of these **today**?" Teston responded that she'd taken two."(R. Vol. VI. 524:1; 538-539) (Emphasis added).

This statement was made at approximately 9 pm, two hours after the accident. (R. Vol. VI. p. 524:15). Brantley, at that time, did not ask her "when today" she took them[32] and admitted that "today" included after 7:09 pm (the approximate time of the accident). (R. Vol. VI. p. 539:1-6). Officer Brantley then testified that Teston, while in route to the hospital to take the blood sample, stated, she had a Xanax[33] and a Goody's right after the crash to calm her down, she said (R. Vol. VI. p. 524).

The introduction of this statement clearly was an attempt to imply to the Jury that the two "Lorcet" were taken before the accident. Both of these statements were purely the result of bad questioning by Brantley and no fault of Teston.

Brantley initially (R. Vol. VI. p. 524) claimed these unrecorded statements were both made on the scene, however on cross-examination, it was revealed these statements were not contemporaneous with each other, but were two separate statements. (R. Vol. VI. p. 539:17-19). In fact, Brantley admitted in his written report (on the night of the accident):

> I asked her how many Lorecet has she taken today. She said she had taken two. **I transported Teston** and Mr. Stewart **to the station.** I asked Ms. Teston if she would

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[32] This is the same officer who failed perform any field sobriety testing, failed to use videotape equipment, failed to follow his training as a DUI Enforcement Officer (R. Vol. VI. p.541-545) and waited three (3) hours to drawn Teston's blood for testing. (R. Vol. VI. p. 568-570).

[33] Blood Testing by the Mississippi Crime Lab detected "no Xanax". (R. Vol. VI. p. 597:16-25).

consent to a blood test, and she replied yes. Teston **advised me that she had taken a Xanax and a Goody's PM right after the crash to calm her down** while she was transported to the Biloxi ER, and blood was drawn by the lab tech, Jennifer Gallaspy, at approximately 22:09.

(R. Vol. VI. p. 541:5-14) (Emphasis added).

Brantley had the ability to record both of these earlier statements but did not do so. (R. Vol. VI. p. 572; 10-21).

2. EXCLUSION OF PORTIONS OF TESTON'S RECORDED STATEMENT

Teston was taken to the Biloxi Police Department where she voluntarily submitted to another statement, which was the only statement recorded. At the time, Teston gave this recorded statement she did not know that she was being investigated for causing the subject accident. (See Motion 1/17/07 Exhibit 1 p. 4 lines 2-6; R. Vol. V. p. 414).

For first time, under questioning by a Biloxi Investigator, with Officer Brantley present and participating, Teston advised "when" she took her prescription medicines:

Q. Okay. How about the Lorecets?

A. Lorecets, yeah. I have taken one today. I took one this morning, and after the accident I took one and a half, and a half a more. Because my boyfriend gave it to me because I couldn't breathe. I was having an anxiety attack, because I can't see people like that, because of my brother dying and all that.

(R. Vol. V. p. 414 - Exhibit 1 to Brantley Proffer p. 14 lns 25 to p. 15 lns 1-7)

Teston's full statement confirmed that she had taken her medications after the accident, which was fully consistent with Brantley's close observations in his initial encounter with Teston, and his subsequent encounter, in which he observed obvious signs of impairment. The trial court allowed the State to mislead the Jury by offering only portions of Teston's voluntary statements. This was fundamentally unfair and contrary to *Mississippi Rules of Evidence*, Rule 106 and 611(a)(1).

The State should not have been allowed to mislead the Jury based upon the officer's bad questioning and allowed the jury to receive an incomplete and misleading picture of the Statements given to them. See *U. S. v. Glover*, 101 F.3d 1183, 1189 (7th Cir. 1996). The State should have been required to introduce all or none of the statements of Teston on the issue of when she took her prescription medicine. Alternatively, Teston should have been allowed to introduce in cross-examination of Brantley (R. Vol. VI. pp. 559-566 – proffer), the portions of the recorded statements of Teston wherein she specifically responded as to when and how much of her prescription medicine she took. (R. Vol. VI. pp. 559-566).

Rule 106 of the *Mississippi Rules of Evidence*, allows the introduction of "any other...recorded statement":

> Rule 106. Remainder of or related writings or recorded statements
>
> When a writing or recorded statement or part thereof is introduced by a party, an adverse party may require him at that time to introduce any other part or any other writing or recorded statement which ought in fairness to be considered contemporaneously with it. (emphasis added).

Rule 106 is a codification of the common law rule of completeness and the common law rule of completeness is applicable to all statements, including oral statements. See Comments, Rule 106, Miss. Rules Evid.

The federal equivalent of Rule 611(a) of the *Mississippi Rules of Evidence* has been also held to be applicable to oral statements. Rule 611(a) of the *Mississippi Rules of Evidence* grants the courts the same authority regarding oral statements which M.R.E. 106 grants regarding written and recorded statements. *See, United States v. Haddad*, 10 F.3d 1252, 1258 (7th Cir. 1993); *United States v. Li*, 55 F.3d 325, 329 (7th Cir. 1995); *see also, United States v. Mussaleen*, 35 F.3d 692, 696 (2nd Cir. 1994). Rule 611(a), *Mississippi Rules of Evidence* states: "The court shall exercise

reasonable control over the mode and order of interrogating witnesses and presenting evidence so as to (1) make the interrogation and presentation effective for the ascertainment of the truth..."

The Trial Court, despite the specific provisions of Rules 106 and 611(a), erroneously believed that "other statements" were not within the purview of Rule 106 and/or that the State was allowed as part of its trial strategy to introduce a portion of the Statements of Teston, which were misleading to the Jury. (R. Vol. V. p. 407). Such is simply contrary to the common law rule of completeness, Rules 106 and 611(a), Miss. Rules Evidence. It also defies common sense that a party, particularly the State of Mississippi, could possibly be permitted to mislead a jury in any case, criminal or civil, based upon ambiguous questions then exclude answers to specific questions asked as a follow-up.

Mississippi has relatively few cases addressing the rule of completeness. *See, e.g., Kniep v. State*, 525 So.2d 385, 390 (Miss. 1988) (addressing Rule 106 and noting the purpose is to avoid misleading the fact finder).

The Supreme Court stated in *Davis v. State*, 230 Miss. 183, 188, 92 So.2d 359, 361 (1957):

> It is an elementary rule of law that when admissions of one on trial for the commission of a criminal offense are allowed in evidence against him, all that he said in that connection must be permitted to go to the jury either through the cross-examination of the witness who testified to the admission or through witnesses produced by the accused. Moreover, the fact the declarations were made by the accused were self serving does not preclude their introduction in evidence as part of his whole statement, if they are relevant to statements introduced by the state and were made on the same occasion as the statements introduced by the state.

See also, Sanders v. State, 237 Miss. 772, 115 So.2d 145 (1959).

Miss. Rules Evid. Rule 106 is identical to the *Federal Rules of Evidence*, Rule 106. *United States v. Walker*, 652 F.2d 708, 710 (7th Cir. 1981). The test for admission of the "other...recorded statements" once relevance is established is (1) whether the additional evidence explains the

evidence already admitted; (2) whether it places the admitted evidence in its proper context; (3) whether its admission will serve to avoid misleading the trier of fact; and (4) whether its admission will "insure a fair and impartial understanding of all of the evidence." *Id...*; 1-106 *Federal Evidence Manual* §106.1, Matthew Bender, 2004; *United States v. Branch, infra.* All four tests were clearly met with regard to the Statements of Teston and the Court erred in not admitting the portion of the recorded statement of Krystal Teston. *See e.g., U.S. v. Swiess*, 800 F.2d 684, 689-690 (7th Cir. 1986) vacated on rehearing, 814 F.2d 1208 (1987) [involving multiple recorded conversations over several months – but proper foundation for admissibility not laid]; *United States v. Branch*, 91 F.3d 699, 728 (5th Cir. 1996) cert. denied, 117 S. Ct. 1466, 1467 (1997). [discussing Rule 106 and noting that "[a]lthough different circuits have elaborated Rule 106's 'fairness' standard in different ways, common to all is the requirement that the omitted portion be relevant and necessary to qualify, explain, or place into context the portion already introduced"].

The Court also erred in prohibiting Teston from confronting Brantley with recorded statements made by Teston in his presence and with his participation. This violated Teston's right to confront the witnesses against her. The right of confrontation and cross-examination extends to and includes the right to fully cross examine the witness on every material point relating to the issue to be determined that would have bearing on the credibility of the witness and the weight and worth of his testimony." *Myers v. State*, 296 So.2d 695, 700 (Miss. 1974). The Trial Court allowed misleading partial statement in evidence, and then unfairly restricted cross-examination of Brantley as to the subsequent recorded statement wherein Brantley was present and participated in questioning of Teston. (R. Vol. VI. pp. 559-567). Teston was also prohibited from impeaching Brantley with recorded statement of Teston for example as to her demeanor and impairment at the

time the recorded statement was taken or that they had her in a room with videotape equipment and did not videotape her. (R. Vol. V. pp. 406-414).

These rulings were clearly in error and caused substantial prejudice to Teston's right to a fair trial. The Court should reverse and remand for a new trial.

D. THE TRIAL COURT ERRED IN REVERSING ITS RULING, *IN LIMINE*, PROHIBITING EVIDENCE OF THE DEFENDANT BEING CHARGED WITH DRIVING WITH SUSPENDED LICENSE) AND ERRED IN DOING SO AFTER *VOIR DIRE* AND SELECTION OF THE JURY.

Mississippi law guarantees the right of Defendant to question the prejudices of prospective jurors and investigate their thoughts on matters directly related to the issues to be tried. *West v. State*, 553 So.2d 8, 22 (Miss. 1989). Such questions enable parties to conscientiously challenge prospective jurors for cause and provide valuable clues for the exercise of peremptory challenges. *Harris v. State*, 532 So.2d 602, 606 (Miss. 1988).

Before trial Teston filed a Motion in limine to prohibit the State from introducing evidence that Teston was charged with driving with a suspended driver's license on the night of the accident. (R. 103-104). The State confessed the Motion in limine and the Order was entered. (R. 105; Hearing June 9, 2006 at p. 3-4; R. Vol. IV. p. 213-222). Immediately before the trial commenced that State sought to withdraw its confession of the Motion in Limine and sought permission to introduce the evidence of Teston being charged with suspended driver's license. The Court refused and entered the Order prohibiting the introduction of said evidence. (R. Vol. I. 105; R. Vol. IV. pp. 213-222).

The trial proceeded with voir dire and jury selection. In reliance of the Court's ruling and the State's confession prohibiting the introduction of other crimes, wrongs or acts of Teston including "driving with a suspended driver's license" on the night of the accident, the prospective jurors were not asked during voir dire by Teston about the effect of Teston having a suspended driver's license

at the time of the accident on their ability to be fair and impartial or to serve as jurors. The Jury was selected and presentation of evidence commenced.

> After jury selection and opening statements, the Court reversed its ruling at the behest of the prosecutor before Brantley took the stand. (R. Vol. VI. pp. 498-507). The State then called Officer Brantley who was allowed to testify that Teston was arrested at the scene for driving with a suspended driver's license
>
> (R. Vol. VI. p. 522, lns 9-18) (emphasis added).

Contrary to the specific representation by the State to the Court, to obtain a reversal of its ruling, that it intended to offer this evidence as the reason Officer Brantley did not perform any field sobriety tests on Teston, Officer Brantley was never even asked the question by the State (R. Vol. VI. p. 522) and did not offer such explanation on cross-examination[34]. (R. Vol. VI. pp. 507-574). Additionally, Brantley did not arrest Teston until after 8:53 pm (R. Vol. VI. p. 522:28), almost two hours after accident. Obviously, the State's purported reason for admitting that Teston was arrested for driving with a suspended driver's license at the time was merely a ruse to get prejudicial evidence before the Jury that Teston was driving with a suspended license **at the time of the accident**. This evidence was neither relevant nor material to any issue before Jury and if it was, then any such relevance was outweighed by its prejudicial effect. *Miss. Rules Evid.* 401, 402, 403 and 404.

More importantly, the Court's reversal of its ruling after jury selection, violated Teston's right to question the prejudices of prospective jurors and investigate their thoughts on the issue of Teston driving with a suspended driver's license **at the time of the accident**, as to the ability to be

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[34] On redirect examination the State did asked Brantley about not removing the handcuff's and being on the interstate to conduct field sobriety testing, but such was not the explanation offered by the State in seeking reversal of the confessed order *in limine*. (R. Vol. VI. p. 573).

fair and impartial. *West v. State*, supra; *Harris v. State, supra.* This matter should be reversed and remanded for new trial on this ground.

E. THE COURT ERRED IN ALLOWING THE STATE TO PROCEED TO TRIAL ON COUNTS V-VIII OF THE INDICTMENT REQUIRING THE DEFENDANT TO DEFEND SAID CHARGES.

The State indicted Krystal Teston in an eight (8) Count Indictment. (R.E. 11-15). The State charged this Defendant with two (2) counts *for each* death and injury based on the same other substance under Section 63-11-30(1) (b) Mississippi Code of 1972. Counts I-IV charged driving under the influence of simply "other substance", being a prescription drug, hydrocodone, and Counts V-VIII charged driving under the influences of "other substance" without identifying any substance other than a "drug or controlled substance". These clearly were not alternatives of proving the same thing, but were, in fact, the same charge 8 times. Teston filed a Motion to Dismiss Counts V-VIII charging the same crime, as Counts I-IV. (See R. E. _____). Section 63-11-30(1) (b) Mississippi Code of 1972 prohibits driving "under the influence of *any other substance which has impaired* such person's ability to operate a motor vehicle". The State identified only one "other substance" but added Counts just "other substance", such was improper and highly prejudicial. Unlike cases approving alternatively charging under Section 63-11-30(1)(a), (b) or (c), Mississippi Code of 1972, where an element of each is different, e.g., under the influence of alcohol requires proof of impairment, while driving with a BAC of eight one-hundredths percent (.08%) does not, these counts charge the same crime exactly. Section 63-11-30(1) (b) Mississippi Code of 1972 does not make it a separate crime for "each" "other substance" nor was such an alternative method of proving the same thing. *See e.g., Young v. City of Brookhaven*, 693 So.2d 1355 (Miss. 1997). Allowing the State to proceed to trial on these counts caused substantial prejudice to the Appellant, Teston and violated her Constitutional rights to be informed of the charges filed against her and her rights against double jeopardy.

F. THE COURT ERRED IN FAILING TO INSTRUCT THE JURY AS TO THE CORRECT BURDEN OF PROOF IN THIS CASE, THE EVIDENCE BEING ENTIRELY CIRCUMSTANTIAL.

In *Keys v. State*, 478 So.2d 266 (Miss. 1985), the Supreme Court explained the procedure behind a circumstantial evidence instruction.

> It is the law in this state that, where the evidence for the prosecution is wholly circumstantial in nature, the accused is entitled upon request to have the jury instructed that, before they may convict, they must find that each element of the offense has been established beyond a reasonable doubt and to the exclusion of every reasonable hypothesis consistent with innocence.

The instruction must be given where the prosecution is without a confession and wholly without eyewitnesses to the gravamen of the offense charged. *Id.*.

The gravamen of the offense charged in this case was that the Defendant "did...drive and operate a motor vehicle...while under the influence of a drug or controlled substance....which impaired [her] ability to operate a motor vehicle, and did thereby in a negligent manner cause the death of....a human being". (See Indictment R. 12-16). Teston gave a written statement, introduced into evidence by the State, stating she was looking into her rear view mirror and saw another car come into the SUV's lane causing an accident. (See State's Exhibit 5 R. Vol. VI. p. 517). There were only other two testifying witnesses to this accident, Stacy Ross and Nicole Thurman. Neither witness could identify Teston as the driver of the black Honda at the time of the accident. (Ross, R. Vol. V. pp. 449, 452, 474; Thurman, R. Vol. VII. pp. 619-620). Where the evidence against an accused is wholly circumstantial, a circumstantial evidence instruction must be given. *Windham v. State*, 602 So.2d 798, 800 (Miss. 1992). The Trial Court erroneously ruled that there was direct evidence in that Teston admitted driving her vehicle. Officer Brantley did not ask her if she was driving at the "time of accident" only if she was "driving". (R. Vol. VI. p. 519, ln 14). Teston written statement merely admits she was driving "her vehicle" and saw another vehicle swerve into the SUV. (See State's Exhibit 5 R. Vol. VI. p. 517). The Trial Court erred in overruling

Teston's objections to the Jury instructions (R. Vol. VIII. pp. 733, 734, 740-742) not setting forth the correct burden of proof in this circumstantial evidence case: that each element of the offense has to be established beyond a reasonable doubt and to the exclusion of every reasonable hypothesis consistent with innocence. (S-1, S-2, S-3, S-4, and not granting D-3, D-5, D-6, D-7, D-8, D-9, D-10), R. Vol. VII. pp. 731-743). This matter should be reversed and remanded for new trial with appropriate instructions.

G. THE STATE IMPROPERLY COMMENTED IN OPENING STATEMENT AND IN CLOSING ARGUMENT ON TESTON'S FAILURE TO TESTIFY

During opening statement, the prosecutor made the following statement:

> This is not an accident that just happened. She chose to fly down this highway. She chose to pull in front of that car. She chose to do that drug. Those were her decisions, and **she can't come here now and say, oops, and we're all sorry about the dead kids.** That's just not how it works.

(R. Vol. V. p. 422:17-22).

Teston's motion for mistrial was denied. (R. Vol. V. p. 423 lns 17-22). This error was then compounded by the State's closing argument when the State improperly argued:

> **She can't come here with a straight face and tell you** I lied for whatever kind, sweet reason counsel opposite might have you believe and just —
>
> Mr. Tim Holleman: Your Honor, to which we would object.
>
> The Court: Overruled.
>
> Mr. Ward: --and say well, maybe we got a little benefit of time, but its not our fault because the police should have. That's just not the way it is. She lied because she's impaired on hydrocodone, and she wanted to wait as long as she could.
>
> The Court: Mr. Ward, direct your comments to the Jury.[35]

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[35] While making these improper statements, the State was improperly referring directly to Teston at the defense table until the Court admonished him to direct his comments to the jury. *See, Clark v. State*, 260 So. 2d 445, 446 (Miss. 1972).

Mr. Ward: Yes, sir.

(R. Vol. VIII. p. 774:10-25).

As this Court stated long ago: "no ingenuity, however artful, no subtlety, however refined, can escape the conclusion that this statement made by the prosecuting counsel held up to the jury the failure of the defendant to testify". See *Gurley v. State*, 101 Miss. 190; 57 So. 565 (1911). Likewise, here the comments by "prosecuting counsel" were clearly direct comments on Teston's failure to testify and requires reversal of the verdict in this case. This court has held many times, that the State is prohibited from making both direct comments and those "which could be reasonably construed by a jury as a comment on the defendant's failure to testify." *Griffin v. State*, 557 So.2d 542, 556 (Miss. 1990). This right not to testify becomes meaningless if comment or insinuation can be made reflecting upon her failure to testify. A criminal defendant has the right to elect not to take the witness stand in his/her own defense. *Miss. Const.*, Art. XXVI; *U. S. Const.* Amend. V.; *Wright v. State*, No. 2005-KA-01729, para. 20 (Miss. April 2007). The first comment in opening statement was a direct comment on what Teston would say before Teston had either testified or elected not to testify ["she can't come her now and say, oops, and we're all sorry about the dead kids"[36]]. The error was compounded after Teston exercised her right not to take the witness stand by the State's rebuttal argument ["she can't come here with a straight face and tell you...."]. The State's arguments here were clearly not merely "innuendo and insinuation" or even just a comment on the failure of Teston to present a defense or even on her defense. *See e.g.*, *Shook v. State*, 552 So.2d 841, 851 (Miss. 1989). This was a direct argument to the jury that Teston had failed "to come here with a straight face and tell you." the truth. *Jimpson v. State*, 532 So.2d 985, 991 (Miss. 1988). Either

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[36] This improper "argument" in the State's opening statement occurred before any defense had been offered by Teston.

separately or together, these statements were "an outright violation" of Teston's constitutional right against self-incrimination as protected by the Fifth Amendment to the *United States Constitution* and Art. 3 § 26 of the *Mississippi Constitution* and requires reversal on this issue alone. This was particularly error considering the lack of evidence against Teston. *Headrick v. State, infra.* The Trial Court erred in overruling the contemporaneous objection to improper opening statement and motion for mistrial and contemporaneous objection to the rebuttal argument and in denying Teston's Motion For Acquittal Or J.N.O.V; Motion For New; Renewed Motion For Mistrial; Motion To Exclude The Evidence And Direct A Verdict. *See, Williams v. State*, 684 So.2d 1179 (Miss. 1998). This conduct was clearly improper and requires reversal of Teston's convictions and remand of new trial.

H. DEFENDANT'S SENTENCE OF 15 YEARS ON EACH COUNT FOR A TOTAL OF 60 YEARS TO RUN CONSECUTIVELY WITH 30 YEARS SUSPENDED WAS GROSSLY DISPROPORTIONATE TO THE CRIME

A sentence which falls within the permissible range designated by statute will generally not be disturbed on appeal. *Corley v. State*, 536 So.2d 1314, 1319 (Miss. 1988). The exception to this rule is for proof of disproportionality. *Hoops v. State*, 681 So.2d 521, 538 (Miss. 1996). The threshold inquiry on a claim of disproportionality is whether the punishment is excessive for the crime committed. *Id.*. This Court should review a sentence, where it is alleged that the penalty imposed is disproportionate to the crime charged. *See, Ashley v. State*, 538 So.2d 1181, 1184-85 (Miss. 1989); *Davis v. State*, 510 So.2d 794, 797 (Miss. 1987); *Presley v. State*, 474 So.2d 612, 618 (Miss. 1985). The three factors to be considered are: (1) the gravity of the offense and the harshness of the penalty; (2) the sentences imposed on other criminals in the same jurisdiction; and (3) the sentences imposed for commission of the same crime in other jurisdictions. *Solem v. Helm*, 463 U.S. 277, 303-304 (1983).

This same Trial Court approximately 7 months before this case, sentenced a young man (State v. Rutland) to 1 year of house arrest for DUI causing the death of six college-age friends in Cause Number 2006-42 in the Circuit Court of Stone County, Mississippi (See R. Vol. VIII. p. 844; Exhibit 1 to Motion for New Trial etc.). *See, Kram v. State*, 949 So.2d 18 (Miss. 2007) [20 year DUI sentence – hit and run - fled the scene]; *Travis v. State*, 2007 Miss. App. LEXIS 342 (Miss. Ct. Appeals decided May 15, 2007) [25 year sentence, 15 suspended for a total of 10 years]; *Smith v. State*, 956 So.2d 997 (Miss. Ct. App. 2007) [DUI two seriously injured 10 years, 7 years suspended]; *Smith v. State*, 942 So.2d 308 (Miss. Ct. App. 2006) [one with catastrophic injuries 20 years, 15 suspended, 5 years Intensive Supervision Program]. Teston was sentenced to 15 years for each count to run consecutively, for a total of 60 years, 30 years suspended for the deaths of 3 college-age students and one injury. Teston's "consecutive" sentence is grossly disproportionate to the crime, the facts of this case and is a denial of equal protection of the laws. *Ramage v. State*, 914 So.2d 274 (Miss.Ct. App. 2005). The sentence is inconsistent with other sentences imposed in other cases in the same jurisdiction and the same Trial Court. This matter should be reversed and rendered as to the "consecutive" sentence to a concurrent sentence or alternatively remand for resentencing by the Trial Court.

I. THE COURT ERRED IN PERMITTING THE INTRODUCTION OF BLOOD DRAWN IN VIOLATION OF SECTION 63-11-8, MCA, 1972

Miss. Code Ann. §63-11-8(1) (Rev. 2000) requires "Any blood withdrawal required by this section shall be administered by any qualified person and shall be administered within two (2) hours after such accident, if possible." *Smith v. State*, 942 So.2d 308 (Miss. Ct. App. 2006). This statute mandates that a test for determining blood drug or alcohol content be performed on the operator of any motor vehicle involved in an accident resulting in death. Miss. Code Ann. §63-11-8(1) (Rev. 2000). Subject to their being probable cause. *McDuff v. State*, 763 So.2d 850 (Miss. 2000). The

statute further provides that such test shall be administered within two hours of the accident "if possible". *Id.*.

The accident occurred at approximately 7:09 pm. When Brantley arrived on the scene approximately 23 minutes after the accident, he knew at least one person was deceased and two seriously injured. (R. Vol. VI. p. 543:21-24). After his initial encounter with Teston, Brantley next approached Stacey Ross and gave her a witness form. Ross told Brantley at that time the black Honda (allegedly Teston's vehicle) had contributed to the accident. According to Ross, this conversation occurred within approximately 20 minutes of the accident. (R. Vol. VI. pp. 461-462).

Brantley did not request the blood test from Teston until after he arrested her for driving with a suspended license at approximately 9 pm. He even waited on a tow truck to arrive before going to the station. (R. Vol. VI. p. 525). There were numerous other police officer and investigators on the scene that could have assisted in obtaining the blood sample. (R. Vol. VI. p. 547-548). When asked, Teston readily consented to a blood test, yet her blood was not drawn until 10:09 pm, 3 hours after the accident. It was not disputed that the State did not comply with the two hour limitation of Miss. Code Ann. §63-11-8(1) (Rev. 2000). The prosecution bears the burden of proving beyond a reasonable doubt each fact that is a prerequisite for admissibility of the evidence. *Kirkland v. State*, 559 So.2d 1046 (Miss. 1990).

Teston filed a motion to suppress this blood evidence. (R. E. 45-51; R. Vol. I pp. 90-96) The matter came on for hearing not once but two times and the State failed to call any witnesses to establish the validity of the taking of the blood of Teston At the hearing, the State offered no testimony to establish that it was not "possible" to comply with the mandates of Miss. Code Ann. §63-11-8(1) (Rev. 2000). (R. Vol. IV. p. 238). The court summarily, without hearing any testimony or evidence opposing the motion and without requiring the State to meet its burden, ruled that the

three (3) hour delay did not violate Miss. Code Ann. §63-11-8(1) (Rev. 2000) (R. Vol. IV. pp. 251-252). Such was in error.

In *Acklin v. State*, 722 So.2d 1264, 1266 (P9) (Miss. Ct. App. 1998) in the Mississippi Court of Appeals noted:

> Absent any indication that, in the intervening time between the accident and the time his blood was drawn, Acklin had ingested additional alcohol, proof that Acklin's blood contained alcohol some two or two and a half hours after the accident would necessarily make it "more probable than it would be without the [test result]" that Acklin was under the influence of alcohol **at the time of the accident.**

In this case, there is overwhelming evidence that in the intervening time between the accident and the time Teston blood was drawn, Teston ingested her prescription medicine. The testimony of Brantley and Barbieri established that Teston took hydrocodone after the accident. This is not a case where a citizen was supervised between the time of accident and blood being drawn so that no alcohol or medications could be consumed between the accident and the blood being drawn. *See e.g.*, *Wash v. State,* No. 1999-KA-00738-COA (Miss. Ct. App. 2001) Para 10; *Acklin v. State*, supra. The State failed to comply with clear statutory law with respect to the subject blood testing to the prejudice of Teston. When a Motion to Suppress was filed the State failed to meet its burden to show it was not "possible" to obtain this sample earlier. Therefore, the Court erred in not sustaining Teston's Motion to Suppress. (R. Vol. IV. pp. 238-252).

V. CONCLUSION

That a person can be convicted of this evidence is frightening. In this case, a young woman has been sentenced to the better part of her life in prison for the simple negligent act of not seeing the SUV in her blind spot before attempting to change lanes. There is no competent evidence of impairment and by all accounts, she took her medications after the accident during the 3-hour period before she was asked to submit a blood sample. The observations of a trained DUI officer, within

minutes of the accident establish beyond reasonable doubt that Teston was not impaired at the time of the accident. The observations of this same officer that Teston was impaired when he interviewed her the second time prove beyond genuine dispute that Teston took her medications after the accident.

Although Barbieri's opinions should not have been admitted, what he gave the State, he took away. Even Barbieri conceded that the undisputed Brantley testimony established that Teston was not impaired at the time of the accident, but became so after she took her medications following the accident. Barbieri also conceded that some of Teston's conduct described by the witnesses was not consistent with impairment.

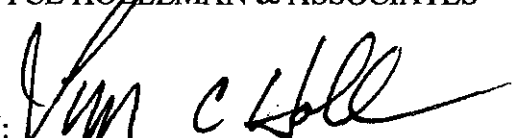
The State failed to present *any proof* that Teston, under their theory, took more than four pills in a combination that could only mean that she was impaired at the time of the accident.

For these and other reasons argued above, these convictions should be reversed and a judgment of acquittal on all rendered. Alternatively, the convictions should be reversed and the case remanded for a new trial.

Respectfully submitted, this the 18th day of September, 2007.

KRYSTAL MARIE TESTON, By And Through Her Attorneys Of Record

BOYCE HOLLEMAN & ASSOCIATES

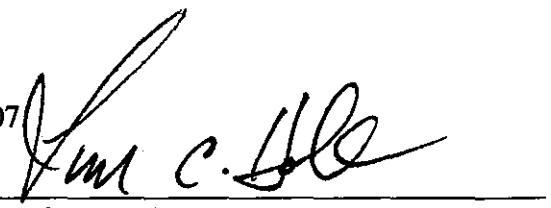
BY: 

TIM C. HOLLEMAN

CERTIFICATE

I, TIM C. HOLLEMAN, attorney of record for the Appellant in the above-styled and numbered cause, do hereby certify that I have on this date forwarded a true and correct copy of the above and foregoing to Mark Ward, Esquire, Assistant District Attorney, 730 Martin Luther King Boulevard, P O. Box 1444, Biloxi, Mississippi 39533; James Hood, Esquire, Attorney General for the State of Mississippi, MS Attorney General's Office, P.O. Box 220 Jackson, MS 39205 and Honorable Stephen B. Simpson, Circuit Court Judge, P.O. Box 1570, Gulfport, MS 39502, by United States Mail, postage prepaid.

THIS, the 18th day of September, A. D., 2007



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APPENDIX

Journal of Chromatography, 130 (1977) 243–249

A

CHROM. 9334

GAS CHROMATOGRAPHIC DETERMINATION OF HYDROCODONE IN SERUM

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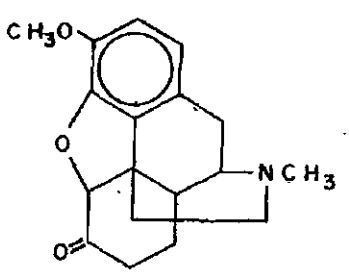
(Received April 26th, 1976)

SUMMARY

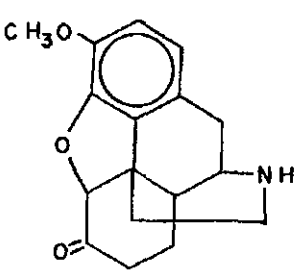
A procedure for the determination of hydrocodone (dihydrocodeinone) in serum has been developed. Hydrocodone and N-isobutyldihydronorcodeinone, the internal standard, are extracted from serum by chloroform–isopropyl alcohol (9:1, v/v). The extracts are purified by back-extraction into 0.1 *N* sulfuric acid and a final basic extraction into benzene. The pentafluorophenylhydrazone derivatives are formed and determined using electron capture gas chromatography. As little as 1 ng/ml of hydrocodone in serum can be determined. A closely related compound and potential metabolite, dihydronorcodeinone, does not interfere. Serum hydrocodone levels were determined in dogs after oral and intravenous doses of 0.5 mg/kg, and in humans after a 10-mg oral dose of the bitartrate. A mean peak serum drug concentration of 23.6 ng/ml and a terminal half-life of 3.8 h resulted from the human study. The terminal half-life in serum was 1.8 h after the intravenous dose in dogs.

INTRODUCTION

Hydrocodone (dihydrocodeinone) is a widely used antitussive agent[1]. Little is known about the pharmacokinetic or metabolic characteristics of this drug in spite of its widespread usage. Although the determination of hydrocodone (I) in biological samples was mentioned in the literature, it was in the context of a screening procedure for forensic purposes and no data were reported[2,3]. These procedures lacked the sensitivity to determine the drug in serum after therapeutic doses. A new gas chromatographic procedure for the determination of the drug in serum with a lower limit of 1



I



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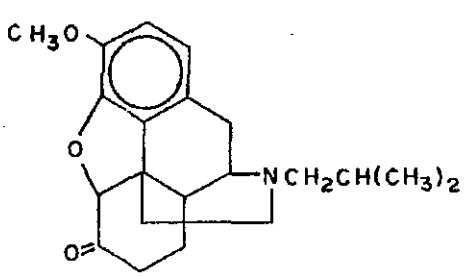

III

ng/ml was devised utilizing electron capture detection of the pentafluorophenylhydrazone derivative. A similar approach has been used for the determination of plasma estrone[4].

EXPERIMENTAL

Instrumentation

A Hewlett-Packard Model 7610A gas chromatograph (Hewlett-Packard, Avondale, Pa., U.S.A.) with a ^{63}Ni electron capture detector was used with a 3 ft. × 4 mm I.D. silanized glass column filled with commercially available packing, 3% OV-7 on Supelcoport 100–120 mesh (Supelco, Bellefonte, Pa., U.S.A.). The column oven temperature was 265°, and the injection port and detector temperatures were 280° and 300°, respectively. The carrier gas (5% methane in argon) flow-rate was 40 ml/min. The pulse interval for the electron capture detector was 150 μsec. Under these conditions, the pentafluorophenylhydrazones of compounds I, II, and III had retention times of 9.4, 10.6, and 12.9 min, respectively.

Reagents

All organic solvents listed in the procedure were nanograde quality (Mallinckrodt, St. Louis, Mo., U.S.A.). Pentafluorophenylhydrazine (PFPH) was obtained from Regis (Morton Grove, Ill., U.S.A.), hydrocodone bitartrate and methadone hydrochloride from Mallinckrodt, and oxycodone hydrochloride and hydromorphone hydrochloride from Merck (Rahway, N.J., U.S.A.).

N-Isobutyldihydronorcodeinone (III) and dihydronorcodeinone (II) were synthesized from hydrocodone bitartrate as the starting material using published procedures[5,6]. Compound III was freed from small amounts of contaminating compound II by passing a methanolic solution of compound III free base through a 1 × 8 cm silicic acid column (Bio-Sil HA; Bio-Rad Lab., Richmond, Calif., U.S.A.) and eluting with methanol. Compound III eluted in the first 20 ml and compound II was retained on the column. A working solution was prepared by diluting 0.10 ml of the methanolic solution containing approximately 1 mg/ml to 100 ml with 0.01 *N* sulfuric acid. All other reagents were analytical-reagent grade.

Procedure

A sample containing 1–2 ml of serum, internal standard, 0.5 ml of 2 *N* potassium hydroxide, and 2 ml of distilled water was extracted with 4.5 ml of chloroform–isopropyl alcohol (9:1, v/v) for 5 min. The aqueous phase was discarded with the aid of centrifugation and the organic phase was decanted into another tube. Basic substances in the organic phase were extracted with 2 ml of 0.1 *N* sulfuric acid by mixing for 1 min on a rotary mixer. After centrifugation, the aqueous layer was transferred to another tube, 0.2 ml of 2 *N* potassium hydroxide was added, and the sample was mixed vigorously with 2 ml of benzene for 1.5 min on a rotary mixer. The sample was centrifuged and the benzene layer was transferred to a small test tube. Solvent was evaporated with nitrogen in a warm (50°) sand bath. Derivatization was accomplished by adding 0.1 ml of 1% (v/v) acetic acid in methanol and 0.1 ml of PFPH in methanol (2 mg/ml). After 2 h at room temperature, 2 ml of water and 0.1 ml of 2 *N* potassium hydroxide were added, and the sample was mixed vigorously with 2 ml of benzene for

1 min on a rotary mixer. The benzene was transferred after centrifugation to a small vial and evaporated to dryness. The residue was dissolved in 50–100 μl of benzene–methanol (9:1, v/v). At least three standards in serum were carried through the procedure and all standards and samples were done in duplicate. Peak height ratios (I/III) were calculated and plotted *versus* the concentration of I for the standard curve. A typical standard curve is shown in Fig. 1.

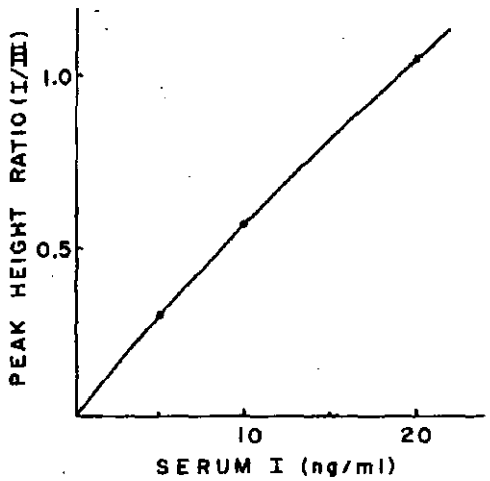

Fig. 1. Standard curve for the quantitative analysis of hydrocodone in serum.

Dog studies

Two male (No. 4258 and 986) and two female (No. 898 and 863) mongrel dogs weighing 21.3, 26.5, 23.7, and 20.8 kg, respectively, received a single intravenous (i.v.) dose of 0.5 mg/kg of I bitartrate (USP) in 0.9% saline via the cephalic vein. The animals were fasted for 12 h prior to and during the experiment, but had free access to water. Blood samples (15 ml) were taken at selected intervals from 0 through 6 h after dosing. Serum was collected and stored at −15°. One week later the experiment was repeated in the same animals using oral intubation of the drug solution.

Human studies

Five male human subjects from 21 to 26 years old, weighing 70, 61, 59, 77, and 77 kg were given a single 10-mg oral dose of I bitartrate. The formulation, a commercial tablet, also contained 60 mg of pseudoephedrine·HCl. The subjects were fasted overnight before dosing, but were given a light snack 2 h after dosing and lunch 5 h after dosing. The diet was not supervised after 8 h. Blood samples (20 ml) were taken at selected intervals from 0–12¼ h after dosing. Serum was collected and stored at −15°.

RESULTS AND DISCUSSION

Test analyses

A series of analyses of control serum containing known concentrations of hydrocodone was performed as a test of the reproducibility of the method (Table I).

TABLE I

REPLICATE ANALYSES OF CONTROL SERUM CONTAINING KNOWN AMOUNTS OF HYDROCODONE

Actual concentration of hydrocodone in serum (ng/ml)	*Concentration of hydrocodone found in serum (ng/ml)*	*Mean (ng/ml)*	*Coefficient of variation (%)*
0	0.0, 0.0, 0.1, 0.0	0.0	0.0
1.25	1.1, 1.3, 1.2*, 1.3*	1.2	7.9
7.5	7.5, 7.6, 7.4*, 7.5*	7.5	1.1
8.5	8.5, 8.3, 7.9*, 8.0*	8.2	3.4
10.0	10.3, 10.2, 9.9, 10.5, 10.2, 9.4, 9.2, 9.7, 10.2, 9.7	9.9	4.3
16.0	14.5, 14.2, 15.6*, 15.7*	15.0	5.1
21.0	20.2, 21.7, 21.6*, 19.0*	20.6	6.2
25.0	25.1, 24.9, 25.2, 25.0, 26.0, 23.5, 25.2, 25.0, 24.9, 25.4	25.0	2.5

* 2.0 ml serum sample.

There was no material difference in the results obtained using 1- or 2-ml serum samples, so these data were combined for statistical analysis. An overall accuracy of 98.5% of theoretical was obtained, with a coefficient of variation of 4.4%.

Specificity

Compounds lacking a basic functional group would not be expected to survive the extraction techniques used in this procedure. Hydromorphone, a compound with both basic and acidic functional groups, did not interfere when tested at the 1-μg/ml level, and, in fact, was not extracted at the high pH used in this method. Direct derivatization of hydromorphone produced a compound with a relative retention of 0.67 compared to the derivative of I. Methadone was also tested at the 1-μg/ml level, and did not interfere. Oxycodone was readily detected and could perhaps be used as an internal standard, since it and III formed derivatives with the same retention time. However, the oxycodone peak had considerably more tailing.

Analytical conditions

Hydrocodone is a weak base and can be extracted from aqueous solution with organic solvents at elevated pH. Chloroform and benzene were found to be good extracting solvents whereas hexane and diethyl ether were poor. Back extraction of the amines with dilute acid and subsequent extraction of the free amines after pH adjustment was found to be an adequate cleanup of serum extracts. Derivatization with PFPH required a small amount of acid and an extended time period for adequate reaction (Table II). The conditions selected were 0.5% acetic acid concentration, 1.0-mg/ml PFPH concentration, and a 2-h reaction time. The PFPH derivative of the internal standard (III) was separated chromatographically from those of both I and a potential metabolite (II). Peak height ratios (I/III) were plotted *versus* concentration of I (Fig. 1) to yield linear or nearly linear standard curves. II was not quantitated, but the peak heights were substantially less than those for equal quantities of I. Whether this was due to an actual difference in sensitivity or poor recovery was not determined. Some representative chromatograms are shown in Fig. 2.

TABLE III

SERUM HYDROCODONE LEVELS AFTER I.V. OR ORAL ADMINISTRATION OF HYDROCODONE BITARTRATE (0.5 mg/kg) IN DOGS

Time (h)	*Serum hydrocodone (ng/ml, as the free base)*					
	Dog No.					
	4258	*986*	*898*	*863*	*Mean*	*S.D.*
Intravenous						
0	0.3	0.2	0.6	0.3	0.4	0.2
¼	106	103	107	106	106	1.7
½	86	68	86	86	82	9.0
¾	70	61	74	68	68	5.4
1	61	55	64	50	58	6.2
1½	37	38	46	33	38	5.4
2	31	33	34	24	30	4.5
3	22	24	22	15	21	3.9
4	10	12	12	10	11	1.2
6	5.4	7.1	6.4	4.9	6.0	1.0
Oral						
0	0.0	0.0	0.0	0.0	0.0	0.0
¼	52	1.8	7.3	0.8	15	25
½	94	5.4	42	25	42	38
¾	78	10	69	68	56	31
1	68	26	62	60	54	19
1½	48	33	40	45	42	6.6
2	36	28	32	32	32	3.3
3	23	16	23	24	22	3.7
4	14	10	15	17	14	2.9
6	5.6	8.0	5.6	7.9	6.8	1.4

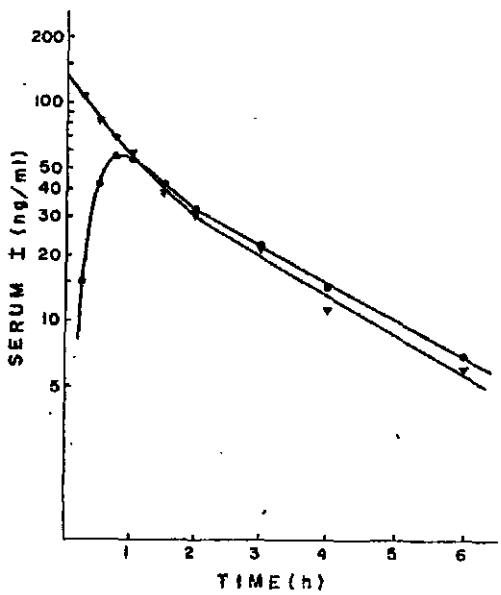

Fig. 3. Mean serum hydrocodone levels in four dogs after a single intravenous (▼) or oral (●) dose.

oral availability is indicative of good absorption and no major first pass metabolic effect.

The metabolism of hydrocodone has not been reported; however, by analogy to similar compounds, such as morphine and codeine[8], N-demethylation would be one potential route. Although the present study was not primarily a metabolic study, the N-demethylated compound (II) was separated chromatographically and could therefore be detected. A component with the same elution time as II was detected in some serum extracts (Fig. 2). This peak was more pronounced after oral administration. Quantitation was not attempted, but it should be remembered that the sensitivity and/or recovery of II was poor.

Human study

Considering that the dose in human was about 0.14 mg/kg the observed serum drug levels (Table IV) compare quite favorably with those obtained in the dog. The mean peak concentration was 23.6 ± 5.2 ng/ml while the corresponding canine value

TABLE IV

SERUM HYDROCODONE LEVELS AFTER ORAL ADMINISTRATION OF HYDROCODONE BITARTRATE (10 mg) IN HUMANS

Time (h)	*Serum hydrocodone (ng/ml, as the free base)*						
	Subject					*Mean*	*S.D.*
	103	*106*	*107*	*110*	*112*		
0	0.2	0.0	0.2	0.0	0.0	0.1	0.1
½	6.6	6.4	12	6.0	7.0	7.6	2.5
1	24	20	32	15	15	21	7.1
1½	24	22	29	18	21	23	4.1
2½	19	22	23	14	19	19	3.5
5	13	10	14	10	13	12	1.9
8	7.0	6.5	8.8	4.9	7.6	7.0	1.4
12¼	3.8	3.7	3.3	1.9	3.5	3.2	0.8

was 66 ng/ml. The time required to reach maximum drug levels was 1.3 ± 0.3 h compared to 0.9 h in the dog. After maximum levels were attained the drug disappeared from serum with a first-order rate, and the half-life of this portion of the curve was 3.8 ± 0.3 h. There was no prominent II peak in human serum extracts (Fig. 2), suggesting that the drug may be metabolized to a lesser degree or by different routes than in the dog.

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FEB 26 1997

B

Clinical Pharmacology/Biopharmaceutics Review

Hydrocodone Bitartrate 7.5mg &
Ibuprofen 200mg Tablets
NDA 20-716 Orig.
Vicoprofen® Tablets
Reviewer: E.D. Bashaw, Pharm.D.
APW

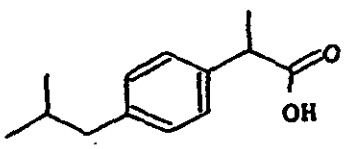
Knoll Pharmaceutical
Mt. Olive, NJ

Submission Date:
April 26, 1996

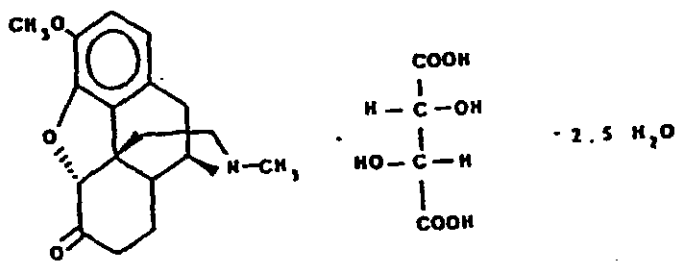
Review of an NDA

I. Background

Knoll Pharmaceutical currently markets a number of analgesic products including Dilaudid® (hydromorphone) and Vicodin® (hydrocodone bitartrate and acetaminophen). The combination of an opioid analgesic and a non-steroidal anti-inflammatory agent is a rational combination of analgesics with two different modes of action. Products related to the one proposed in this application include Percodan® (oxycodone and aspirin), Percocet® (oxycodone and acetaminophen) and the applicant's own product Vicodin®. The product that is the subject of this NDA is intended for use in the treatment of moderate to severe pain. Because of its obvious similarity this product, to some degree, can be considered a pseudo-line extension of the Vicodin® product line. The substitution of a NSAID for acetaminophen should offer some advantages by the inclusion of anti-inflammatory activity to the dual mode analgesic effect. The proposed product will be produced as only 1 strength (hydrocodone 7.5mg/ibuprofen 200mg). Based on the rating of Vicodin®, it is anticipated by the applicant that this product will be classified as a schedule-III narcotic combination under the Controlled Substances Act. Throughout the review the following abbreviations will be used: HC for hydrocodone, IBU for ibuprofen. Reproduced below are the associated chemical structures of HC and IBU:



Benzeneacetic acid,
1-methyl-4-(2-methylpropyl),(±)



Morphinan-6-one,4,5-epoxy-3-methoxy-17methyl-,(5α)-,[R-(R*,R*)]
-2,3-dihydroxybutanedioate

As part of this NDA the applicant has submitted the results of four in vivo pharmacokinetic studies. These studies were designed to investigate the pharmacokinetics of both the individual components of the product given singly and in combination. In addition the

effect of gender and formulation effects were also investigated. As part of the clinical development of this product a pk/pd study was conducted to investigate the additive effects of combining an opioid analgesic with a NSAID. This information along with in vitro dissolution data makes up the core of information regarding the biopharmaceutic portion of this application. At this time the application is incomplete in two respects:

1.) All of the pharmacokinetic studies and most of the clinical development of this product was carried out using doses of two tablets (15mg HC and 400mg IBU). As single tablet doses are going to be used, it should have been investigated to demonstrate the dose proportionality of the finished dosage form.

2.) The applicant did not perform a food effect study. Such a study has been a pre-approval requirement for controlled release drug products for a number of years and has over the last two years been extended into the immediate release category.

These "deficiencies" in the package were noted in the filing memo for this application. In negotiation with the applicant prior to the filing date they admitted that these requests had been made during the development of this product but they had "slipped through the cracks". A decision was made by the reviewing medical division that as the applicant is making a good faith effort to correct these deficiencies and that completion of these items is expected shortly, that the submission of them should not be a condition of approval. This finding was based partly on the well known nature of both drugs, given both singly and in combination with other agents. It was decided that until completion the outstanding nature of these items would be reflected in the proposed package insert. These statements will indicate that the effect of food on the dosage form is unknown and that dose proportionality has not been demonstrated.

II. Recommendation

At the present time the sponsor is rapidly bringing these two "deficiencies" into compliance. A protocol was submitted to the Agency for review in Sept. for a three-way crossover study comparing a single tablet to two tablets with and without food. At the present time (Jan. 1997) the clinical portion of the study is done and the applicant is expecting submission of the data in the first 2 months of 1997. As both of the components of this product are well known and are not considered "bio-problem" drugs, the filing of this application was acceptable given that the applicant has initiated positive action to resolve these issues in a rapid manner.

Given this agreement with the applicant, the only outstanding issue from a biopharmaceutic perspective is the final selection of an appropriate in vitro dissolution method. The proposed method has been evaluated by both this reviewer and the reviewing chemist (Ms. Charlotte Yaciw) and found to be deficient (i.e., it lacks sensitivity). This was conveyed to the applicant in a memo dated Oct. 3, 1996. Until this issue is resolved the application can only be considered approvable from a biopharmaceutic perspective.

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Appendix I-Studies

III. PK Studies Overview

As noted in the background section of this NDA, the applicant submitted four in vivo pharmacokinetic studies. These studies encompass two different strengths of product, two different formulations, and differences in manufacture. The final product was studied pharmacokinetically in a head-to-head manner with the clinically studied formulation in study VP-30. From a pharmacokinetic standpoint the studies were well designed and incorporated adequate numbers of subjects. Although one of the four studies used a dose ratio of HC to IBU that is not being approved, it is being included in this review as this study addresses the issue of individual components vs. finished product (i.e. an interaction study). While it is true that the Agency is awaiting the results from a single dose pk study and a food effect study, there is sufficient breadth of information present in the NDA for review given the nature of the products involved.

IV. Analytical Methods

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information

IV. Summary of In Vivo Pharmacokinetic Trials

Study#VP-02: *Single-dose, Three-Way Crossover Bioavailability Study of Vicoprofen® (hydrocodone bitartrate 5mg with ibuprofen 200mg) and Its Active Components.*

As noted in the title above, this study was designed to investigate the interaction between the individual components of the dosage form and the proposed dosage form. This study is noteworthy as it is one of the first studies done in the development of this NDA and as such uses a ratio of HC to IBU that was subsequently abandoned. The product in this study uses 5mg of HC compared to 7.5mg of HC in the final to-be-marketed dosage form, but is otherwise the same product. This increase in the opioid component of the product was done based on both a revised potency ratio for HC and also with clinical evidence of a need to increase the HC to maintain/achieve effective analgesia. The study's continued applicability to this application is that, as a "drug interaction" study, the end-point of interest is not strict bioequivalence (although it would be preferable) but to detect if either component hinders or accelerates the absorption/elimination of the other. As such, the formulation differs only in the amount of HC present in each tablet, and as gross measures of "equivalence" are employed, it is acceptable.

The study itself was a straight forward three-way bioequivalency study. A total of 26 healthy male subjects were enrolled in this trial and successfully completed all three phases of the trial. Attached as pages 2-7 of Appendix I are the study summary sheets and supportive data from this trial. Reproduced below is a summary data table detailing the observed differences seen between the test (Vicoprofen-5®) and reference products:

Study VP-02, Mean Pharmacokinetic Data (%C.V.)

	Hydrocodone			Ibuprofen		
	Vicoprofen-5® (2 tablets)	Hydrocodone (2x5mg tabs.)	Log Transformed 90% C.I.	Vicoprofen-5® (2 tablets)	Ibuprofen (2x200mg tabs.)	Log Transformed 90% C.I.
AUC0-inf*	123(38%)	121(36%)	94-107	99(18%)	108(20%)	89-99
Cmax*	18.6(22%)	16.9(22%)	101-117	27.2(20%)	23.7(16%)	105-127**
Tmax (hrs)	1.3(35%)	1.7(52%)	n.a.	2.2(53%)	2.3(55%)	n.a.
T1/2 (hrs)	4.4(36%)	4.2(35%)	n.a.	1.6(24%)	1.9(21%)	n.a.

*AUC0-inf units for HC=ng*hr/ml, for IBU=ug*hr/ml
Cmax units for HC=ng/ml, for IBU=ug/ml
**Confidence Interval outside the 80-125% acceptance limit.

Technically, the study that the sponsor performed here, a three-way crossover study, to investigate the effect of drug-drug interaction in a combination product, is not properly designed. Instead of using a three-way model, the study should have been a randomized four-way trial. The leg of the trial that is missing is the administration of hydrocodone and ibuprofen concomitantly as two immediate release components administered together. Although seemingly repetitive, this treatment leg would be able to establish whether or not there was a drug interaction that was not formulation based. It would also establish the degree of in vivo bioavailability by using an "idealized" i.e., solution reference treatment for each component. Ideally such a treatment leg would utilize commercially available liquid dosage forms administered in a combined manner. The failure of the sponsor to do so in this study is critical but not fatal to the application. With the existence of in vivo clinical data supporting the approval of this application the need for definitive bioavailability is somewhat reduced but not removed. The study itself does demonstrate the relative bioavailability of the test product to "reference products", but the reference products used were manufactured by the applicant and were not approved products. While the two reference products do meet the USP specifications for hydrocodone and ibuprofen tablets, this is not an assurance of in vivo bioequivalency with an approved product. Had there not been adequate in vivo clinical data and had the two components in question not been drugs with a long history of marketing and use, then the acceptance of this study for the purposes of establishing the lack of a combination drug interaction would not be possible.

As noted earlier, strict bioequivalence is not a requirement for this study, per se. At the request of this reviewer the applicant did provide a supplemental analysis of the data from this trial that included calculation of log transformed confidence intervals. From their analysis there appears to be a slight difference in the peak plasma levels produced by IBU. Examination of the individual plasma concentration profiles (Appendix I, page 6) shows a fair degree of variability in the data. This variability is reflected here in the calculation of Tmax which for both products has a %CV in the 50's. This variability is not especially surprising as the pka for IBU is approximately 5.5 and as such is poorly soluble in the gastric fluid. Gastric emptying time and accordant transit time into the high pH in the small intestine is being translated into both the Cmax and Tmax values. The fact that the Vicoprofen-5® tablets show higher Cmax values than those from the reference ibuprofen treatment, suggests that the formulation of the ibuprofen product may be less than ideal. In any case the magnitude of the difference between the two products is small and there is no sign of any significant differences beyond this. From a therapeutic standpoint, there does not appear to be any meaningful interaction between the individual components.

Study#VP-30: *A Single Oral Dose, Two-Way Crossover Bioequivalence Study Comparing Direct Tablets to Tablets of Vicoprofen® (hydrocodone bitartrate with ibuprofen).*

As part of the manufacturing scale up for this product the applicant switched from . Prior to the change the applicant was purchasing IBU drug substance from . This material came from the supplier ready for use where 318mg of the contained 200mg of actual IBU. This change in formulation is discussed in more detail in the chemistry review.

Attached in Appendix I, page 9 is a comparative formulation between the

This study was designed to demonstrate bioequivalence between the two formulations given as a dose of two tablets of either formulation (15mg Hydrocodone and 400mg ibuprofen) in a random manner with a 7 day washout period between treatment groups. A total of 33 subjects were enrolled in this trial (14 males and 19 females). Two subjects were withdrawn from this trial (1 male and 1 female) due to abnormal lab values prior to the second treatment phase, leaving 31 complete sets of data. Due to the number of subjects present in this study the applicant was asked to undertake a secondary analysis of the data to evaluate gender effects. Attached in Appendix I as pages 8-18 are the associated study summary sheets and supportive data from this trial. Reproduced below is a summary data table from the appendix.

Study VP-30, Mean Pharmacokinetic Data (%C.V.)

	Hydrocodone			Ibuprofen		
			Log Transformed 90%C.I.			Log Transformed 90%C.I.
AUC0-inf*	211.7(33%)	216.2(25%)	99.1-109.8	131(29%)	135.6(26%)	98.7-108.4
Cmax*	27(35%)	27.3(22%)	96.8-110.6	28.5(23%)	30.2(23%)	97.4-115.1
Tmax (hrs)	2.1(83%)	1.7(65%)	n.a.	2.8(81%)	1.78(101%)	n.a.
T1/2 (hrs)	4.6(29%)	4.5(25%)	n.a.	2.5(39%)	2.2(18%)	n.a.

*AUC0-inf units for HC=ng*hr/ml, for IBU=ug*hr/ml
Cmax units for HC=ng/ml, for IBU=ug/ml

Examination of the data from this study indicates that the two formulations are bioequivalent. What is of interest from this data is the continued variability seen in the Tmax values. In this study, unlike the previous one, there is not a statistical difference in Cmax for IBU, even though the Tmax values are different. Interestingly, HC also shows wide variability in Tmax and yet has a relatively tight confidence interval for Cmax, suggesting, but not necessarily proof of, the proposed solubility and formulation issues of IBU raised in the review of Study#VP-02. In any event, the applicant, through this study, has successfully linked their to-be-marketed formulation to their clinically studied formulation.

As noted before the applicant at the request of the FDA used the data obtained in this trial to assess the presence or absence of a gender effect on the pharmacokinetics of HC and IBU. The applicant did not understand the FDA guidance properly and initially did an analysis within gender across dosage form, that is male vs. males and females vs. females While an interesting way to look at the data, this analysis (referred to by the applicant as the primary gender analysis) does not answer the question of is there a difference in the pharmacokinetics of HC and IBU based on gender alone? This issue was addressed by the applicant by a second analysis (referred to by the applicant as the secondary gender analysis) after input from the Agency. Appendix I page 17 contains the summary statistical data tables for the so-called "primary analysis". As it does not really address the issue at hand it is included in the appendix for interest only. The proper gender analysis (the so-called "secondary analysis") is summarized below (the supportive statistical tables are attached in Appendix I as page 18):

Study#VP-30, Secondary Gender Analysis

	Females (n=18)	Males (n=13)	Log Transformed 90% C.I.
Hydrocodone			
AUC0-inf(ng*hr/ml)	210.53	213.41	78.5-116.9*
Cmax(ng/ml)	26.53	27.69	80.9-118.8
Tmax(hrs)	2.61	1.44	-
Cl(ml/min/kg)	1.85	1.4	
Ibuprofen			
AUC0-inf(ug*hr/ml)	143.89	117.51	102.7-141.7*
Cmax(ug/ml)	27.99	29.26	80.9-110.2
Tmax(hrs)	1.89	1.39	-
Cl(ml/min/kg)	0.72	0.68	

	Females (n=18)	Males (n=13)	Log Transformed 90% C.I.
Hydrocodone			
AUC0-inf(ng*hr/ml)	220.63	210.03	89.7-122.9
Cmax(ng/ml)	28.41	25.7	94.3-124.8
Tmax(hrs)	3.57	1.81	-
Cl(ml/min/kg)	1.77	1.42	
Ibuprofen			
AUC0-inf(ug*hr/ml)	144.91	122.84	99.5-137.9*
Cmax(ug/ml)	30.39	29.93	88.2-118.2
Tmax (hrs)	2.67	1.08	-
Cl(ml/min/kg)	0.71	0.64	

*Outside of standard Bioequivalency acceptance limit of .

Examination of the data presented above indicates that for ibuprofen there is not a detectable gender difference. The data for hydrocodone does suggest a possible gender difference with Cl being approximately 25% faster for females than males on a per kilogram basis. The high degree of agreement between the calculated Cl values between the two dosage forms indicates that this is a reproducible difference and is not likely to be an artifact of the data. Whether or not this is a clinically significant difference is impossible to tell from this data. Beyond this alteration in Cl there does not seem to be "gender" based difference for any of the other parameter values contained either in this summary table or in the appendix.

Picking up on an issue raised earlier in this review is the apparent high degree of variability present in the Tmax data. Although split up into a number of different comparisons there appears to be some difference in the Tmax values for HC and especially for IBU. Whether or not these differences are gender linked or is more a function of formulation issues inherent in each dosage form is unknown at this time. Attached as pages 19 and 20 in Attachment I are the individual subject plots of IBU from both the formulations. For both males and females there appears to be quite a bit of variability in the plasma levels. In regards to Tmax the subjects break down as follows:

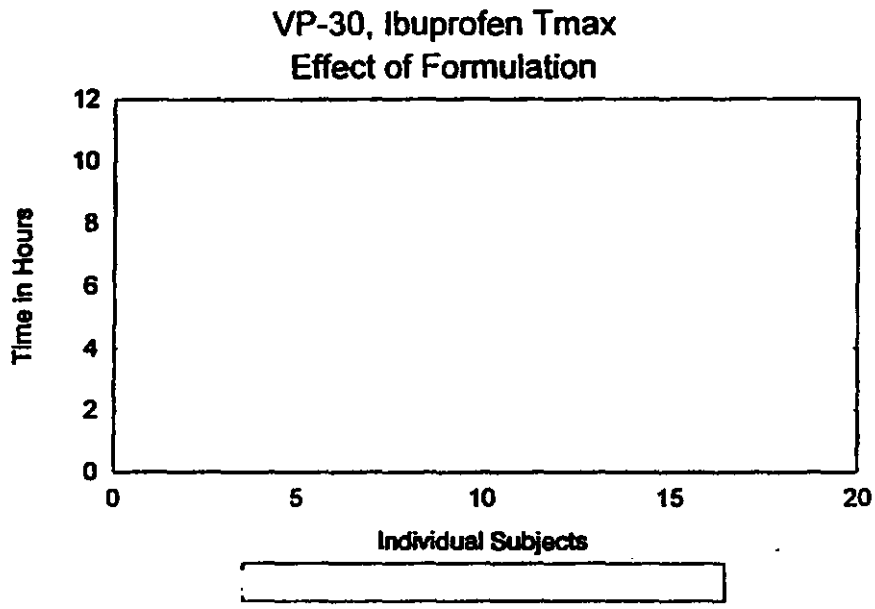
Study#VP-30, Ibuprofen Tmax Comparison

Time in hrs.	# of Observations Females (n=18)	# of Observations Males (n=13)	# of Observations Females (n=18)	# of Observations Males (n=13)
0				
0.5	5	4		1
1	4	7	4	7
1.33	2	1	2	1
1.67			2	1
2				
2.33				
2.67				
3	2			1
3.33			1	
3.67	1	1		
4	1			
5	2		7	2
6			1	
8	1			
10			1	
12				

If we use 2 hrs. a break-point for Tmax it works out that for the formulation only 44% of female subjects and 77% of male subjects have peak concentrations occurring at 2 hours or less. The formulation does improve this situation somewhat by raising the 2hr. rates to 61% and 92% for females and males, respectively. Considering that this product is intended as an analgesic, this data suggest that there may be problems with either onset of effect or the peak magnitude of effect in females. Possible explanations of this finding for IBU include solubility issues, retention of the dosage form in the stomach, formulation related issues, and/or gender related issues such as retention time or gastric pH .

As mentioned in the discussion on page 9, it is impossible to tell whether or not the variation seen in Tmax is due to gender or to other formulation specific issues or a combination of both. While an assessment of Tmax variability is not specifically part of a general gender analysis, it was decided by this reviewer to look at the intra-subject distribution of Tmax values as primarily a formulation issue. The reasoning being that if a formulation related pattern developed then one could more easily remove gender as a cause of Tmax variability. Reproduced below is a plot of the Tmax values for each subject and treatment. Inspection of the figure reveals that of the 18 pairs, 13 of them show a reduction in Tmax from

3 pairs are unchanged, and 2 pairs show a prolonged Tmax with the



While other factors certainly are playing a part in this issue, i.e. the inherently poor solubility of IBU, it appears from this perspective that the formulation and/or method of /manufacture, in addition to intrasubject variability, is the underlying issue with regards to changes seen in the distribution of Tmax values. Due to the study design used in this trial the relative contributions of intrasubject variability and "formulation" effects cannot be separated. While they both contribute to the observed variability, it is this reviewer's opinion that the "formulation" effects are driving the differences observed in the data.

Study#VP-22: *A Characterization of the Pharmacokinetic/Pharmacodynamic Relationship of Single Oral Doses of Vicoprofen® (hydrocodone bitartrate 15mg with ibuprofen 400mg) Tablets for the Treatment of Acute Postoperative Dental Pain*

This study was undertaken as part of the clinical development plan to investigate the use of Vicoprofen® in the treatment of dental pain. The pain model used was the standard impacted molar extraction model. Anesthesia was accomplished with a combination of nitrous oxide and either a short acting barbiturate or benzodiazepine. The only opioid analgesic allowed in the trial was small doses of sufentanil citrate. A total of 72 subjects were enrolled in the trial (36 males and 36 females) and completed all phases of the trial. As part of the trial all subjects were asked to rate their pain according to two scales: 1.) a four point categorical scale for pain intensity and 2.) a five point categorical scale for pain relief. In addition the subjects were asked to indicate the time when first noticeable pain relief occurred and to provide an overall

assessment of their pain relief at the conclusion of the study. Attached as pages 21-27 in Appendix I are the associated study summary sheets and supportive pk/pd data from this trial.

It should be noted that this trial employed a "double-dummy" design, in that all treatments had a corresponding placebo. That is the subjects randomized to receive Vicoprofen® tablets also received a placebo suspension and the subjects who received the active ibuprofen suspension had a placebo tablet. By implication there was also a true placebo treatment group which received both the placebo tablet and placebo suspension.

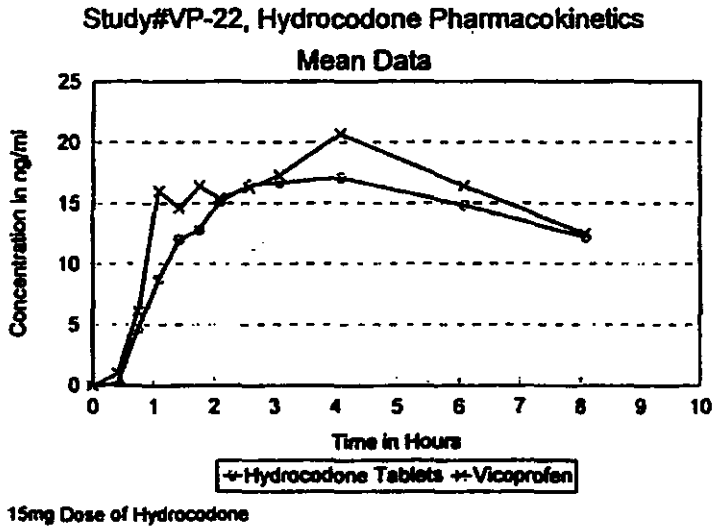
Pharmacokinetic Analysis

The pharmacokinetic results for HC from this study are very comparable to those in the previous study (VP-30). The only obvious difference in the data is the prolonged Tmax and $T_{1/2}$ noted in this study. The significance of this prolonged Tmax will become evident in the analysis of the pharmacodynamic portion of this NDA. It is likely due to the combination of the effects of dental surgery and pain on gastric secretions and G.I. transit time (i.e, a fight or flight response). In general these factors tend to slow down gastric transit and can result in prolonged Tmax values. Reproduced below is a summary data table for HC:

Study#VP-22, Hydrocodone-Mean Pharmacokinetic Data (%CV)

15mg Dose	Cmax (ng/ml)	Tmax(hrs)	AUC_{0-inf}	AUC_{0-t}	$T_{1/2}$ (hrs)
Hydrocodone Tablets	22.31(40%)	3.43(64%)	217.55(37%)	106.1(44%)	6.21(30%)
Vicoprofen	28.28(35%)	2.94(58%)	283.79(94%)	120.33(25%)	7.71(128%)

From the table above the calculation of AUC_{0-inf} by the applicant appears to be flawed. Inspection of the raw data indicates that this value of AUC is being driven by two "outliers". They do not appear to be due to analytical error and the overall shape of their plasma level time curves does not appear out of the range of possibilities. For this reason and the fact that there was not a good criteria to use to reject the data, these two subjects were retained in the analysis. Reproduced below is a plot of the mean HC data from this study:

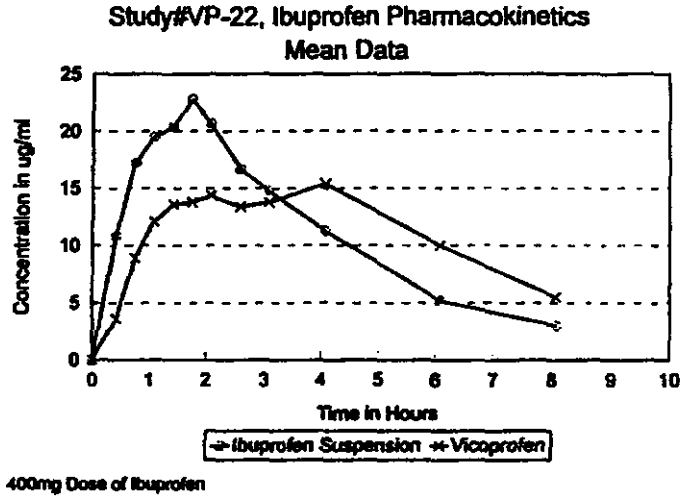


As for the ibuprofen component of this study, the data results are somewhat mixed. Some of the results (Cmax, half-life) tend to agree with the previous study, while other parameters do not (AUC0-inf, and Tmax). Reproduced below is a summary data table from this trial:

Study#VP-22, Ibuprofen-Mean Pharmacokinetic Data (%CV)

400mg Dose	Cmax (ng/ml)	Tmax(hrs)	AUC_{0-inf}	AUC_{0-t}	$T_{1/2}$ (hrs)
Ibuprofen Suspension	29.09(24%)	1.49(60%)	98.07(29%)	89.16(25%)	1.88(26%)
Ibuprofen (Vicoprofen®)	28.12(31%)	2.74(62%)	105.94(29%)	87.87(26%)	2.15(28%)

On the surface of the data there does not appear to be any remarkable differences between the two treatments except for Tmax. When the mean data is plotted out, however, a slightly different picture emerges:



This data clearly shows a lag for the plasma concentrations for ibuprofen from the Vicoprofen® tablets. The clinical implications of this could be dramatic as dental pain, i.e. "bone pain", is usually more response to NSAID's than to opioids. Admittedly the comparison is between that of a tablet and a suspension, and one could in general expect quicker levels with the suspension treatment, but the magnitude of the difference in mean levels is more than one would normally expect. Examination of the individual subject data (page 24, Appendix I) does show a delay in the inital rise in plasma concentrations for the mean data, but it also shows that there is a high degree of inter-subject variability. This suggests that while the mean data may be suppressed, this "suppression" in plasma levels is due to averaging concentrations across the timepoints. For any individual subject it is equally likely that they will get "rapid" pain relief or pain relief of a somewhat slower onset.

Pharmacodynamics

The pharmacodynamic endpoints of interest in this study are time to onset of measurable pain relief (a measure of rate), pain intensity difference (a measure of the extent of pain relief), and time to remedication (a measure of duration). In order to collect information in all groups, including placebo, all subjects were encouraged to refrain from re-medication until 2

hours post-dose. Once re-medication/rescue occurred, the subject was dropped from the pharmacodynamic assessment portion of this trial.

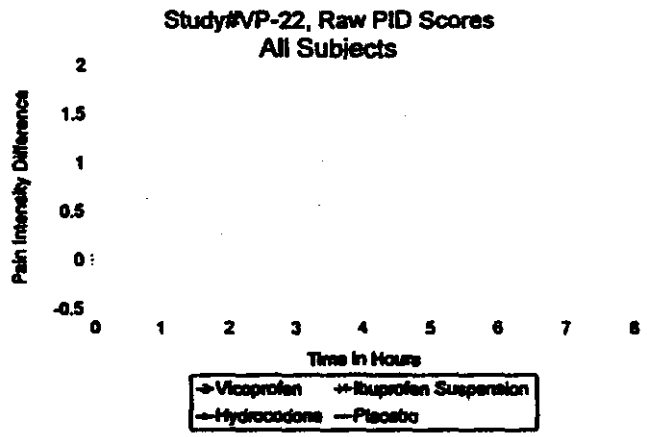
Onset of pain relief was assessed by asking all subjects to record on their case report forms when they first noticed pain relief. This data was then tabulated and a median value was calculated.

Study#VP-22 Time to Onset (hrs.)

	Placebo n=18	Hydrocodone n=18	Ibuprofen n=18	Vicoprofen® n=18
Patients with positive pain relief	12 (66.7%)	9 (50%)	18 (100%)	15 (83.3%)
Median Time	0.84	>1.67	0.33	0.33

From this data an interesting result is that placebo actually beats the hydrocodone treatment phase. While it is not suprising that the pure opioid did poorly in this assessment, it is unusual that the median time to pain relief was >1.67hrs. Calculation of a time to onset after this timepoint was not possible due to dropouts. As for Vicoprofen® it shows a high percentage of early onset scores that are comparable to the ibuprofen suspension. While not a definitive test, one of the desirable properties of any analgesic is an early onset/perception of pain relief. On the basis of this data it can be concluded that Vicoprofen® does demonstrate an early onset of pain relief in this model. It also suggests that the majority of its activity in this model is due to the ibuprofen component and not the opioid component.

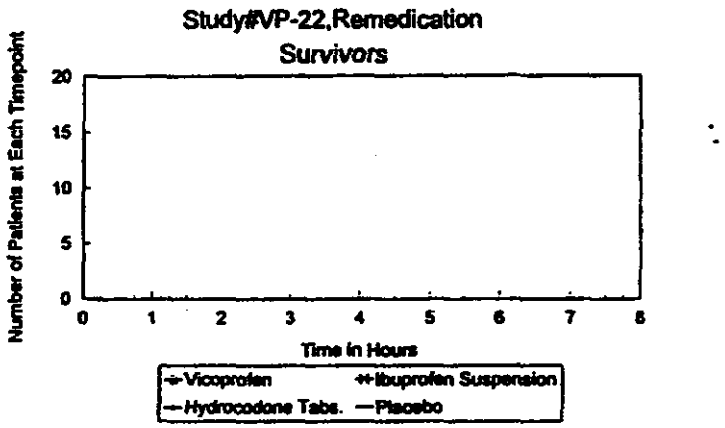
As for the actual pattern of pain relief, each subject was asked to initially rate their pain on a 4 point scale. Subsequent to dosing the subjects were asked to reassess their pain relative to their original score. This difference in pain is referred to as the Pain Intensity Difference or PID. In a general sense, using this pain model, a good analgesic is one that can cause a reduction in pain of 1 unit. Attached in Appendix I as pages 25-27 are the PID scores for all subjects over time and by sub-set (see below). A graphical representation of the PID scores for all subjects and all treatments is presented below:



Analysis of the PID data reveals an unexpected finding that the IBU suspension performed better than the Vicoprofen® combination product (unexpected in that one would normally assume that hydrocodone, a known opioid analgesic, would be expected to potentiate the analgesic effect of ibuprofen). The reason for this is unclear but is thought to be due to the

observation that the peak plasma levels of IBU produced by the suspension are superior to those from the Vicoprofen® tablet. In an attempt to find an association between the PID scores and treatments the applicant did alternative analyses of the PID data using initial assessment of pain as a variable. Copies of the results of these analyses are attached as pages 26 and 27 of Appendix I. Neither attempt by the applicant to use stratification by initial pain rating appreciably improved the scoring of this trial. As it was the conclusion drawn from this study by this reviewer that the combination of HC with IBU was inferior to IBU suspension in terms of overall pain relief. Considering that the dose of IBU is identical across the two treatment groups it implies that rate is a primary determinant.

As for the final pharmacodynamic measure, time to remedication, a plot of time to remedication as the number of subjects remaining in the trial versus time was prepared:



The data represented here is consistent with that seen with the PID scores, that is that the IBU suspension was superior to all treatments. Vicoprofen® on the other hand was inferior to IBU suspension for the majority of the observation internal as measured by dropout rate. It was superior to placebo and to single entity HC.

The net results of the pharmacodynamic analysis is that Vicoprofen® is an analgesic, it has a rapid onset of action, and it is superior to placebo and single entity HC in acute postoperative dental pain. It is, surprisingly inferior to IBU suspension. A possible explanation of this finding may be related to the double dummy nature of this protocol. An examination of IBU pharmacokinetics from both the IBU suspension and the Vicoprofen® tablet suggests that the placebo suspension may have impeded the absorption of IBU from the tablet. In an effort to assess this the applicant undertook a study to investigate the formulation interaction effects of the suspension formulation.

Study#VP-27: A Single Oral Dose, Three Way Crossover Pharmacokinetic Study Comparing Vicoprofen (hydrocodone bitartrate with ibuprofen) Administered Alone and in Conjunction with a Sorbitol-Containing Suspension.

This study was designed to investigate the impact of a sorbitol containing placebo suspension on the absorption of IBU from the Vicoprofen® tablet and from IBU tablets. This study was an outgrowth of the inconsistent clinical results seen in study VP-22. This was

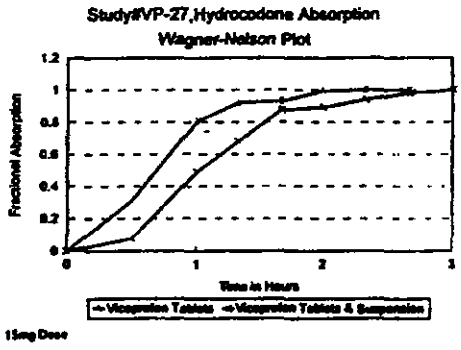
designed as a three-way crossover study using doses of two tablets of Vicoprofen® versus the combination of Vicoprofen® tablets with a sorbitol suspension and ibuprofen tablets administered alone to 34 healthy male and female subjects. Attached as pages 28-37 are the study summary sheets and supportive data tables. A summary data table is presented below:

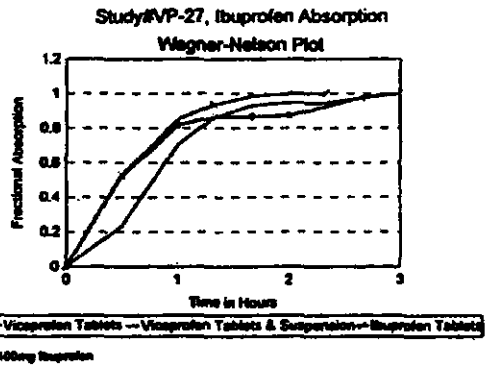
Study#VP-27, Mean Data (%CV)

	Hydrocodone		Ibuprofen		
	Vicoprofen	Vicoprofen & Suspension	Vicoprofen	Vicoprofen & Suspension	Ibuprofen Tablets
Cmax*	29.7(23%)	28.9(23%)	32.5(24%)	33.2(19%)	35.8(16%)
Tmax (hrs.)	1.73(45%)	2.58(40%)	1.73(69%)	1.98(60%)	1.67(54%)
$T_{1/2}$ (hrs.)	4.22(23%)	4.09(29%)	2.01(32%)	2.03(44%)	1.92(20%)
AUC_{0-inf}*	211.1(28%)	212.7(28%)	118.2(29%)	122.1(32%)	129.2(30%)

*AUC_{0-inf} units for HC=ng*hr/ml, for IBU=ug*hr/ml
Cmax units for HC=ng/ml, for IBU=ug/ml

The results of this study suggest that the placebo suspension that was used in the clinical study (VP-22) did not significantly impact the AUC or Cmax of IBU from Vicoprofen® tablets. There was, however an impact on the rate of absorption of both HC and IBU as manifested by results of a Wagner-Nelson analysis performed by this reviewer:





Examination of the Wagner-Nelson plots suggests a modest absorption related effect that tends to slow the initial rate of drug absorption. Even so it should be noted that in the dynamic portion of the last study the Vicoprofen® leg of the study was able to demonstrate onset of pain relief within the first half-hour. The fact that it was able to so undercuts the applicant's hypothesis that sorbitol exhibited an inhibitory effect on the absorption of drug from the GI tract. Clearly there was some effect, but Vicoprofen® itself has a significant degree of variability built into it as measured by Tmax in Study#VP-30 (page 7).

The possibility remains that the reduced absorption seen in Study#VP-22 was due to some physiological stress factor related to the "trauma" of the dental procedure itself. The suspension treatment, with drug already in the solubilized and dispersed particulate states would be less effected by such changes. A solid tablet that has to undergo the various stages of dissolution prior to absorption would be subject to changes in the rate and composition of gastric secretions and gastric motility brought about by the body's natural response to injury and

inflammation secondary to the procedure. The present study was not designed to detect such changes and only demonstrates a modest lag in absorption rate.

In conclusion, the results of this study indicate that the relatively poor performance of the Vicoprofen® tablet in Study#VP-22 is not due to an interaction between the tablet and the sorbitol containing suspension treatment.

VI. In Vitro Dissolution

As part of this NDA the applicant, Knoll Pharmaceutical, has submitted in vitro dissolution data on both the ibuprofen and hydrocodone bitartrate components. The method and specification the applicant has proposed for both entities is as follows:

	USP23 Method (Proposed Method)	USP23 Revised Method
Apparatus	USP-1 (basket)	USP-2 (paddle)
Speed	150rpm	50rpm
Media	pH 7.2 phosphate buffer	pH 7.2 phosphate buffer
Volume	900ml	900ml
Specification	Q=70% at 30min.	Q=80% in 60min

This method is essentially the old USP 23 method for ibuprofen tablets. In the most recent USP 23 supplement (Official Nov. 15, 1996) this method was dramatically revised as shown in the table above (see Appendix I, page 38). Even before this revision the applicant was notified by the Agency on Oct. 3, 1996 that the original specification (and the method) were inadequate. Inadequate in that the in vitro performance of the product was very different from the proposed specification. Reproduced below is a summary table of the individual tablet component dissolution from two lots of Vicoprofen® that were used in the in vivo biopharmaceutics portion of the NDA:

Lot Number & Study	Component	Mean % Dissolved* (%CV)	Range
55-0392 Study #VP-22, 27, & 30	Hydrocodone	98% (3.4%)	
	Ibuprofen	97% (2.7%)	
055-K1080-PI-0295 Study #VP-30	Hydrocodone	103% (0.7%)	
	Ibuprofen	101% (0.7%)	

*% Dissolved at 30min using OLD USP 23 Method.

Analysis of the provided dissolution data clearly indicates that the proposed in vitro method is inadequate of assuring product quality except in the most gross manner. Additional dissolution profile data provided in the chemistry portion of the NDA demonstrated that the dissolution rate was fast enough to meet the proposed specification at 15min with little or no possibility of failure.

Unlike many products, the onset of effect of an analgesic is highly correlated with peak plasma levels and by extension with drug release from a dosage form. The current proposed in vitro dissolution specification (OLD USP Method) would allow for lots of drug to have a markedly different in vitro release profile and still past the "test". It is the opinion of both the chemistry and pharmacokinetic reviewers that prior to NDA approval the sponsor should initiate and report on alternative dissolution methods and medias that would provide a better basis for a release specification. This information has been conveyed to the sponsor (see Comment #2, below).

VII. Conclusions

Based on the four pharmacokinetic trials that were submitted in this NDA the following conclusions can be supported.

1. Neither hydrocodone or ibuprofen interact with the absorption or phamacokinetics of each other (Study VP-02).
2. The to-be-marketed formulation is bioequivalent to the clinically studied Vicoprofen® tablets
3. There is not a significant difference in the pharmacokinetics of ibuprofen based on gender. There does seem to be a somewhat faster clearance of hydrocodone (~20%) in female subjects. The cause of this increased clearance is unknown (Study VP-30).
4. Vicoprofen® tablets beat placebo in an acute dental pain model of analgesic effect but are generally inferior to ibuprofen suspension in terms of the onset of analgesic effect and dropout rate (Study VP-22).
5. The pharmacokinetics of Vicoprofen® tablets following a single two tablet dose have been determined.

VIII. Comments

1. At the present time the Agency is still awaiting a response from the applicant concerning a revised in vitro dissolution specification and revised labeling. Until these issues are resolved the application can only be considered approvable from a biopharmaceutic standpoint.
2. Although not a condition of approval, the Agency is also awaiting submission of the results of a single tablet pharmacokinetic study and a food-effect study for this product.

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

CC: NDA 20-716(ORIG),
HFD-550/DIV File
HFD-550/CSO/Lissante
HFD-880(Bashaw)
HFD-880(Fleischer)
HFD-850 (Mira Millison, Drug, Chron Files)
HFD-344(Viswanathan)

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Appendix I-Studies

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NDA/IND# 20-716 Suppl/Amend.# ORIG Submission Date: 4/26/96 Volume: 1.15

Study Type: Bioavailability Study # VP-02

Study Title: A single dose, three-way crossover study of Vicoprofen® to its active components

Clinical Investigator

Site

Analytical Investigator

Site

Single Dose: Y Multiple Dose: N Washout Period: Seven days

Cross-Over Y Parallel N Other Design:

Fasted Y Food Study N FDA High Fat Breakfast N

If fasted, how long (hrs.)? 10hrs.

Subject Breakdown

Normal Y Patients N Young Y Elderly N Renal Hepatic

Subject Type	Males		Group	Males	N=	26	M=	26	F= 0
Weight	Mean	168 Range	Group		N=		M=		F=
Age	Mean	24.8 Range	Group		N=		M=		F=
Subject Type			Group		N=		M=		F=
Weight	Mean	Range	Group		N=		M=		F=
Age	Mean	Range	Group		N=		M=		F=

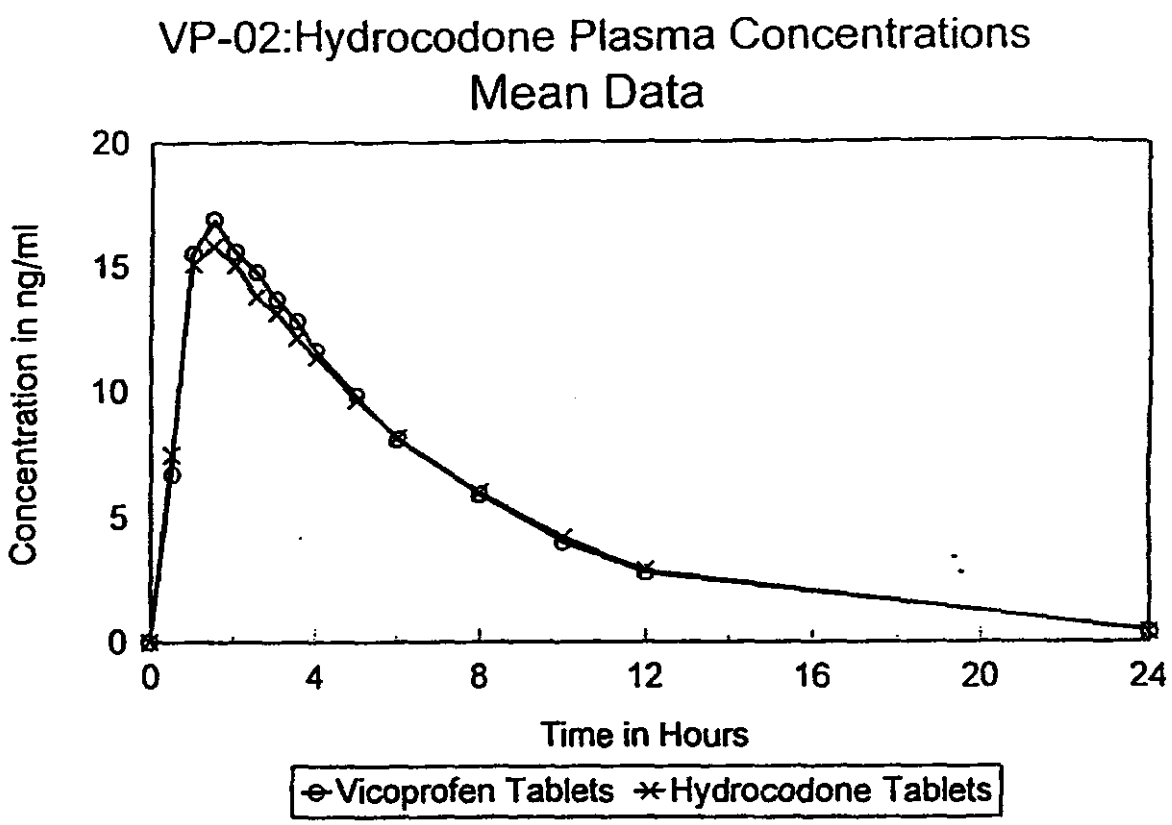
Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
Hydrocodone	10mg	tablet	5mg	02-0186	
Ibuprofen	400mg	tablet	200mg	29-0286	
Vicoprofen®*	10mg HCl/ 400 IBU	tablet	5mg HC/ 200mg IBU	H46-226	

*Experimental tablet formulation

Sampling Times

Plasma: 15ml samples, prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 hours after dosing.

	Hydrocodone	Ibuprofen
Assay Method:		
Assay Sensitivity		
Assay Accuracy		



10mg dose

HYDROCODONE PLASMA CONCENTRATIONS (ng/mL)
Mean (Std. Dev.)

Treatments:	VICOPROFEN® X 2 Tablets	HYDROCODONE 5 mg X 2 Tablets
TIME (HOURS)		
0.00	0.00 (0.00)	0.00 (0.00)
0.50	6.69 (4.85)	7.47 (4.18)
1.00	15.51 (5.48)	15.08 (4.14)
1.50	16.89 (4.28)	15.80 (4.35)
2.00	15.58 (3.94)	15.05 (3.60)
2.50	14.74 (3.74)	13.76 (3.61)
3.00	13.68 (3.70)	13.12 (3.35)
3.50	12.79 (3.85)	12.12 (3.07)
4.00	11.60 (3.33)	11.35 (3.24)
5.00	9.82 (2.89)	9.61 (2.70)
6.00	8.08 (2.97)	8.14 (2.06)
8.00	5.90 (2.49)	6.00 (2.28)
10.00	4.01 (2.01)	4.21 (1.66)
12.00	2.76 (1.51)	2.89 (1.61)
24.00	0.41 (0.63)	0.38 (0.61)

VP-02 Subjects Plasma Hydrocodone Concentration from Vicoprofen 400/10mg

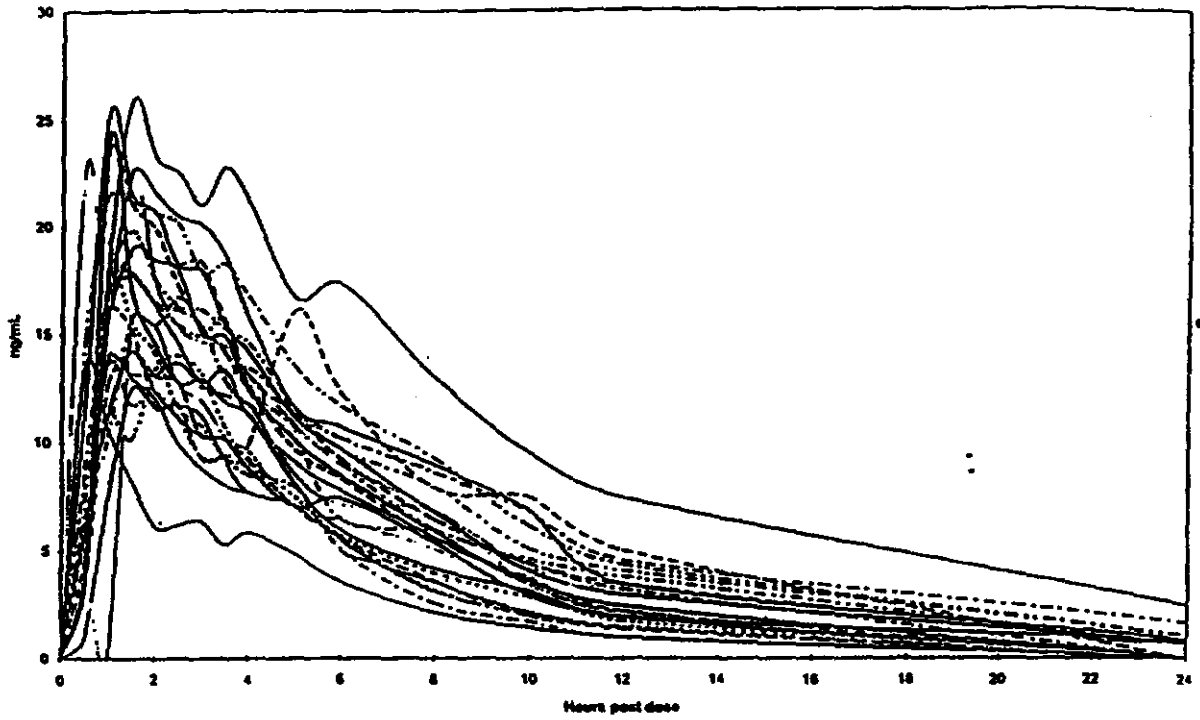


Figure 5

VP-02 Subjects Plasma Hydrocodone Concentrations *from* Hydrocodone 10mg

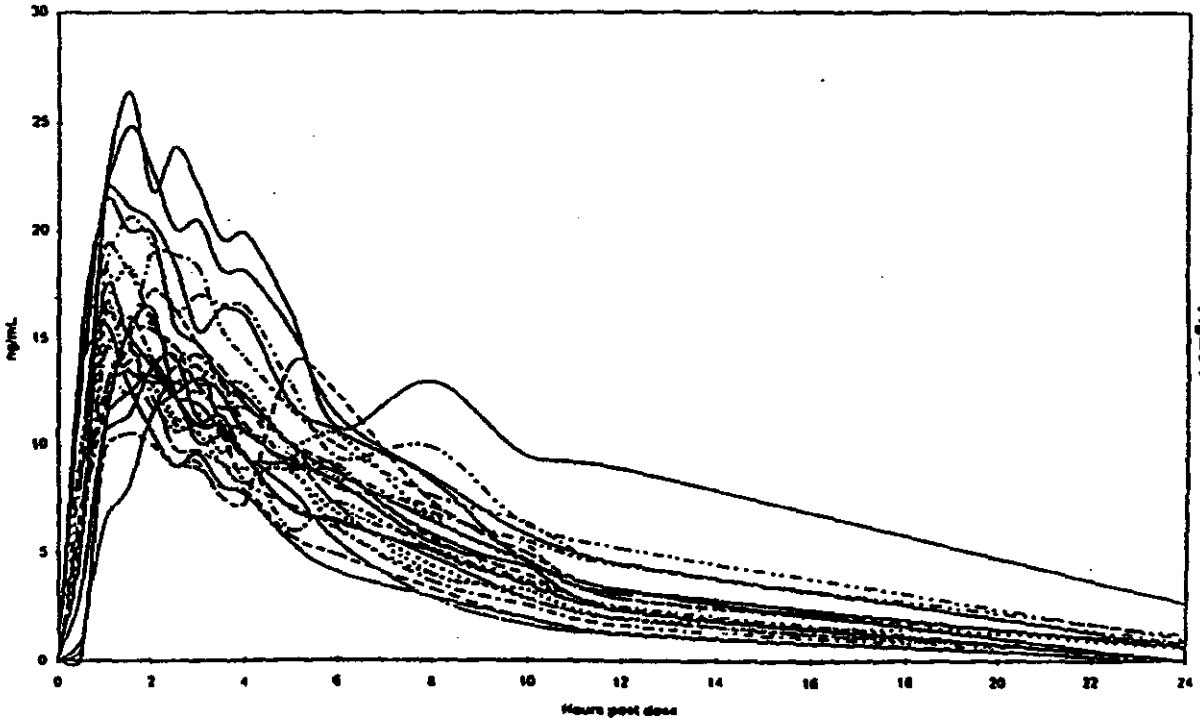
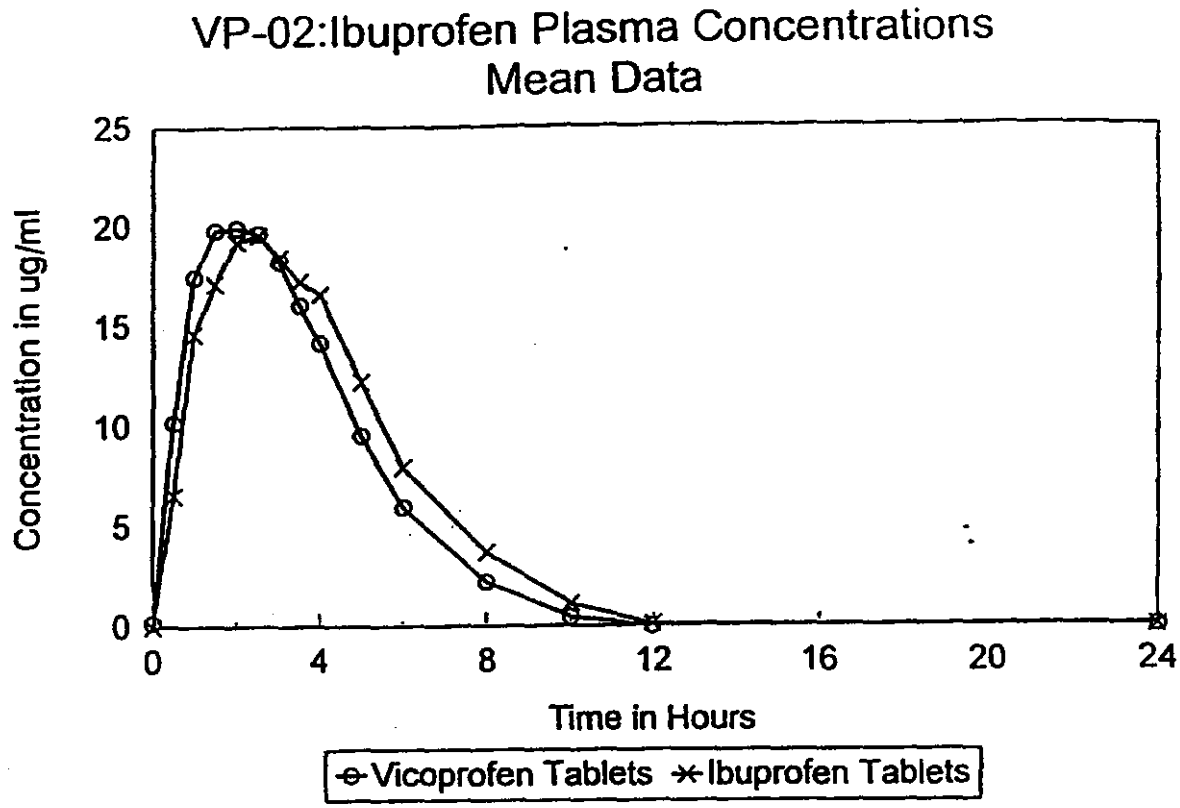


Figure 6



400mg Dose

IBUPROFEN PLASMA CONCENTRATIONS (mcg/mL)
Mean (Std. Dev,)

Treatments:	VICOPROFEN® X 2 Tablets	IBUPROFEN 200 mg X 2 Tablets
TIME (HOURS)		
0.00	0.19 (0.93)	0.00 (0.00)
0.50	10.17 (8.87)	6.55 (5.54)
1.00	17.44 (10.27)	14.58 (7.66)
1.50	19.76 (8.42)	17.07 (8.14)
2.00	19.89 (6.89)	19.19 (6.88)
2.50	19.61 (7.14)	19.51 (5.87)
3.00	18.21 (5.60)	18.42 (5.21)
3.50	16.04 (4.81)	17.20 (4.86)
4.00	14.14 (4.74)	16.57 (4.64)
5.00	9.50 (3.58)	12.20 (4.51)
6.00	5.95 (2.57)	7.92 (3.19)
8.00	2.22 (1.76)	3.70 (1.81)
10.00	0.45 (1.11)	1.15 (1.53)
12.00	0.00 (0.00)	0.10 (0.50)
24.00	0.00 (0.00)	0.00 (0.00)

VP-02 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/10mg

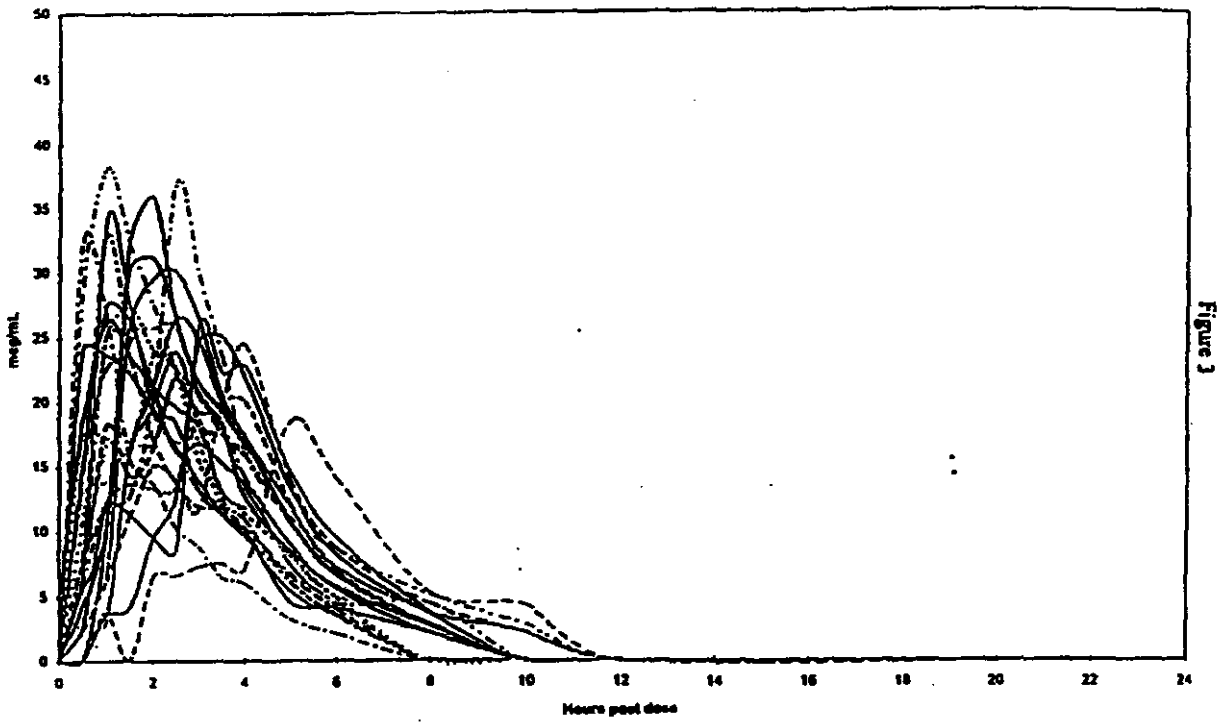


Figure 3

VP-02 Subjects Plasma Ibuprofen Concentrations from Ibuprofen 400mg

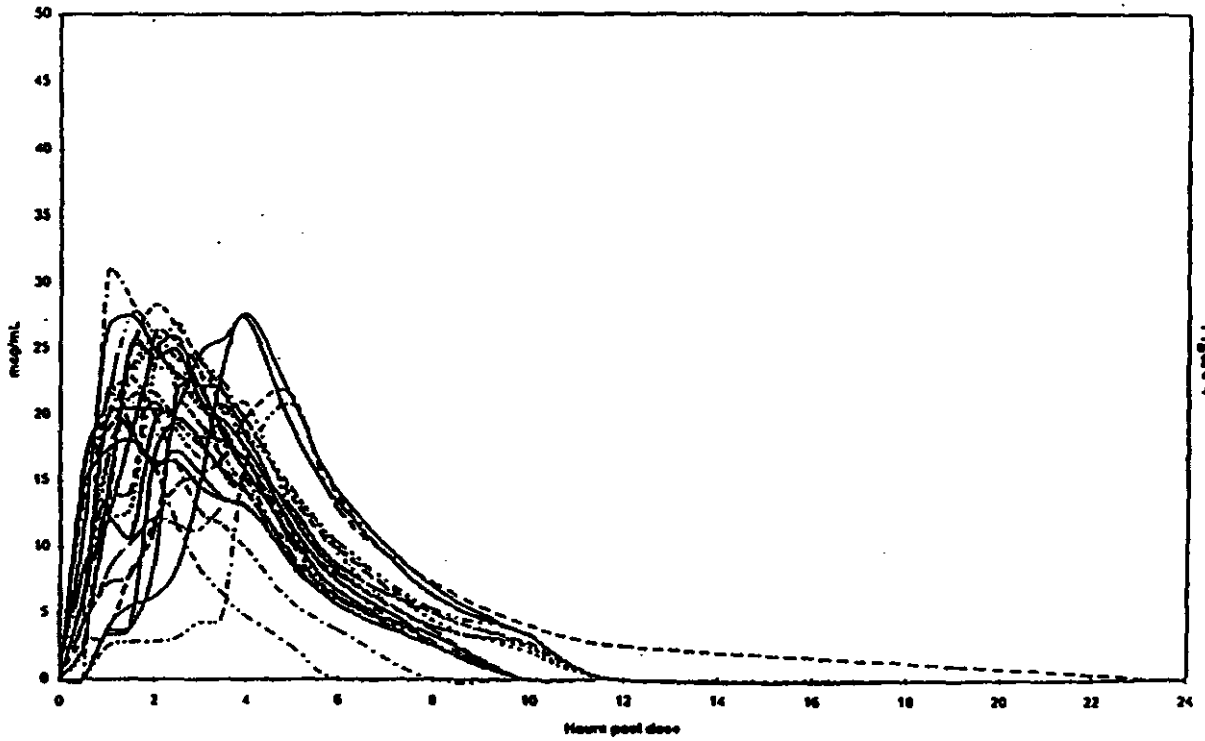


Figure 4

HYDROCODONE SUMMARY STATISTICS

PARAMETERS (UNITS)	VICOPROFEN® X 2 Tablets	HYDROCODONE 5 mg X 2 Tablets	ANOVA PR>F BY TREATMENT	POWER TO DETECT 20% DIFFERENCE
	MEAN (S.D.)	MEAN (S.D.)		
C_{max} (ng/mL)	18.55 (4.11)	16.88 (3.70)	0.043	SIG
T_{max} (Hour)	1.34 (0.47)	1.65 (0.87)	0.157	31
$t_{\frac{1}{2}}$ (Hour)	4.40 (1.61)	4.24 (1.49)	0.649	66
AUC_{∞} (ng/mL * Hr)	123 (47)	121 (44)	0.716	99

NOTE: SIG = Statistically significant.

	Hydrocodone LS Means		Hydrocodone Mean Ratio	90% Confidence Interval	
Parameter	VP 400/10mg	HC 10mg		lower	upper
ln C_{max}	2.895	2.807	1.09	1.01	1.17
ln $AUC_{(0-inf)}$	4.749	4.745	1.00	0.94	1.07

IBUPROFEN SUMMARY STATISTICS

PARAMETERS (UNITS)	VICOPROFEN X 2 Tablets	IBUPROFEN 200 mg X 2 Tablets	ANOVA PR>F BY TREATMENT	POWER TO DETECT 20% DIFFERENCE
	MEAN (S.D.)	MEAN (S.D.)		
C_{max} (mcg/mL)	27.18 (5.51)	23.65 (3.83)	0.017	SIG
T_{max} (Hour)	2.16 (1.16)	2.33 (1.26)	0.625	25
$t_{\frac{1}{2}}$ (Hour)	1.63 (0.39)	1.85 (0.38)	0.022	SIG
$AUC_{0-\infty}$ (mcg/mL * Hr)	99 (18)	108 (22)	0.008	SIG

NOTE: SIG = Statistically significant.

	Ibuprofen LS Means		Ibuprofen Mean Ratio	90% Confidence Interval	
Parameter	VP 400/10mg	Ib 400		lower	upper
ln C_{max}	3.291	3.150	1.15	1.05	1.27
ln $AUC_{(0-inf)}$	4.592	4.657	0.94	0.89	0.99

NDA/IND# 20-716 Suppl/Amend.# Orig. Submission Date: 4/26/96 Volume: 1.9

Study Type: Bioequivalence Study # VP-30

Study Title: A single oral dose, two-way crossover bioequivalency study of formulations.

Clinical Investigator

Site

Analytical Investigator

Site

Single Dose: Y Multiple Dose: N Washout Period: 7 days

Cross-Over Y Parallel N Other Design: n/a

Fasted Y Food Study N FDA High Fat Breakfast n/a

If fasted, how long (hrs.)? 10hrs.

Subject Breakdown

Normal Y Patients Young Y Elderly Renal Hepatic

	Subject Type	Males		Group	ALL	N=	33	M= 14	F= 19
Weight	Mean 184.3	Range		Group		N=		M=	F=
Age	Mean 31.7	Range		Group		N=		M=	F=
	Subject Type	Females		Group		N=		M=	F=
Weight	Mean 141	Range		Group		N=		M=	F=
Age	Mean 34.8	Range		Group		N=		M=	F=

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
	2 tablets	tablet	7.5mg HC/ 200mg IBU	55-0392	35,000
1	2 tablets	tablet	7.5mg HC/ 200mg IBU	055K1080P10295	2,700,000

Sampling Times

Plasma 12ml samples, prior to dosing and at 30, 60, 80, 100, 120, 140, 160, 180, 200, 220min., and 4, 5, 6, 8, 10 and 12 hours after dosing

Assay Method:

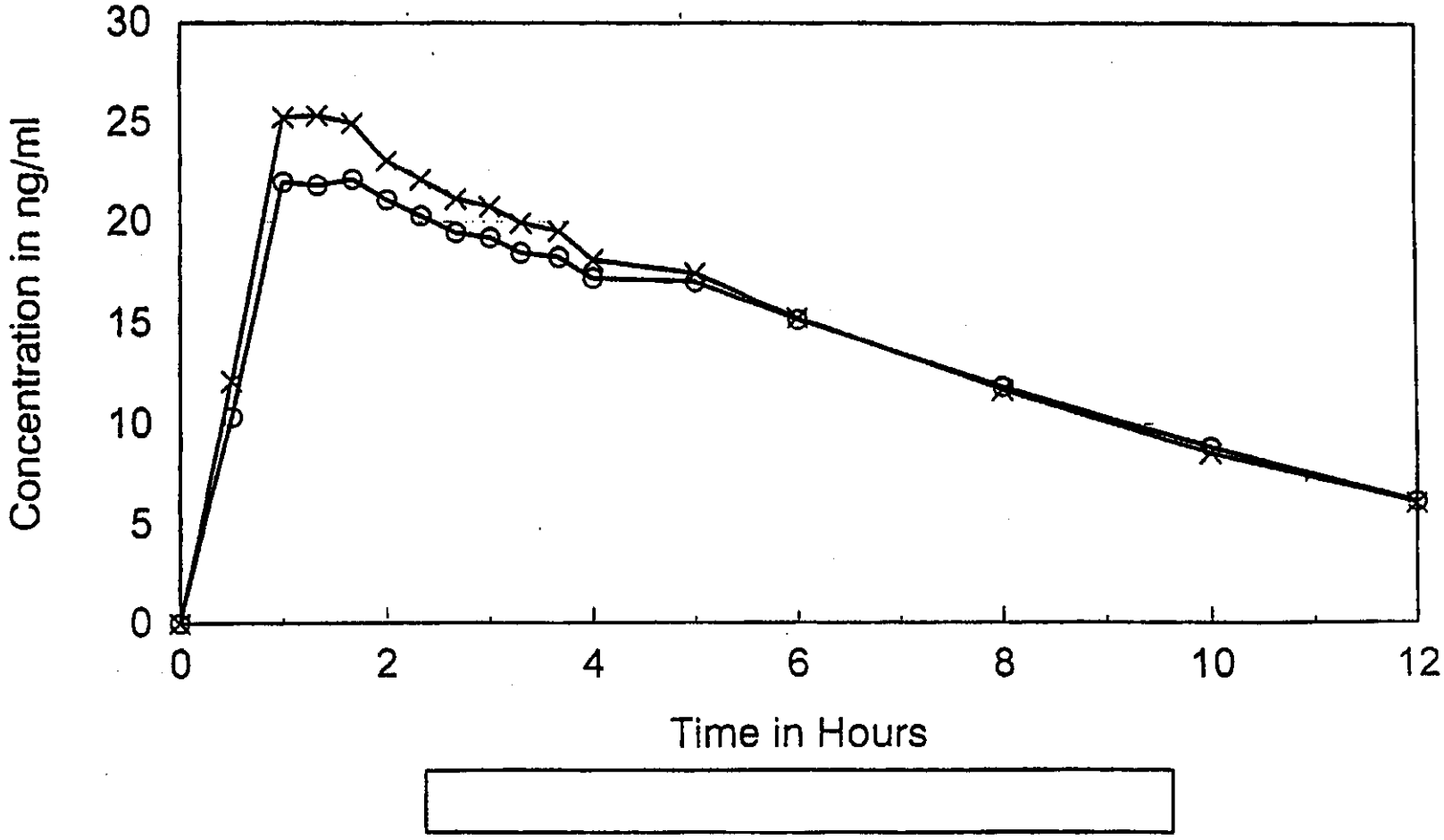
Assay Sensitivity

Assay Accuracy

TABLE 2.8.3. Vicoprofen® Clinical and Market Formulations

	CLINICAL FORMULA	MARKET FORMULA	
CORE			
		Ibuprofen	200 mg
		Corn starch	
		Croscarmellose sodium	
		Microcrystalline cellulose	
		Hydroxypropyl methylcellulose	
		Magnesium stearate	
		Hydrocodone bitartrate	7.50 mg
		Colloidal silicon dioxide	
COATING			
TOTAL			

VP-30:Hydrocodone Plasma Concentrations
Mean Data (all subjects)



2 Tablet Dose (15mg Hydrocodone)

Individual and Mean Plasma Hydrocodone Concentrations (ng/mL)
for Vicoprofen(R) Tablets

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) -1.00	0.50	1.00	1.33	1.67	2.00	2.33	2.67	3.00	3.33	3.67	4.00	5.00	6.00	8.00	10.00	12.0
1	BA	2																	
2	AB	1																	
3	AB	1																	
4	BA	2																	
5	BA	2																	
8	BA	2																	
9	AB	1																	
10	BA	2																	
11	AB	1																	
12	BA	2																	
13	BA	2																	
14	AB	1																	
15	BA	2																	
16	AB	1																	
17	BA	2																	
18	AB	1																	
19	BA	2																	
20	AB	1																	
21	AB	1																	
22	BA	2																	
23	AB	1																	
24	BA	2																	
25	AB	1																	
27	AB	1																	
28	BA	2																	
29	AB	1																	
30	BA	2																	
31	AB	1																	
32	BA	2																	
33	AB	1																	
34	BA	2																	
Mean			0.00	10.34	21.95	21.79	22.09	21.07	20.23	19.44	19.19	18.44	18.22	17.21	17.05	15.19	11.81	8.40	6.1
S.D.			0.00	12.81	10.38	8.73	8.37	7.99	7.17	6.46	6.02	5.46	5.65	5.25	4.36	4.42	4.02	3.46	2.7
C.V.(%)			.	123.84	47.29	40.07	37.88	37.90	35.37	33.25	31.37	29.63	31.03	30.50	25.63	29.07	34.07	41.52	44.5
S.E.M.			0.00	2.30	1.86	1.57	1.50	1.43	1.29	1.16	1.08	0.98	1.02	0.94	0.78	0.79	0.72	0.66	0.4
N			31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.0
Minimum																			
Maximum																			

Samples below the quantifiable limit are reported as 0.00

Individual and Mean Plasma Hydrocodone Concentrations (ng/mL)
for Vicoprofen(R) Tablets

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) -1.00	0.50	1.00	1.33	1.67	2.00	2.33	2.67	3.00	3.33	3.67	4.00	5.00	6.00	8.00	10.00	12.00
1	BA	1																	
2	AB	2																	
3	AB	2																	
4	BA	1																	
5	BA	1																	
8	BA	1																	
9	AB	2																	
10	BA	1																	
11	AB	2																	
12	BA	1																	
13	BA	1																	
14	AB	2																	
15	BA	1																	
16	AB	2																	
17	BA	1																	
18	AB	2																	
19	BA	1																	
20	AB	2																	
21	AB	2																	
22	BA	1																	
23	AB	2																	
24	BA	1																	
25	AB	2																	
27	AB	2																	
28	BA	1																	
29	AB	2																	
30	BA	1																	
31	AB	2																	
32	BA	1																	
33	AB	2																	
34	BA	1																	
Mean			0.00	12.11	25.27	25.34	24.96	23.83	22.89	21.11	20.74	19.93	19.52	18.69	17.47	15.27	11.45	8.58	6.0
S.D.			0.00	10.44	6.00	6.21	5.94	5.51	5.39	4.91	4.90	4.54	4.50	4.07	3.30	3.20	2.74	2.46	2.0
C.V.(%)			.	86.23	23.75	24.53	23.76	23.11	24.41	23.23	23.61	22.76	23.05	22.48	18.87	21.51	23.51	28.90	33.0
S.E.M.			0.00	1.88	1.08	1.12	1.07	0.99	0.97	0.88	0.88	0.81	0.81	0.73	0.59	0.59	0.49	0.44	0.3
N			31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.0
Minimum																			
Maximum																			

Samples below the quantifiable limit are reported as 0.00

VP-30 Subjects Plasma Hydrocodone Concentrations from Vicoprofen 400/15mg

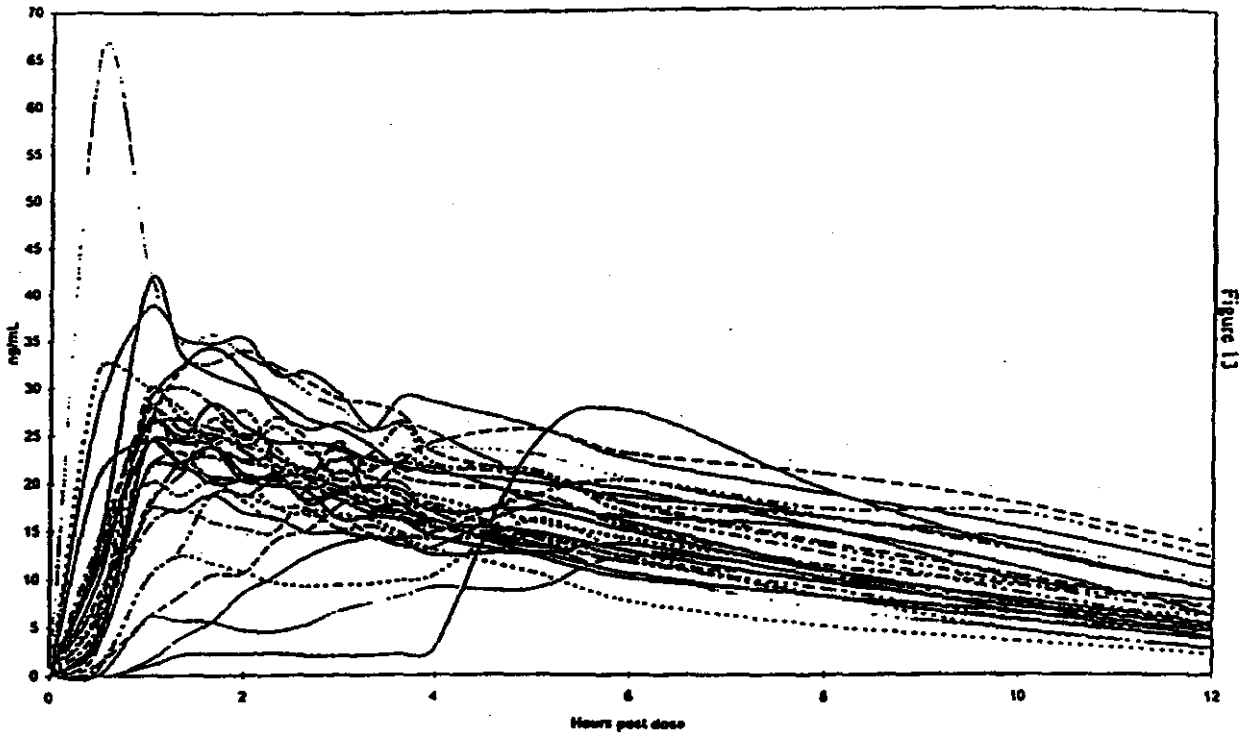


Figure 13

VP-30 Subjects Plasma Hydrocodone Concentrations from Vicoprofen 400/15mg

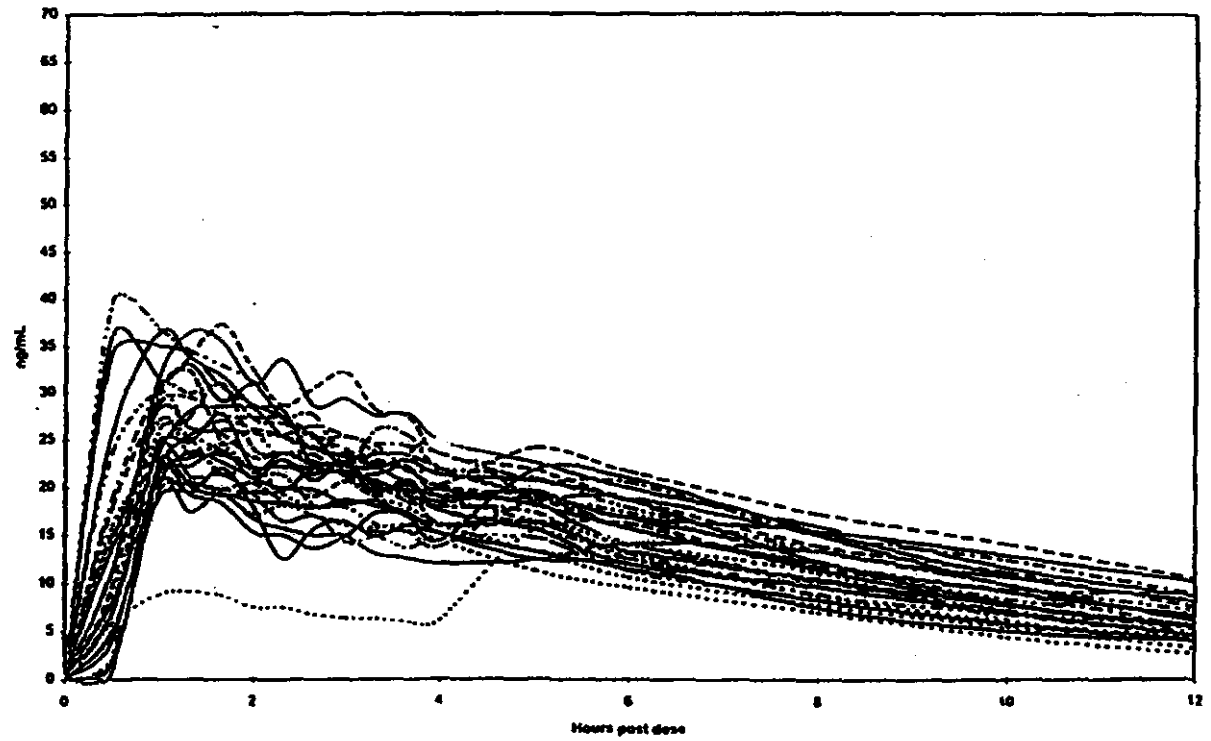
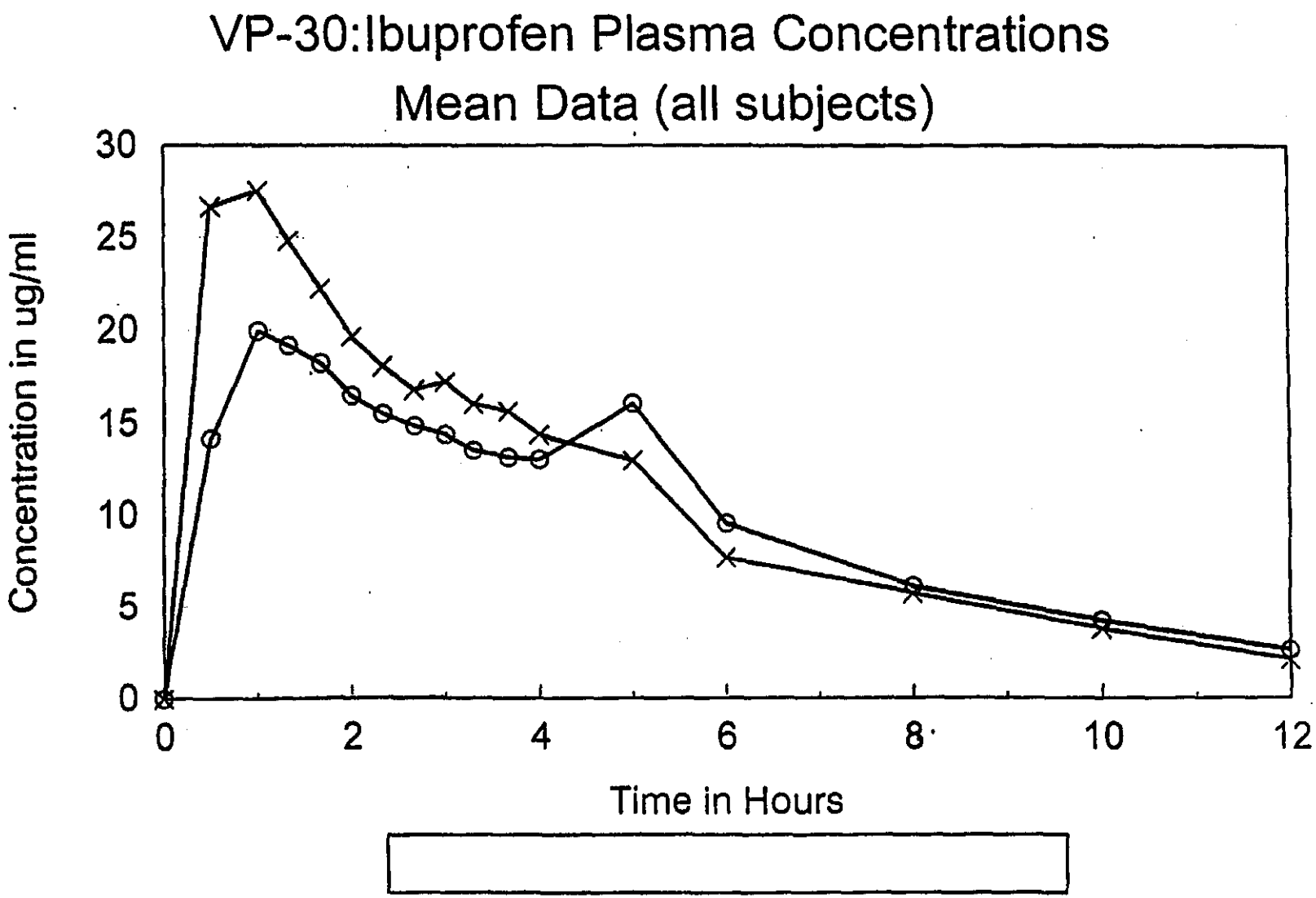


Figure 14



2 Tablet Dose (400mg Ibuprofen)

Individual and Mean Plasma Ibuprofen Concentrations (ug/mL)
for Vicoprofen(R) Tablets

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) -1.00	0.50	1.00	1.33	1.67	2.00	2.33	2.67	3.00	3.33	3.67	4.00	5.00	6.00	8.00	10.00	12.00
1	BA	2																	
2	AB	1																	
3	AB	1																	
4	BA	2																	
5	BA	2																	
8	BA	2																	
9	AB	1																	
10	BA	2																	
11	AB	1																	
12	BA	2																	
13	BA	2																	
14	AB	1																	
15	BA	2																	
16	AB	1																	
17	BA	2																	
18	AB	1																	
19	BA	2																	
20	AB	1																	
21	AB	1																	
22	BA	2																	
23	AB	1																	
24	BA	2																	
25	AB	1																	
27	AB	1																	
28	BA	2																	
29	AB	1																	
30	BA	2																	
31	AB	1																	
32	BA	2																	
33	AB	1																	
34	BA	2																	
Mean			0.00	14.38	19.95	19.15	18.23	16.50	15.51	14.96	14.37	13.52	13.14	12.02	10.09	9.53	6.09	4.22	2.80
S.D.			0.00	10.75	11.41	10.15	9.36	8.37	7.52	6.82	6.51	6.47	5.83	5.61	9.36	5.52	4.53	3.73	2.99
C.V.(%)			.	75.76	57.25	53.01	51.33	50.71	48.47	45.94	45.29	47.85	44.37	43.88	58.18	57.92	74.35	88.38	115.06
S.E.M.			0.00	1.93	2.05	1.82	1.68	1.50	1.35	1.21	1.17	1.16	1.05	1.01	1.68	0.99	0.81	0.67	0.54
N			31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00
Minimum																			
Maximum																			

Samples below the quantifiable limit are reported as 0.00

Individual and Mean Plasma Ibuprofen Concentrations (ug/mL)
for Vicoprofen(R) Tablets

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) -1.00	0.50	1.00	1.33	1.67	2.00	2.33	2.67	3.00	3.33	3.67	4.00	5.00	6.00	8.00	10.00	12.00
1	BA	1																	
2	AB	2																	
3	AB	2																	
4	BA	1																	
5	BA	1																	
8	BA	1																	
9	AB	2																	
10	BA	1																	
11	AB	2																	
12	BA	1																	
13	BA	1																	
14	AB	2																	
15	BA	1																	
16	AB	2																	
17	BA	1																	
18	AB	2																	
19	BA	1																	
20	AB	2																	
21	AB	2																	
22	BA	1																	
23	AB	2																	
24	BA	1																	
25	AB	2																	
27	AB	2																	
28	BA	1																	
29	AB	2																	
30	BA	1																	
31	AB	2																	
32	BA	1																	
33	AB	2																	
34	BA	1																	
Mean			0.00	21.63	27.49	24.80	22.23	19.64	18.05	16.81	17.22	16.04	15.66	14.38	12.97	7.65	5.69	3.76	2.09
S.D.			0.00	9.62	8.13	7.05	5.93	4.75	4.57	4.65	4.70	4.88	5.24	5.34	6.27	3.64	4.93	3.02	1.94
C.V.(%)			.	44.72	29.59	28.45	26.67	24.21	25.32	27.66	28.89	30.43	33.44	37.13	49.11	50.21	86.61	80.49	92.44
S.E.M.			0.00	1.73	1.46	1.27	1.07	0.85	0.82	0.84	1.20	0.88	0.94	0.96	1.14	0.69	0.89	0.54	0.35
N			31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00
Minimum																			
Maximum																			

Samples below the quantifiable limit are reported as 0.00

VP-30 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

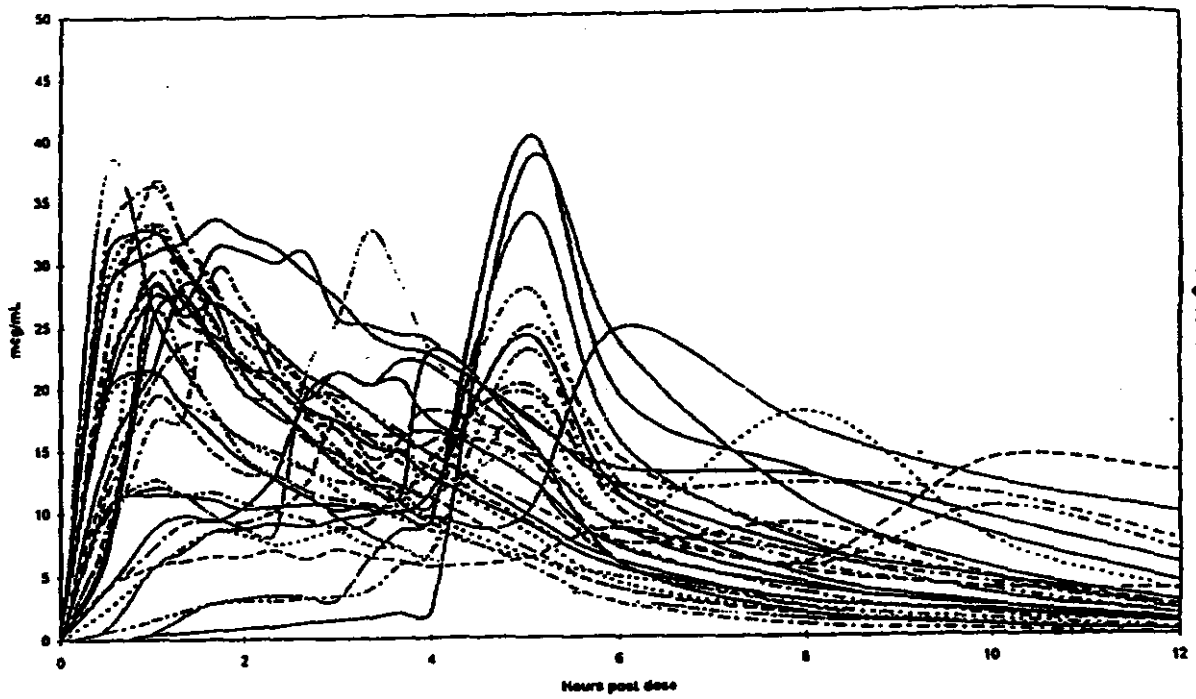


Figure 15

VP-30 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

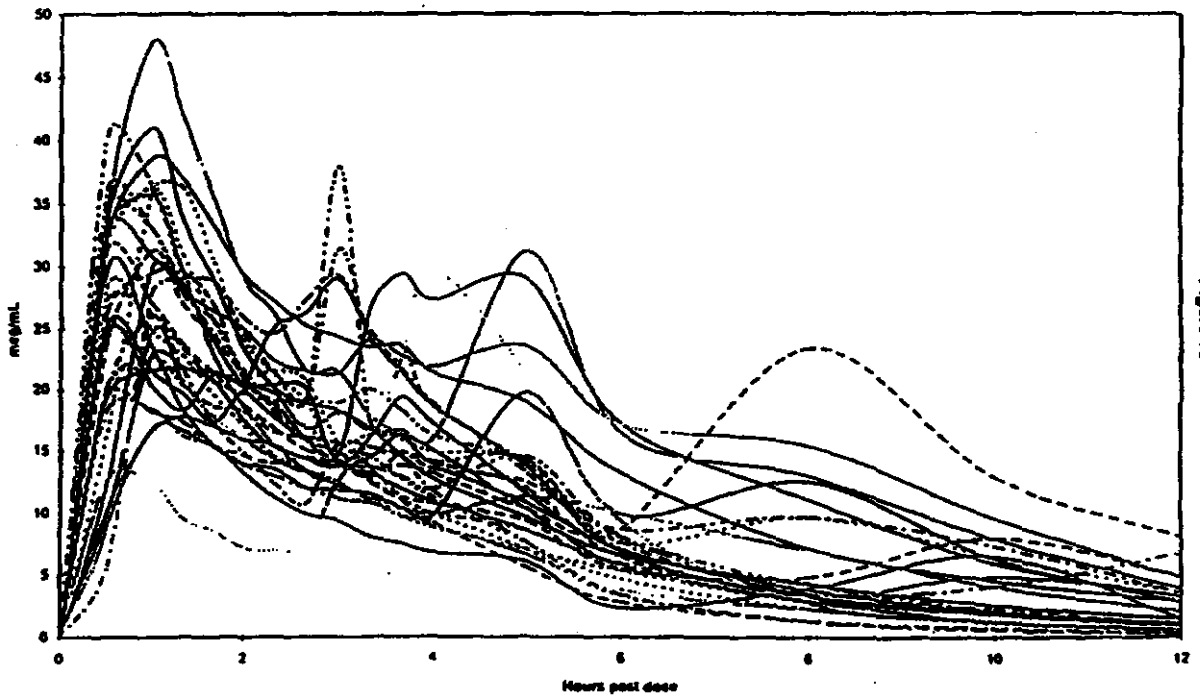


Figure 16

VP-30 Males Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

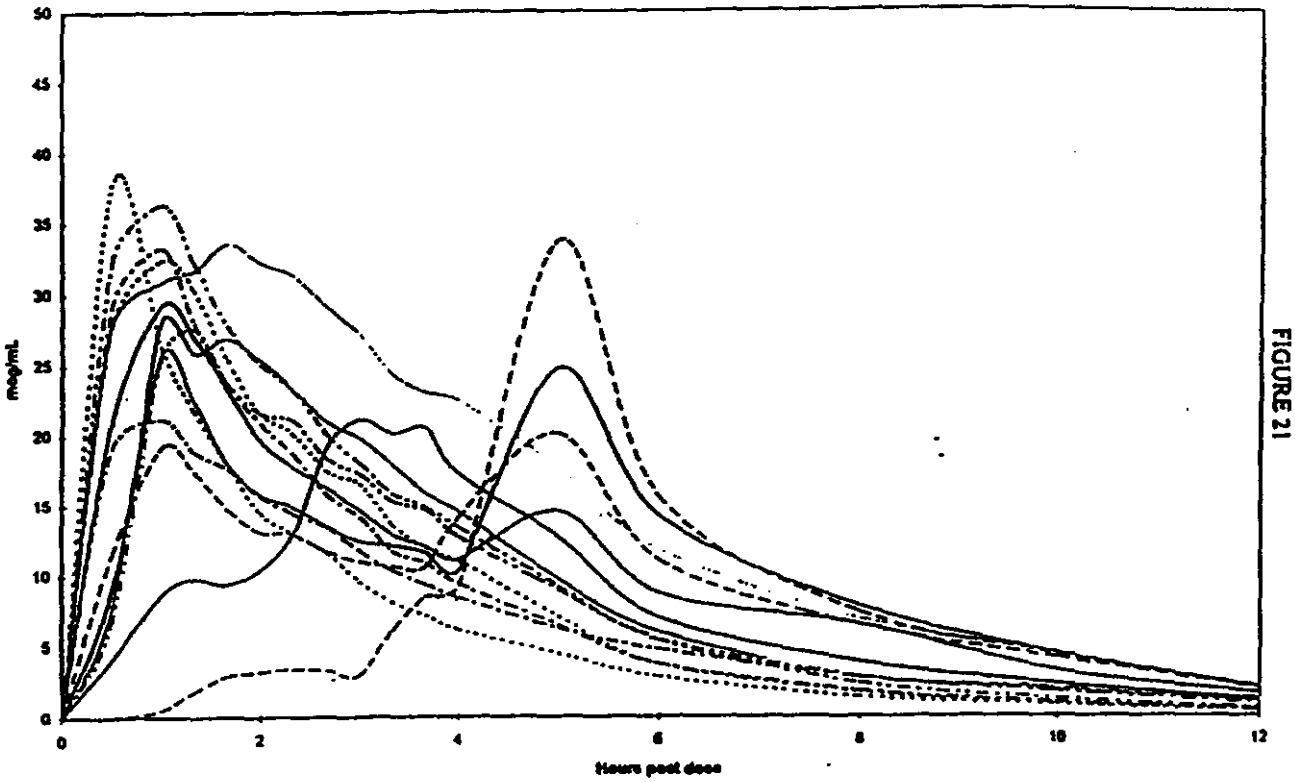


FIGURE 21

VP-30 Females Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

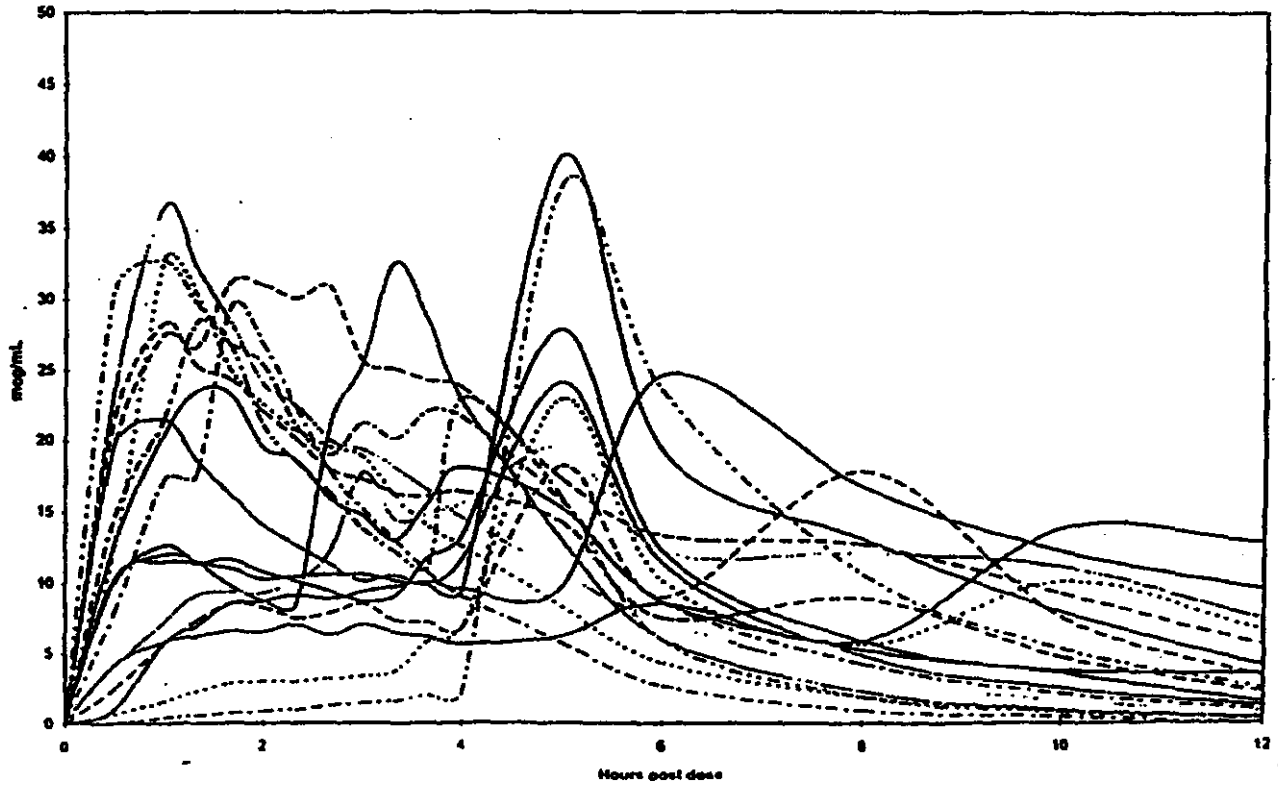


FIGURE 22

VP-30 Males Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

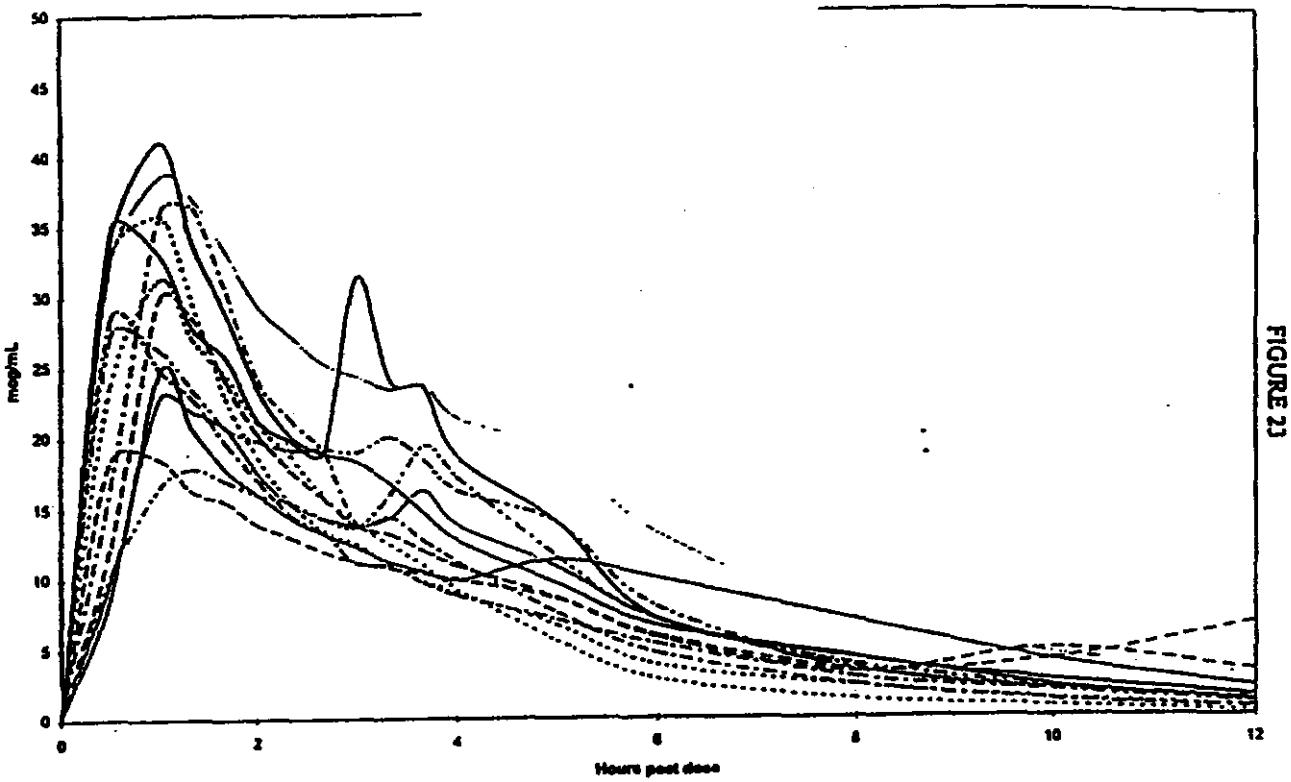


FIGURE 23

VP-30 Females Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

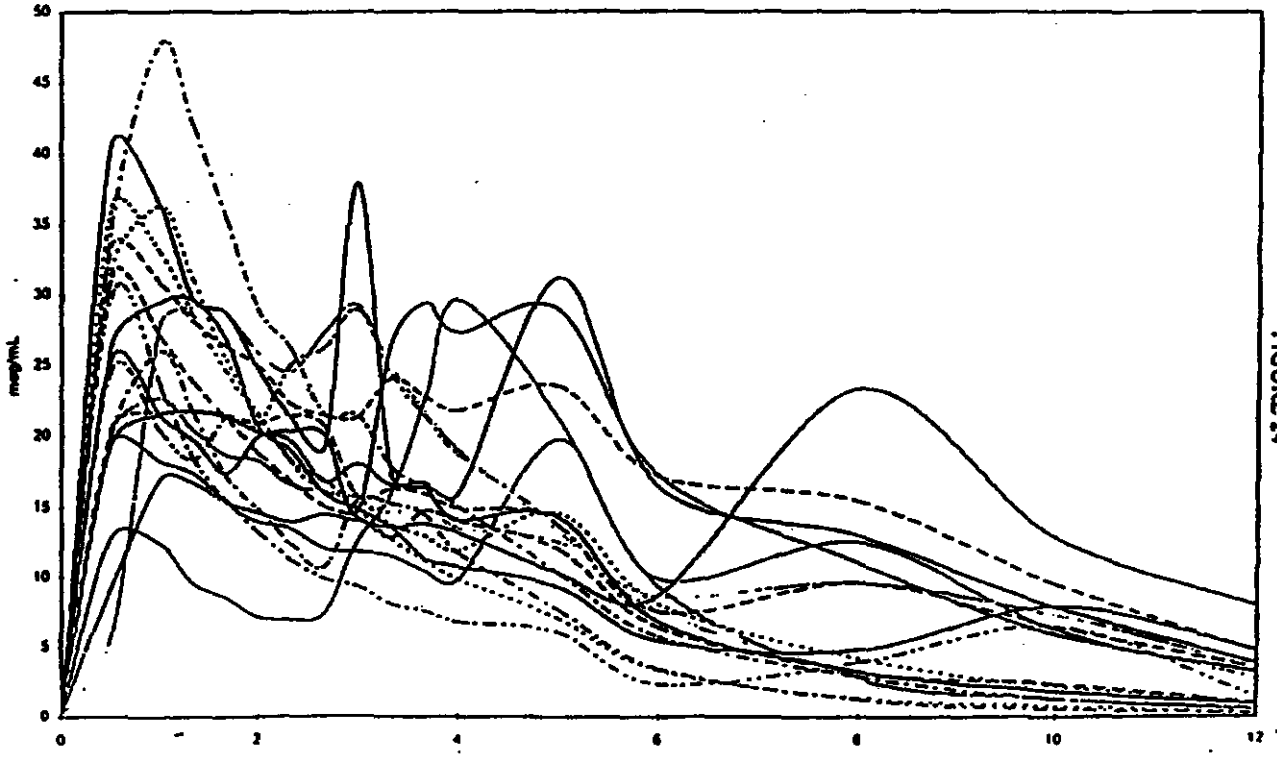


FIGURE 24

NDA/IND# 20-716 Suppl/Amend.# ORIG Submission Date: 4/26/96 Volume: 1.16

tudy Type: PK/PD Study # VP-22

Study Title: A PK/PD characterization of Vicoprofen® tablets in acute post-operative dental pain

Clinical Investigator

Site

Analytical Investigator-*Hydrocodone*

Site

Analytical Investigator-*Ibuprofen*

Site

Single Dose: Y Multiple Dose: N Washout Period: N/A

Cross-Over N Parallel Y Other Design: N/A

Fasted Y Food Study N FDA High Fat Breakfast N

If fasted, how long (hrs.)? (?)

Subject Breakdown

Normal Y Patients Y Young Y Elderly N Renal Hepatic

Subject Type	Males	Group	All	N=	72	M=	36	F=	36
Weight	Mean Range	See Attached	Group		N=		M=		F=
Age	Mean Range		Group		N=		M=		F=
Subject Type	Females		Group		N=		M=		F=
Weight	Mean Range	See Attached	Group		N=		M=		F=
Age	Mean Range		Group		N=		M=		F=

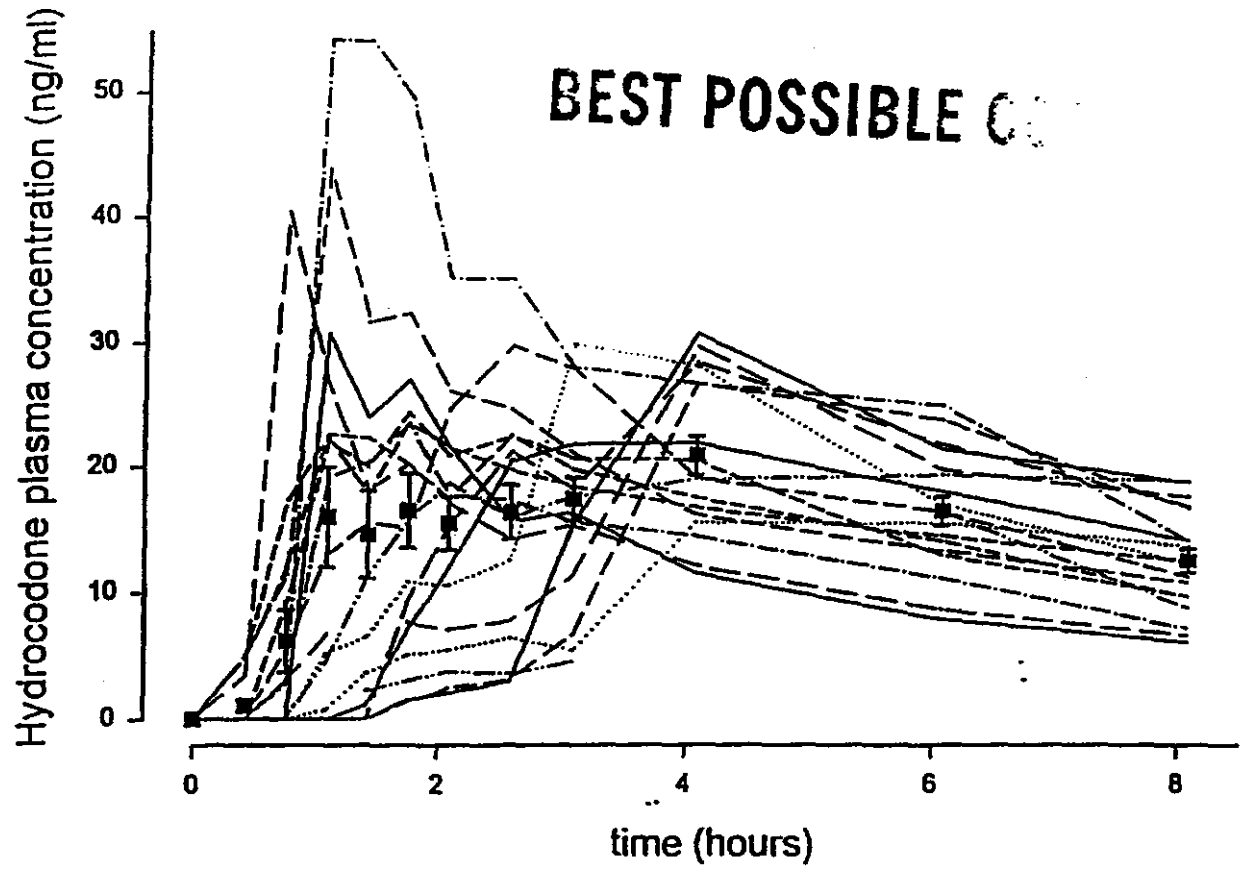
Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
Vicoprofen®	15mg HC/ 400mg IBU	Tablet	7.5mg HC/ 200mg IBU	55-0392	
Ibuprofen Susp.	400mg	Suspension	20mg/ml	131-13	
Hydrocodone	15mg	Tablets	7.5mg	128-0191	
Placebo Tablets		Tablets		120-0191	
Placebo Susp.		Suspension		131-01	

Sampling Times

Plasma Prior to dosing and 20, 40, 60, 80, 100, and 120 min. and 2.5, 3, 4, 5, 6, 7, and 8 hrs after dosing.

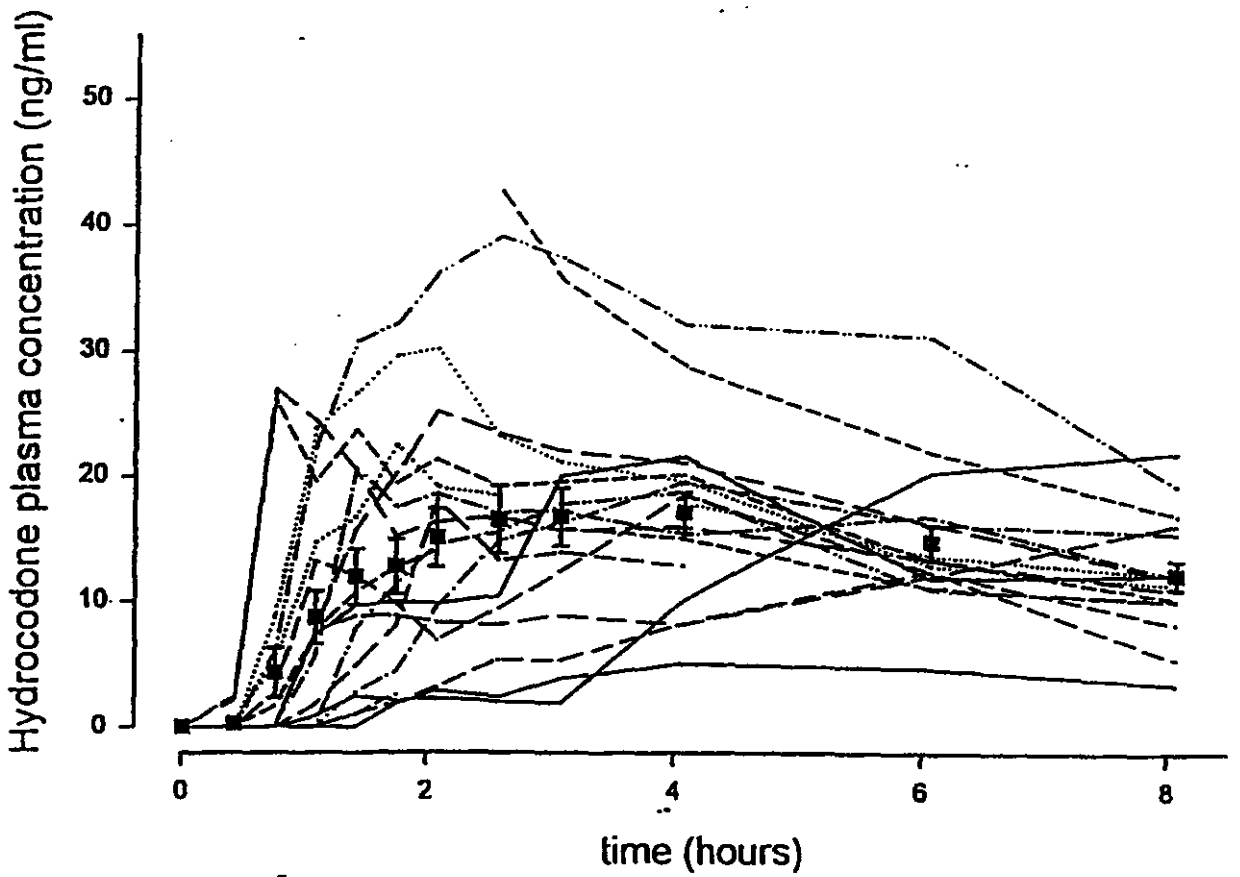
Table C1
Demographic and Background Information

	Placebo (N=18)	Hydrocodone (N=18)	Ibuprofen (N=18)	VICOPROFEN (N=18)	Total (N=72)	Statistic	df	p-value
Age (years)								
Mean	23.1	23.1	23.9	24.9	23.8	F = 0.49	3, 68	0.690 NS
S. D.	4.1	4.6	5.9	6.4	5.3			
Range								
Sex								
Female	10	9	7	10	36			
Male	8	9	11	8	36	X^2 = 1.33	3	0.721 NS
Weight (lbs)								
Mean	153.8	155.8	158.3	155.9	156.0	F = 0.05	3, 68	0.985 NS
S. D.	33.3	30.2	27.7	45.3	34.1			
Range								
Type of Surgery								
Dental	18	18	18	18	72			
Racial Origin								0.897 NS
Caucasian	12	11	11	11	45			
Black	1	4	4	4	13			
Hispanic	2	1	1	0	4			
Asian	1	1	1	1	4			
Other	2	0	1	2	5			
Unavailable	0	1	0	0	1			

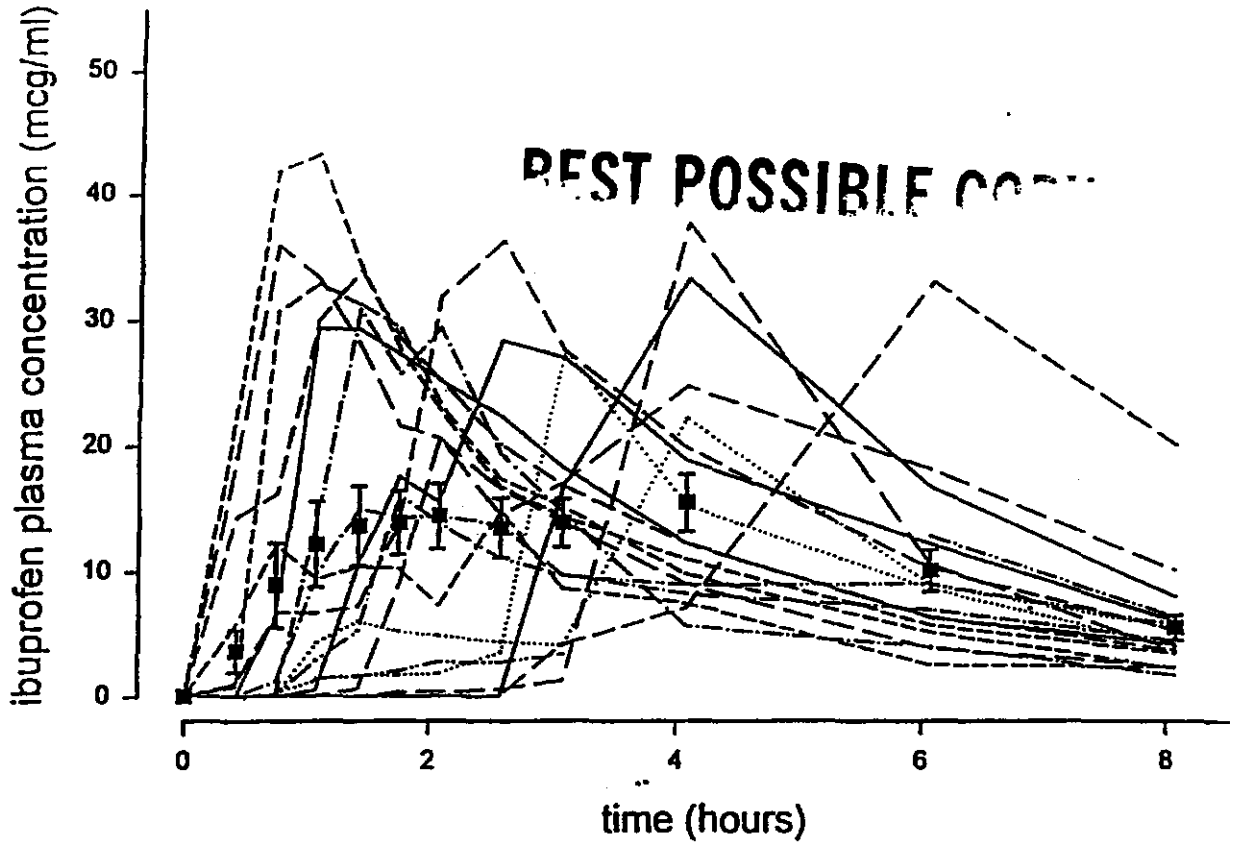


Vicoprofen Protocol VP-22
Plasma Drug Concentration Results

Hydrocodone plasma concentration after vicoprofen 400/15 mg orally.
Each line represents a patient. At missing values the lines are interrupted. The squares indicate the means +/- SE

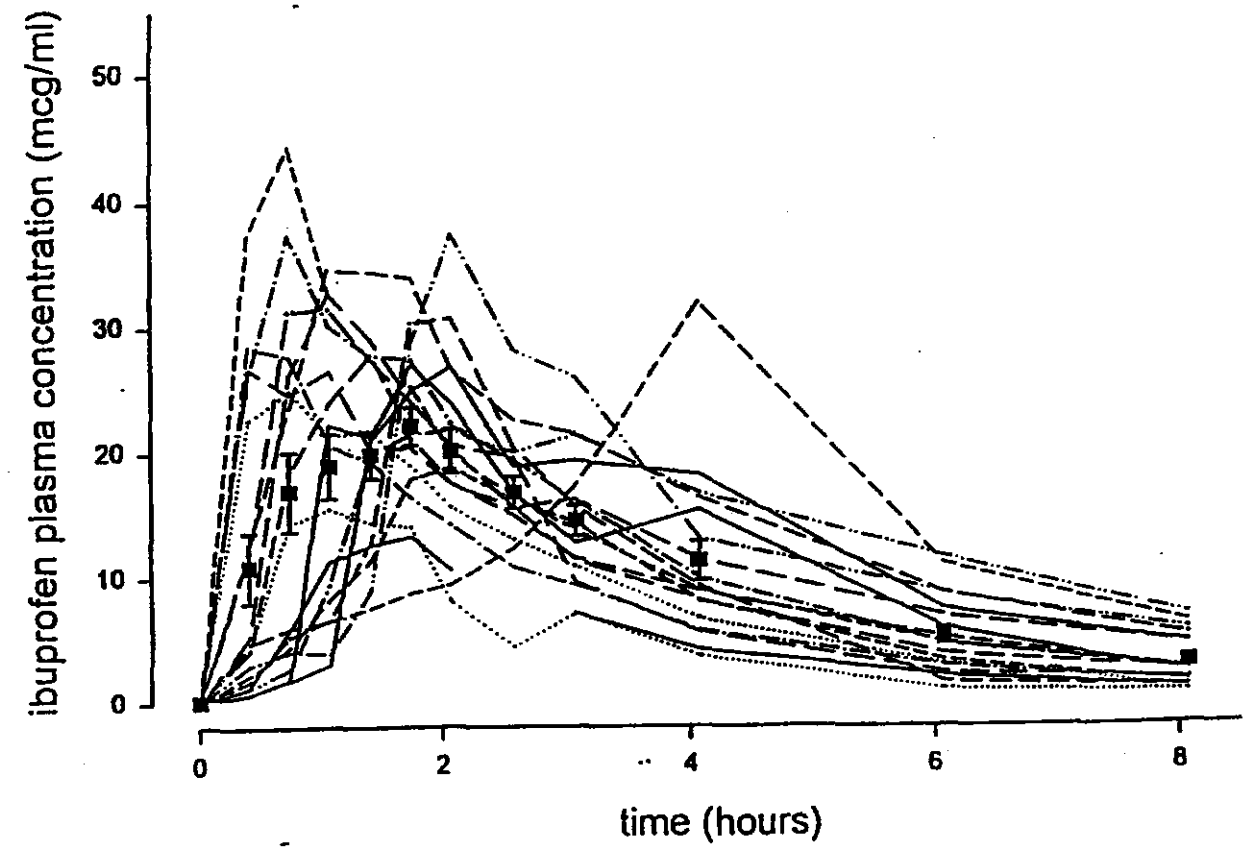


Vicoprofen Protocol VP-22
Plasma Drug Concentration Results



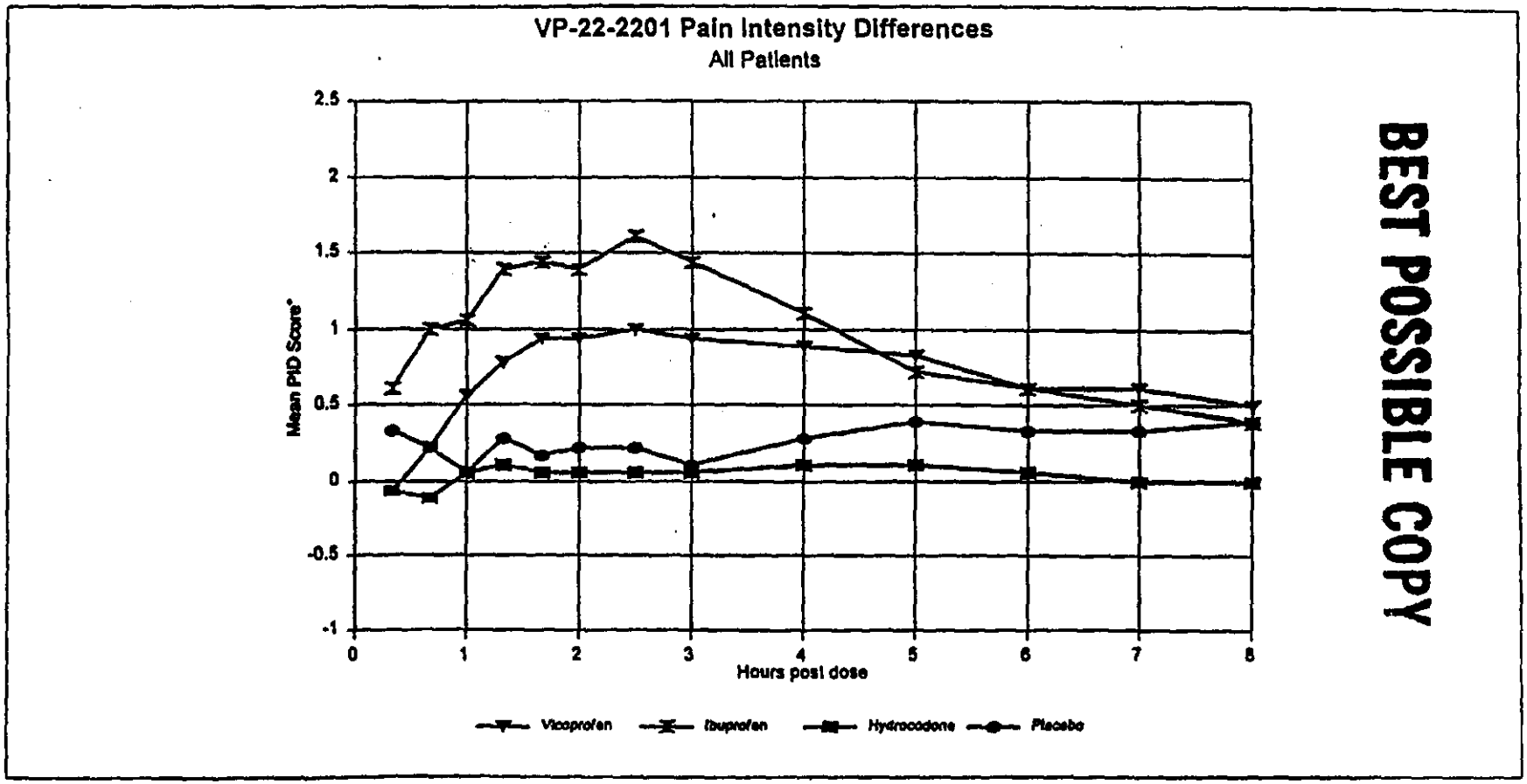
PK 6
Vicoprofen Protocol VP-22
Plasma Drug Concentration Results

Ibuprofen plasma concentration after vicoprofen 400/15 mg orally.
Each line represents a patient. At missing values the lines are interrupted. The squares indicate the means +/- SE.



PK 5
Vicoprofen Protocol VP-22
Plasma Drug Concentration Results

FIGURE 1



		Hours post dose																			
		0.33		0.67		1		1.33		1.67		2		2.5		3		4		5		6		7		8	
Vicoprofen (400/15 mg)	*mean sd	-0.06	(0.64)	0.22	(0.81)	0.56	(0.98)	0.78	(1.00)	0.94	(1.00)	0.94	(1.08)	1.00	(1.08)	0.94	(1.08)	0.89	(1.15)	0.83	(1.20)	0.81	(1.14)	0.81	(1.04)	0.50	(0.99)
	n obs	18		18		18		18		18	X	18	X	18	X	15	X	12		13		12		11		11	
Ibuprofen (400 mg)	*mean sd	0.61	(0.78)	1.00	(0.84)	1.06	(1.00)	1.39	(0.85)	1.44	(0.78)	1.39	(0.78)	1.61	(0.85)	1.44	(0.96)	1.11	(0.68)	0.72	(0.69)	0.81	(0.98)	0.50	(0.92)	0.59	(0.98)
	n obs	18		18	X	18	X	18	X	18	X	18	X	18	X	17	X	18	X	18		12		11		8	
Hydrocodone (15mg)	*mean sd	-0.06	(0.64)	-0.11	(0.45)	0.06	(1.00)	0.11	(1.08)	0.06	(1.00)	0.06	(1.11)	0.06	(1.16)	0.06	(1.16)	0.11	(1.23)	0.11	(1.28)	0.06	(1.11)	0.00	(1.14)	0.00	(1.24)
	n obs	18		18		18		18		14		13		10		7		7		8		6		6		6	
Placebo	*mean sd	0.33	(0.69)	0.22	(0.73)	0.06	(0.73)	0.28	(0.83)	0.17	(0.86)	0.22	(0.88)	0.22	(0.81)	0.11	(0.66)	0.28	(0.89)	0.39	(0.98)	0.33	(0.97)	0.33	(0.97)	0.39	(0.98)
	n obs	18		18		18		18		18		14		11		11		10		10		9		8		8	
	p-value	0.011		<0.001		0.005		<0.001		<0.001		<0.001		<0.001		<0.001		0.010		0.196		0.337		0.306		0.507	

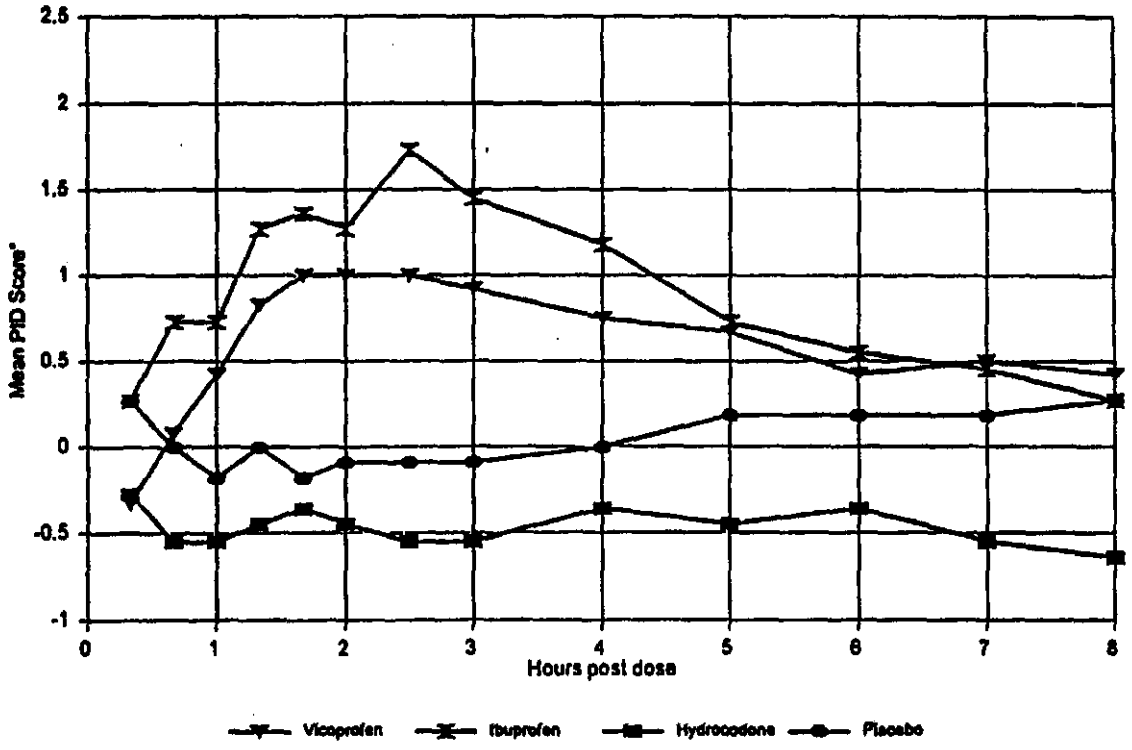
Mean AUC-PID Scores		
	0-4 hr	0-8hr
Vicoprofen	2.72 X	5.38
Ibuprofen	4.85 X	7.91 X
Hydrocodone	0.15	0.34
Placebo	0.88	2.04
p-value	<0.001	0.017

Sample sizes (n) represent number of patients remaining at each evaluation time point. However, mean values and comparisons are based on all patients, with values extrapolated after remedication.

*X=significantly different from placebo (p<=0.05)

VP-22-2201 Pain Intensity Differences

Patients with Moderate Baseline Pain



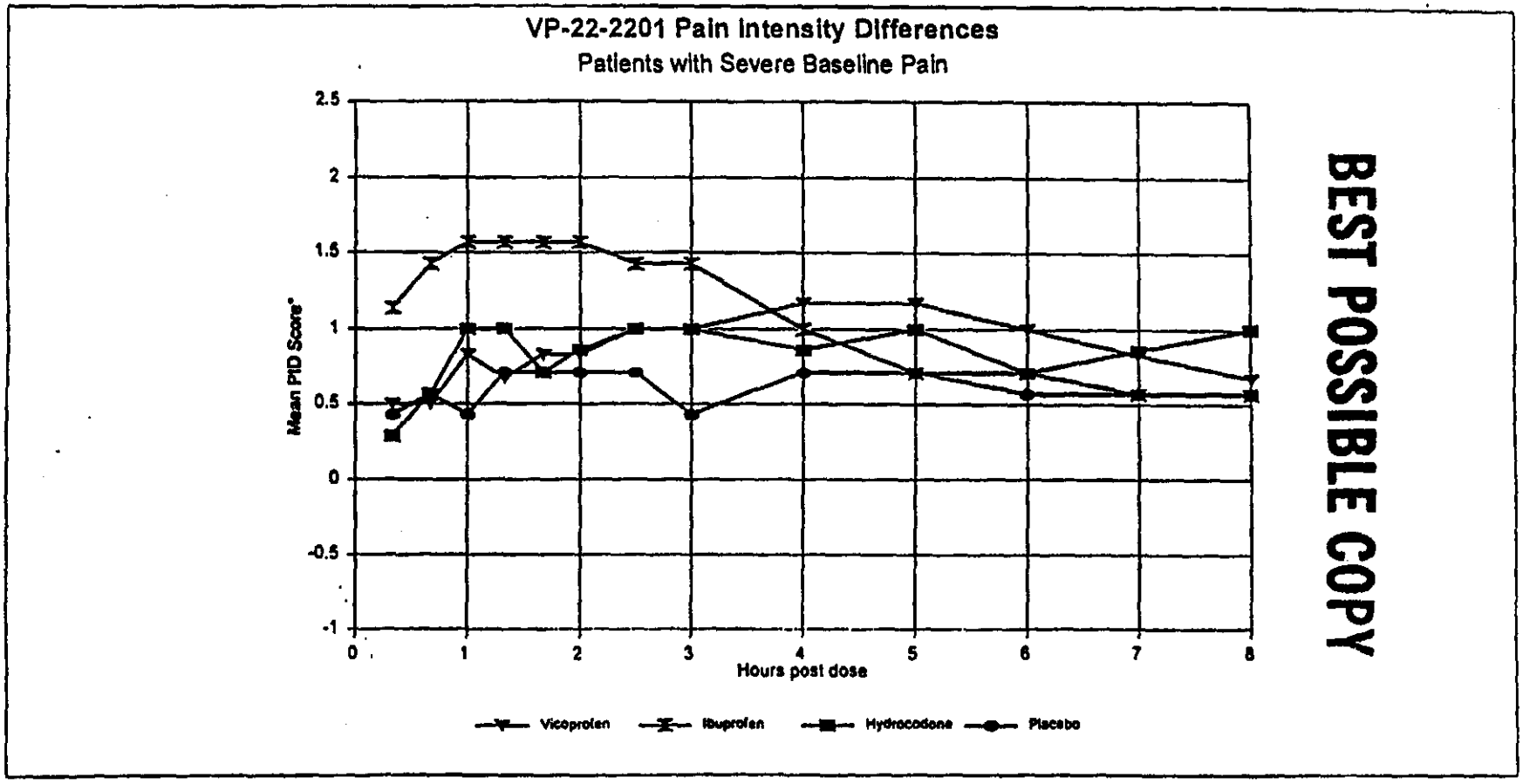
		Hours post dose																					
		0.33		0.67		1		1.33		1.67		2		2.5		3		4		5		6		7		8	
Vicoprofen (400/15 mg)	*mean sd	-0.33	(0.49)	0.08	(0.90)	0.42	(1.08)	0.83	(1.11)	1.00	(1.04)	1.00	(1.13)	1.00	(1.15)	0.92	(1.08)	0.75	(1.06)	0.67	(1.07)	0.42	(0.90)	0.50	(0.90)	0.42	(0.90)
	n sig	12	X	12		12		12	X	12	X	10	X	10	X	10	X	10	X	10	X	8		8		8	
Ibuprofen (400 mg)	*mean sd	0.27	(0.65)	0.73	(0.47)	0.73	(0.65)	1.27	(0.65)	1.36	(0.50)	1.27	(0.47)	1.73	(0.47)	1.45	(0.82)	1.18	(0.60)	0.73	(0.90)	0.55	(1.04)	0.45	(0.93)	0.27	(1.01)
	n sig	11		11	X	11	X	11	X	11	X	11	X	11	X	11	X	11	X	11		9		8		8	
Hydrocodone (15mg)	*mean sd	-0.27	(0.47)	-0.55	(0.52)	-0.55	(0.52)	-0.45	(0.52)	-0.36	(0.52)	-0.45	(0.52)	-0.55	(0.68)	-0.55	(0.68)	-0.36	(1.00)	-0.45	(0.52)	-0.36	1.03	-0.55	(0.52)	-0.64	(0.67)
	n sig	11		11		11		11		8		7		5		3		3		3		3		3		3	
Placebo	*mean sd	0.27	(0.65)	0.09	(0.77)	-0.18	(0.75)	0.00	(0.77)	-0.18	(0.75)	-0.09	(0.83)	-0.09	(0.70)	-0.09	(0.70)	0.00	(0.77)	0.18	(0.98)	0.18	(0.98)	0.18	(0.98)	0.27	(1.01)
	n sig	11		11		11		11		10		9		7		7		6		6		6		6		6	
	p-value	0.015		0.001		0.002		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		0.019		0.184		0.036		0.035	

Mean AUC-PID Scores		
	0-4 hr	0-8hr
Vicoprofen	2.82 X	4.55
Ibuprofen	4.37 X	8.80 X
Hydrocodone	-1.86	-3.57
Placebo	-0.24	0.44
p-value	<0.001	<0.001

Sample sizes (n) represent number of patients remaining at each evaluation time point. However, mean values and comparisons are based on all patients, with values extrapolated after remedication.

*X=significantly different from placebo (p<=0.05)

FIGURE 2



BEST POSSIBLE COPY

FIGURE 3

		Hours post dose																	
		0.33	0.67	1	1.33	1.67	2	2.5	3	4	5	6	7	8
Vicoprofen (400/15 mg)	*mean sd	0.50 (0.53)	0.50 (0.58)	0.83 (0.75)	0.67 (0.82)	0.83 (0.98)	0.83 (0.98)	1.00 (1.10)	1.00 (1.10)	1.17 (1.33)	1.17 (1.47)	1.00 (1.55)	0.83 (1.33)	0.67 (1.21)
	n stg	6	6	6	6	6	6	6	5	3	3	3	2	2
Ibuprofen (400 mg)	*mean sd	1.14 (0.69)	1.43 (1.13)	1.57 (1.27)	1.57 (1.13)	1.57 (1.13)	1.57 (1.13)	1.43 (1.27)	1.43 (1.27)	1.00 (0.82)	0.71 (0.95)	0.71 (0.95)	0.57 (0.98)	0.57 (0.98)
	n stg	7	7	7 X	7	7	7	7	6	3	5	4	3	2
Hydrocodone (15mg)	*mean sd	0.29 (0.76)	0.57 (0.79)	1.00 (0.82)	1.00 (0.82)	0.71 (0.76)	0.86 (1.07)	1.00 (1.15)	1.00 (1.15)	0.86 (1.21)	1.00 (1.41)	0.71 (0.95)	0.86 (1.07)	1.00 (1.29)
	n stg	7	7	7	7	6	6	5	4	4	3	3	3	3
Placebo	*mean sd	0.43 (0.79)	0.57 (0.53)	0.43 (0.53)	0.71 (0.76)	0.71 (0.76)	0.71 (0.76)	0.71 (0.76)	0.43 (0.53)	0.71 (0.95)	0.71 (0.95)	0.57 (0.98)	0.57 (0.98)	0.57 (0.98)
	n stg	7	7	7	7	6	6	4	4	4	4	3	2	2
	p-value	0.140	0.127	0.148	0.251	0.288	0.384	0.877	0.383	0.690	0.660	0.619	0.932	0.874

Mean AUC-PID Scores	0-4 hr	0-8hr
Vicoprofen	3.13	6.96
Ibuprofen	5.10	7.67
Hydrocodone	2.99	6.49
Placebo	3.13	4.66
p-value	0.342	0.071

Sample sizes (n) represent number of patients remaining at each evaluation time point. However, mean values and comparisons are based on all patients, with values extrapolated after remedication.

*X=significantly different from placebo (p<=0.05)

NDA/IND# 20-716 Suppl/Amend.# ORIG Submission Date: 4/26/96 Volume: 1.12

tudy Type: Interaction Study Study # VP-27

Study Title: A study of the interaction between Vicoprofen® tablets administered with and without a sorbitol containing suspension

Clinical Investigator

Site

Analytical Investigator

Site

Single Dose: Y Multiple Dose: N Washout Period: Seven Days

Cross-Over Y Parallel N Other Design:

Fasted Y Food Study N FDA High Fat Breakfast N

If fasted, how long (hrs.)? 10

Subject Breakdown

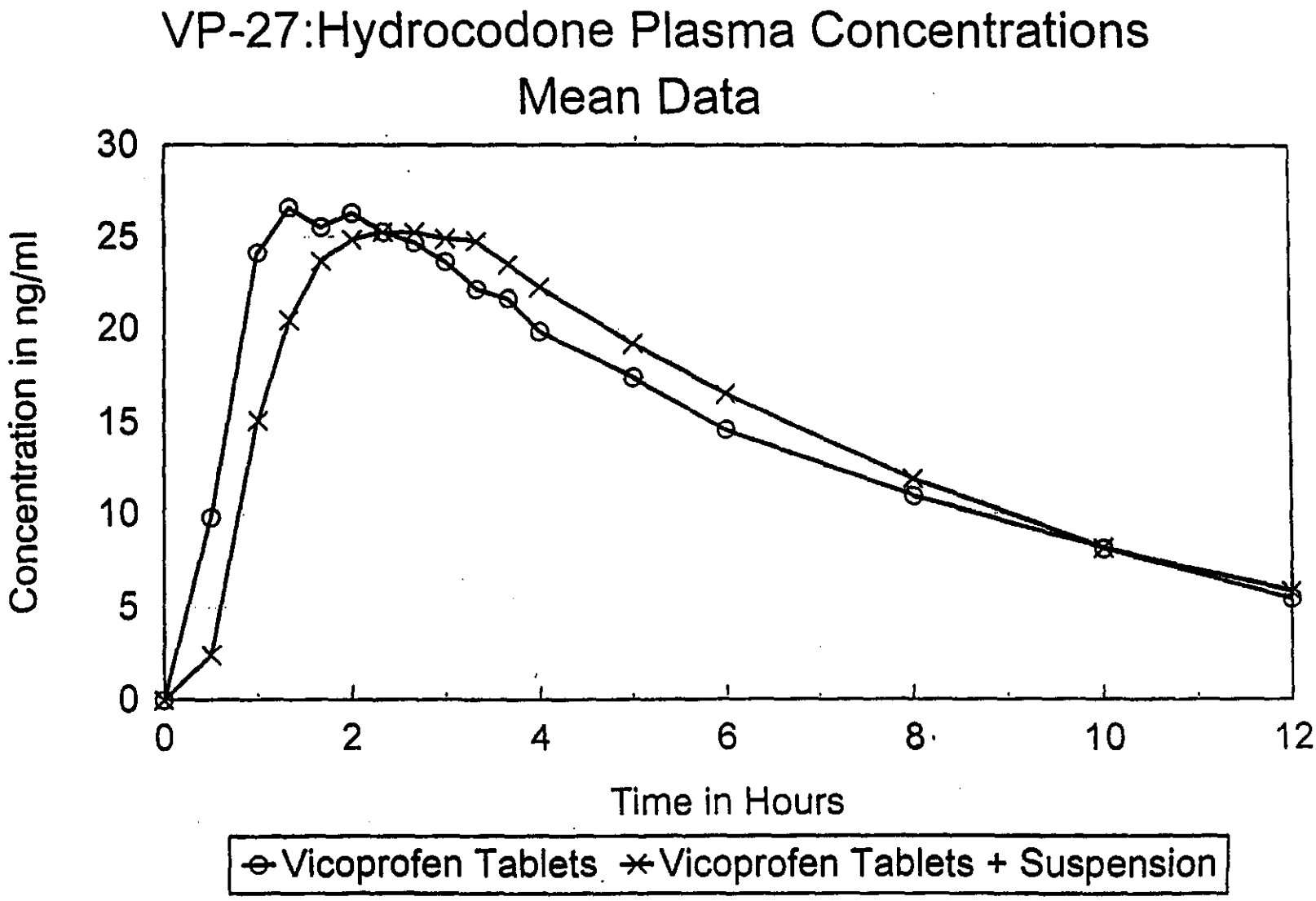
Normal Y Patients N Young Y Elderly N Renal N Hepatic N

	Subject Type	Males		Group	All	N=	34	M= 28	F= 6
Weight	Mean 171	Range		Group		N=		M=	F=
Age	Mean 29	Range		Group		N=		M=	F=
	Subject Type	Females		Group		N=		M=	F=
Weight	Mean 143	Range		Group		N=		M=	F=
Age	Mean 31	Range		Group		N=		M=	F=

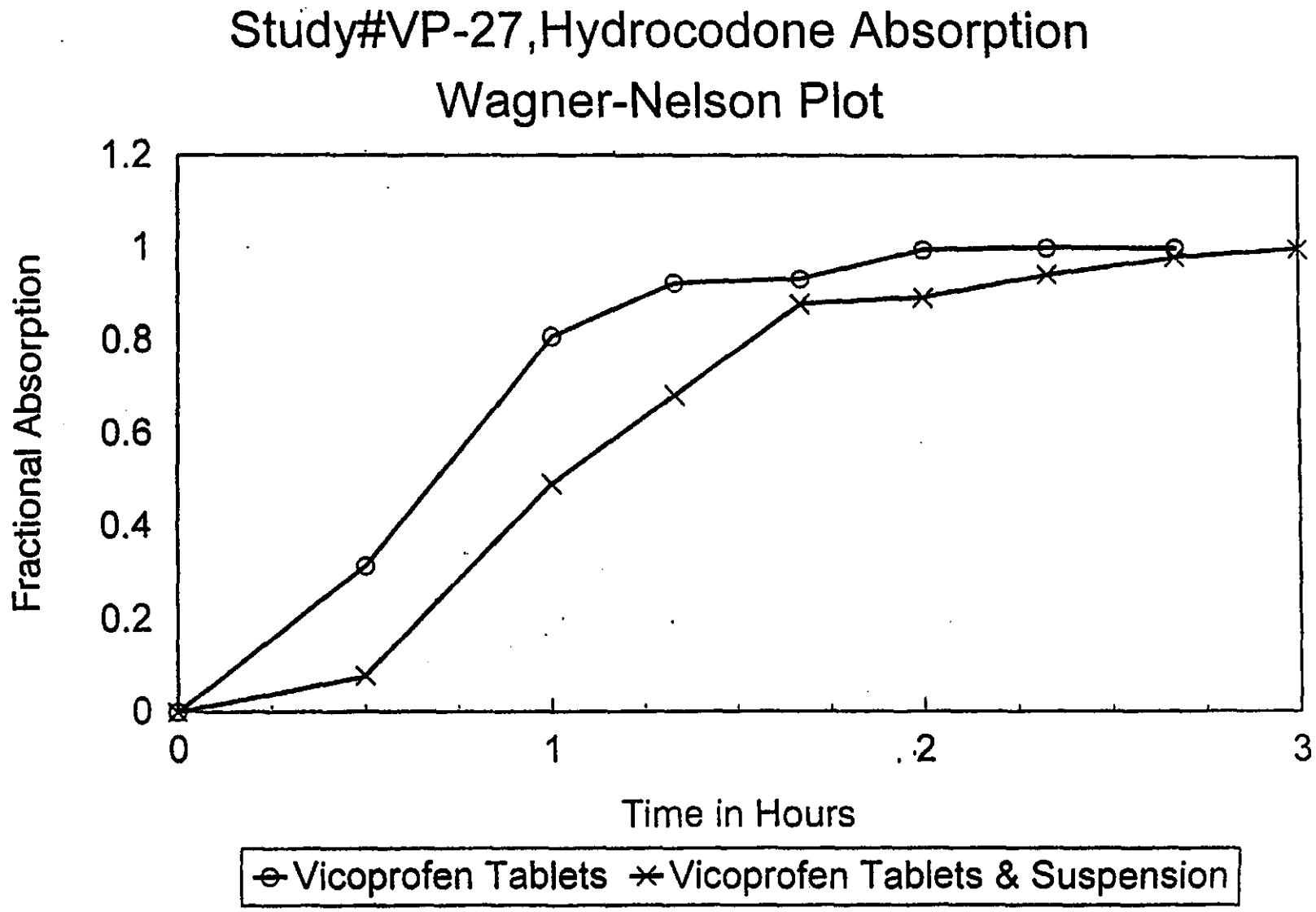
Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
TRT A	2 tablets	tablets	7.5mg HC/ 200mg IBU	55-0932	
TRT B	2 tablets	tablets	7.5mg HC/ 200mg IBU	55-0932	
	20ml	Suspension	Placebo	131-01	
TRT C	2 tablets	tablets	200mg IBU	29-0291	

Sampling Times

Plasma 12ml samples, prior to dosing and at 30, 60, 80, 100, 120, 140, 160, 180, 200, 220min., and 4, 5, 6, 8, 10 and 12 hours after dosing



2 Tablet Dose (15mg Hydrocodone)



15mg Dose

Vicoprofen® Protocol VP-27
Pharmacokinetic Summary Statistics
Mean (+/- S.D.)

Analyte:	Hydrocodone Bitartrate N=32		Ibuprofen N=32			
Parameter (Units)	Vicoprofen	Vicoprofen + Suspension	Vicoprofen	Vicoprofen + Suspension	Ibuprofen	Parameter (Units)
C_{max} (ng/mL)	29.7 (6.9)	28.9 (6.7)	32.5 (7.6)	33.2 (6.2)	35.8 (5.7)	C_{max} (mcg/mL)
T_{max} (hour)	1.73 (0.77) A	2.58 (1.03) B	1.73 (1.19)	1.98 (1.19)	1.67 (0.90)	T_{max} (hour)
$t_{½}$ (hour)	4.22 (0.97)	4.09 (1.17)	2.01 (0.65)	2.03 (0.89)	1.92 (0.38)	$t_{½}$ (hour)
$AUC_{0-\infty}$ (ng/mL_hr)	211.1 (58.4)	212.7 (59.5)	118.2 (34.1)	122.1 (39.2)	129.2 (37.8)	$AUC_{0-\infty}$ (mcg/mL_hr)

Bioequivalence with Respect to Plasma Hydrocodone

Treatment B versus Treatment A

Parameter	Treatment Means B	A	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	(95% Confidence)	Mean Ratio
CMAX	28.905	29.653	-2.52	0.4591	99.97	91.6 - 103.2	90.6 - 104.3	.
TMAX	2.548	1.730	48.94	0.0007*	31.36	127.1 - 170.8	122.6 - 175.3	.
AUC	176.345	176.394	-0.03	0.9913	99.99	95.7 - 104.2	94.8 - 105.1	.
AUC-INF	212.926	211.554	0.65	0.8252	99.99	95.7 - 105.6	94.7 - 106.6	.
REL	0.179	0.171	4.13	0.3012	99.76	97.5 - 110.8	96.1 - 112.2	.
HALF-LIFE	4.092	4.219	-3.01	0.6130	98.79	87.0 - 107.8	85.8 - 109.0	.
LCMAX	3.337	3.365	-0.83	0.4115	99.96	91.9 - 102.9	90.8 - 104.1	97.2
LAUC	5.142	5.144	-0.04	0.9431	99.99	95.4 - 104.4	94.6 - 105.3	99.8
LAUC-INF	5.323	5.316	0.10	0.8620	99.99	95.4 - 106.0	94.4 - 107.1	100.3

Treatment B = 2 x Vicoprofen(R) Tablets + 20 mL Sorbitol Suspension - test
Treatment A = 2 x Vicoprofen(R) Tablets - reference

Values for Treatments B and A are the least-square means (LSMEANS) from the ANOVA
Parameters with the 'L' prefix are log-transformed parameters
. = value was not calculated

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

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

Power = power (%) to detect 20% differences between treatments (a=0.05)

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

VP-27 Subjects Plasma Hydrocodone Concentrations from Vicoprofen 400/15mg

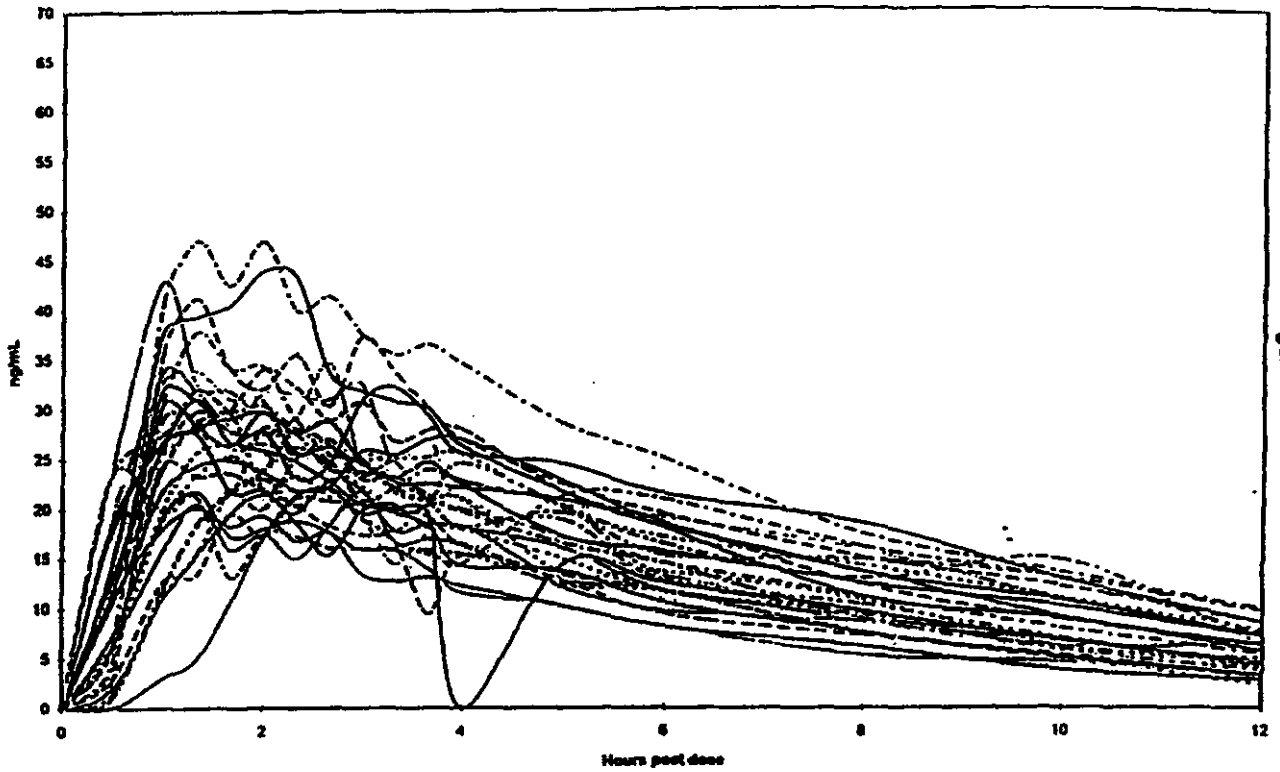


Figure 14

VP-27 Subjects Plasma Hydrocodone Concentrations from Vicoprofen 400/15mg + Placebo Suspension

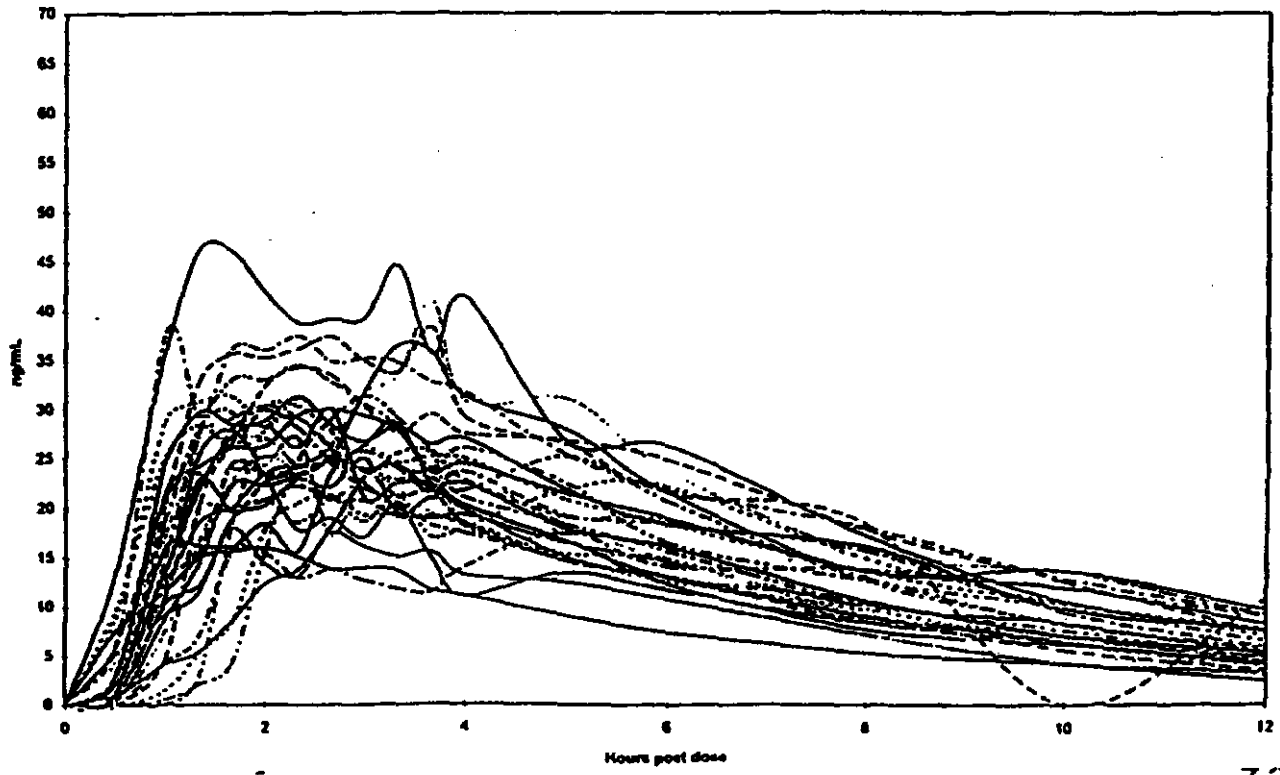
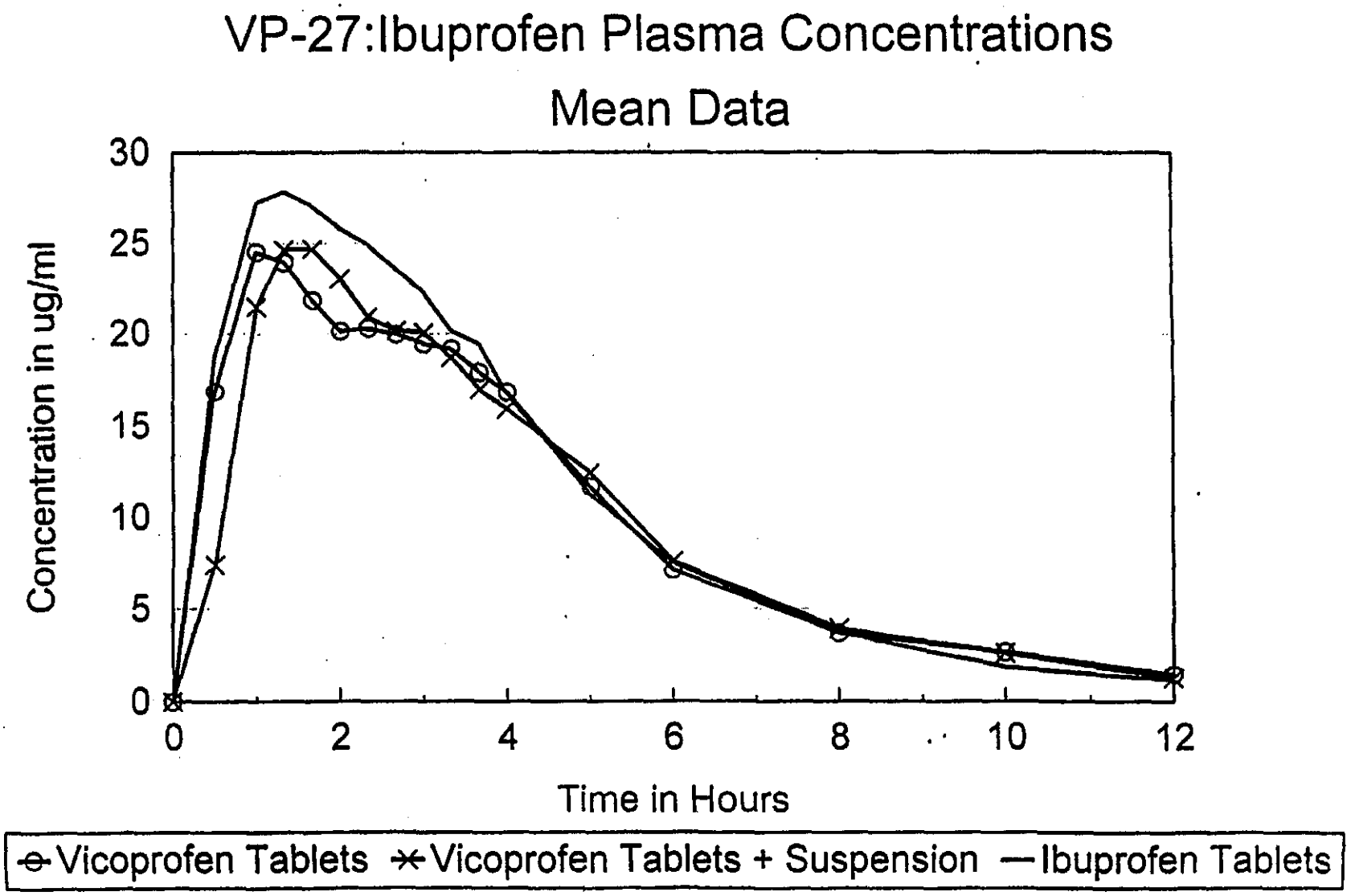
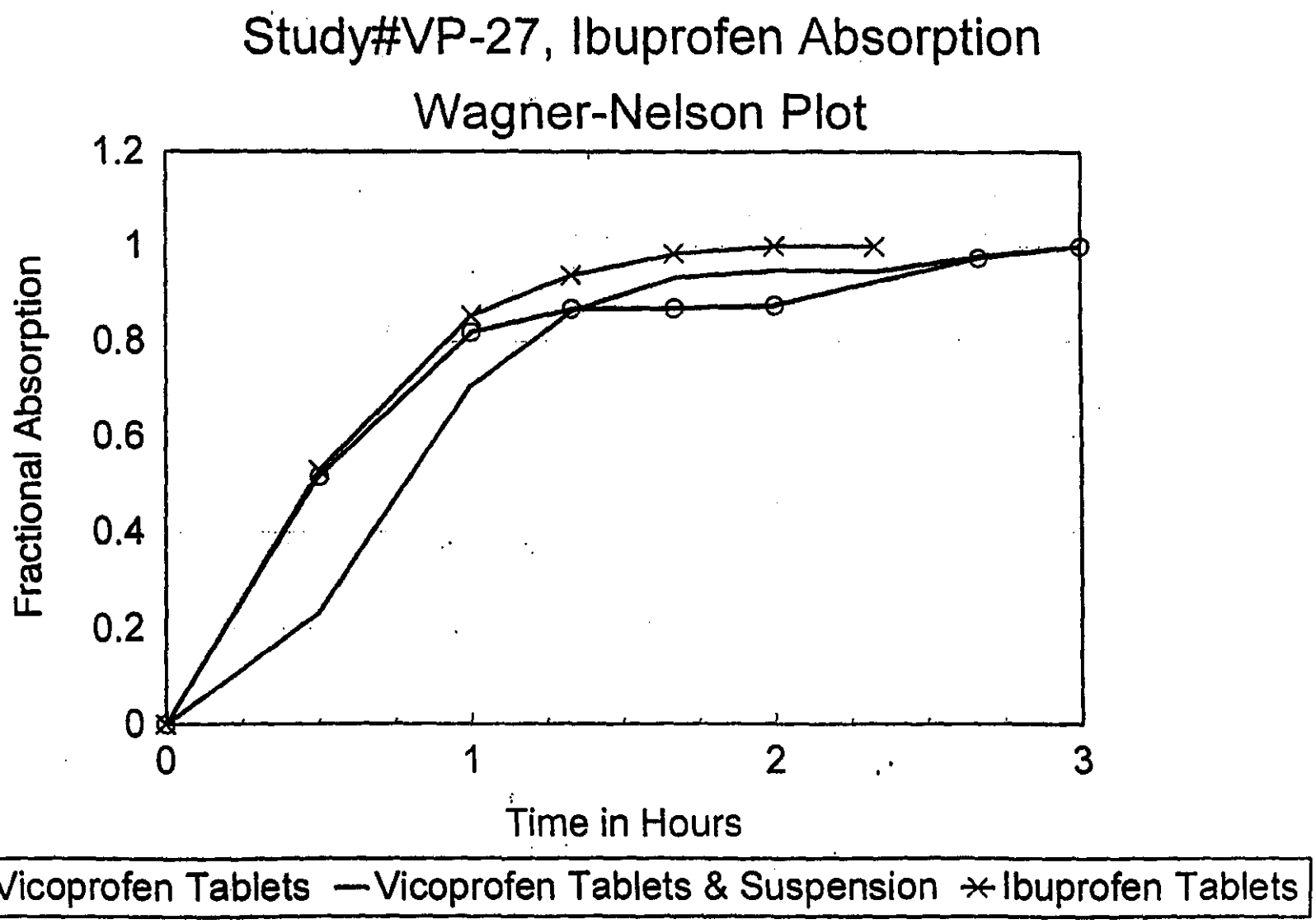


Figure 15



2 Tablet Dose (400mg Ibuprofen)



400mg Ibuprofen

Statistical Comparison of Plasma Ibuprofen Pharmacokinetic Parameters

Treatment A versus Treatment C

Parameter	Treatment Means A	C	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	(95% Confidence)	Mean Ratio
CMAX	32.006	35.474	-9.76	0.0240*	99.99	85.2 - 95.2	84.3 - 96.2	.
TMAX	1.772	1.735	2.13	0.8909	42.92	83.8 - 120.5	80.2 - 124.1	.
AUC	116.000	125.183	-7.34	0.0034*	99.99	89.8 - 95.5	89.3 - 96.1	.
AUC-INF	122.532	128.705	-4.80	0.0483*	99.99	92.4 - 98.0	91.9 - 98.5	.
KEL	0.361	0.373	-3.25	0.2859	99.99	93.2 - 100.3	92.5 - 101.0	.
HALF-LIFE	2.106	1.903	10.79	0.0712	99.71	103.9 - 117.7	102.6 - 119.0	.
LCMAX	3.435	3.556	-3.40	0.0207*	99.96	83.4 - 94.1	82.4 - 95.2	88.6
LAUC	4.719	4.802	-1.74	0.0039*	99.99	89.0 - 95.1	88.4 - 95.7	92.0
LAUC-INF	4.761	4.826	-1.34	0.0273*	99.99	90.6 - 96.9	90.0 - 97.6	93.7

Statistical Comparison of Plasma Ibuprofen Pharmacokinetic Parameters

Treatment B versus Treatment C

Parameter	Treatment Means B	C	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	(95% Confidence)	Mean Ratio
CMAX	32.675	35.474	-7.89	0.0635	99.99	87.1 - 97.1	86.1 - 98.1	.
TMAX	1.968	1.735	14.58	0.3463	42.92	96.2 - 132.9	92.6 - 136.6	.
AUC	116.178	125.183	-7.19	0.0036*	99.99	90.0 - 95.7	89.4 - 96.2	.
AUC-INF	122.606	128.705	-4.74	0.0458*	99.99	92.5 - 98.0	91.9 - 98.6	.
KEL	0.368	0.373	-1.31	0.6575	99.99	95.1 - 102.2	94.4 - 102.9	.
HALF-LIFE	2.062	1.903	8.36	0.1501	99.71	101.5 - 115.2	100.1 - 116.6	.
LCMAX	3.465	3.556	-2.56	0.0758	99.96	86.8 - 97.0	84.9 - 98.2	91.3
LAUC	4.730	4.802	-1.52	0.0102*	99.99	90.0 - 96.1	89.4 - 96.7	93.0
LAUC-INF	4.771	4.826	-1.11	0.0569	99.99	91.5 - 97.9	90.9 - 98.6	94.7

Treatment B versus Treatment A

Parameter	Treatment Means B	A	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	(95% Confidence)	Mean Ratio
CMAX	32.675	32.006	2.09	0.6566	99.99	96.5 - 107.6	95.5 - 108.7	.
TMAX	1.968	1.772	11.19	0.4245	44.44	94.2 - 130.2	90.7 - 133.7	.
AUC	116.178	116.000	0.15	0.9530	99.99	97.1 - 103.2	96.5 - 103.8	.
AUC-INF	122.606	122.532	0.06	0.9806	99.99	97.1 - 103.0	96.6 - 103.6	.
KEL	0.368	0.361	2.00	0.5235	99.99	98.3 - 105.7	97.6 - 106.4	.
HALF-LIFE	2.062	2.106	-2.19	0.6004	99.94	91.6 - 104.0	90.4 - 105.2	.
LCMAX	3.465	3.435	0.88	0.5568	99.96	97.0 - 109.5	95.9 - 110.8	101.1
LAUC	4.730	4.719	0.21	0.7027	99.99	97.8 - 104.5	97.2 - 105.1	101.1
LAUC-INF	4.771	4.761	0.21	0.7263	99.99	97.7 - 104.5	97.0 - 105.2	101.0

Treatment B = 2 x Vicoprofen(R) tablets + 20 mL orbital suspension - test
Treatment A = 2 x Vicoprofen(R) tablets - reference

Values for Treatments B and A are the least-square means (LSMEANS) from the ANOVA
Parameters with the 'L' prefix are log-transformed parameters
. = value was not calculated

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

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

Power = power (%) to detect 20% differences between treatments (a=0.05)

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

VP-27 Subjects Plasma Ibuprofen Concentrations from Ibuprofen 400mg

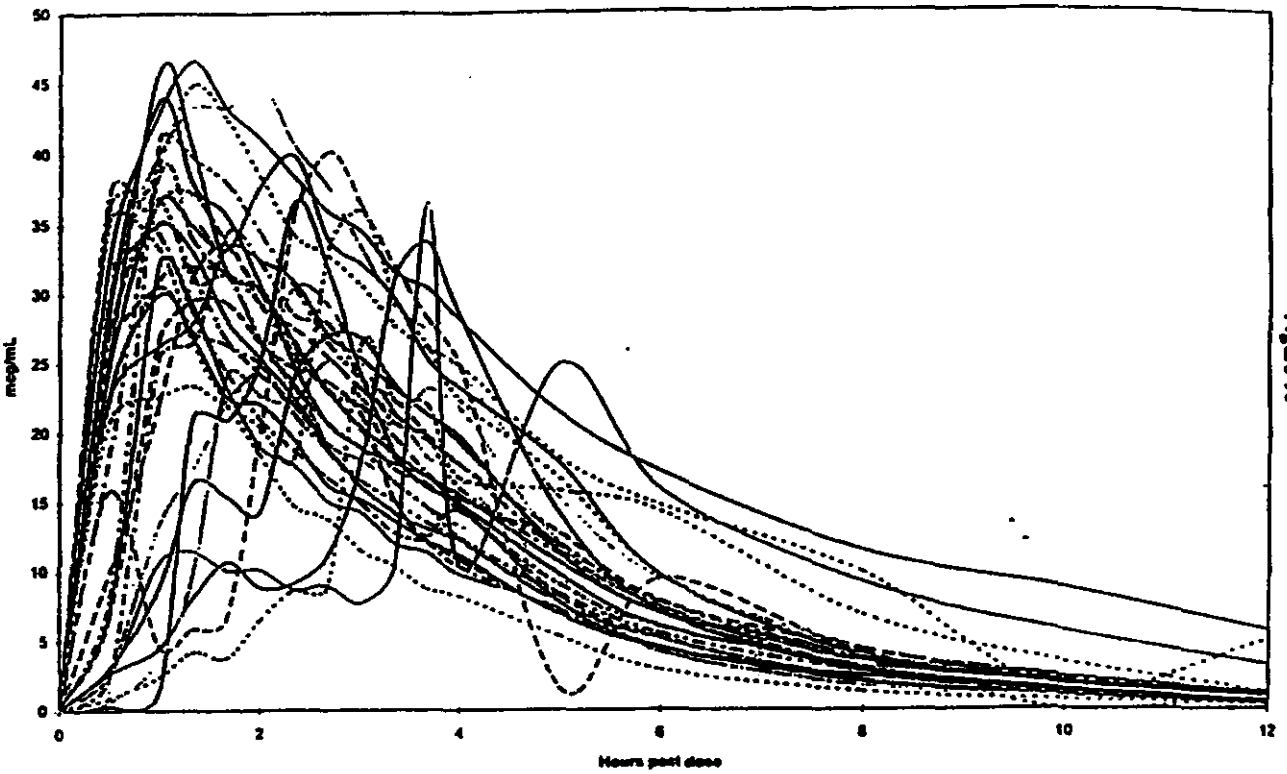


Figure 18

VP-27 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg + Placebo Suspension

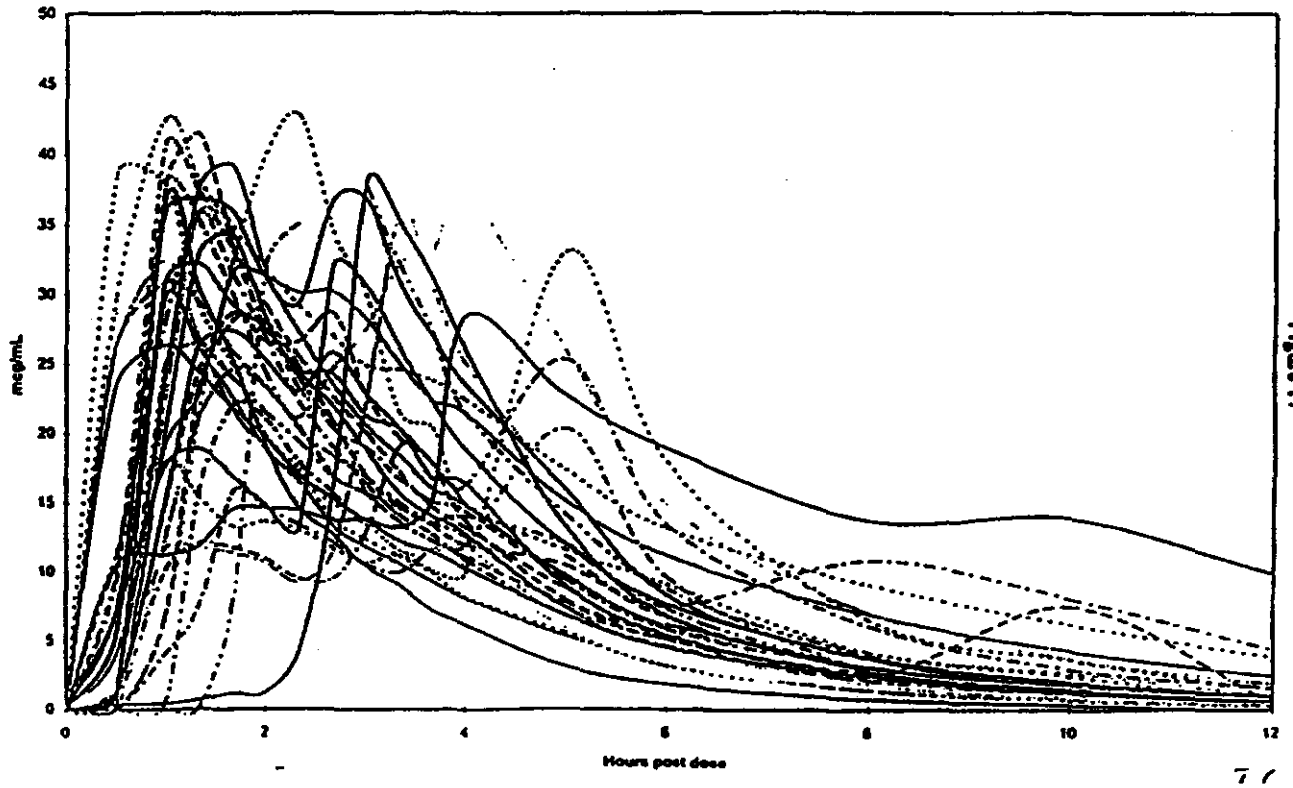


Figure 17

VP-27 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

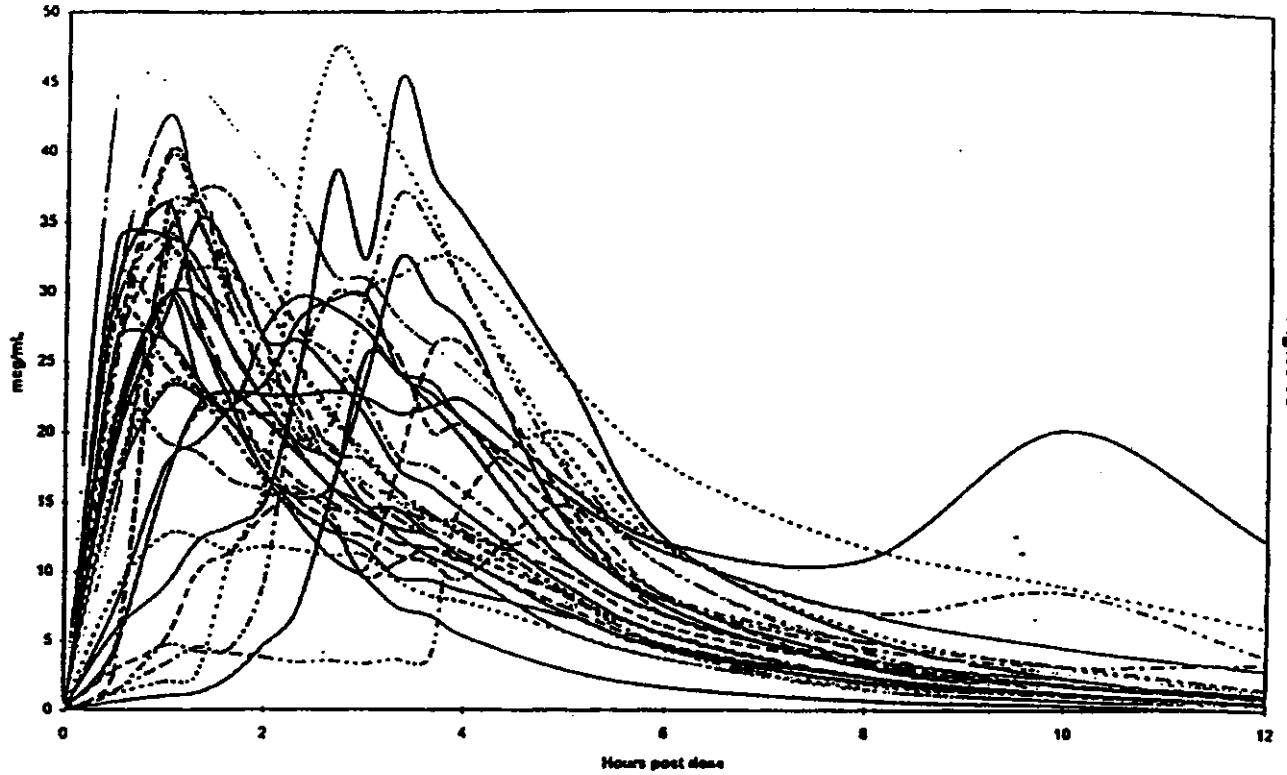


Figure 16

VP-27 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg + Placebo Suspension

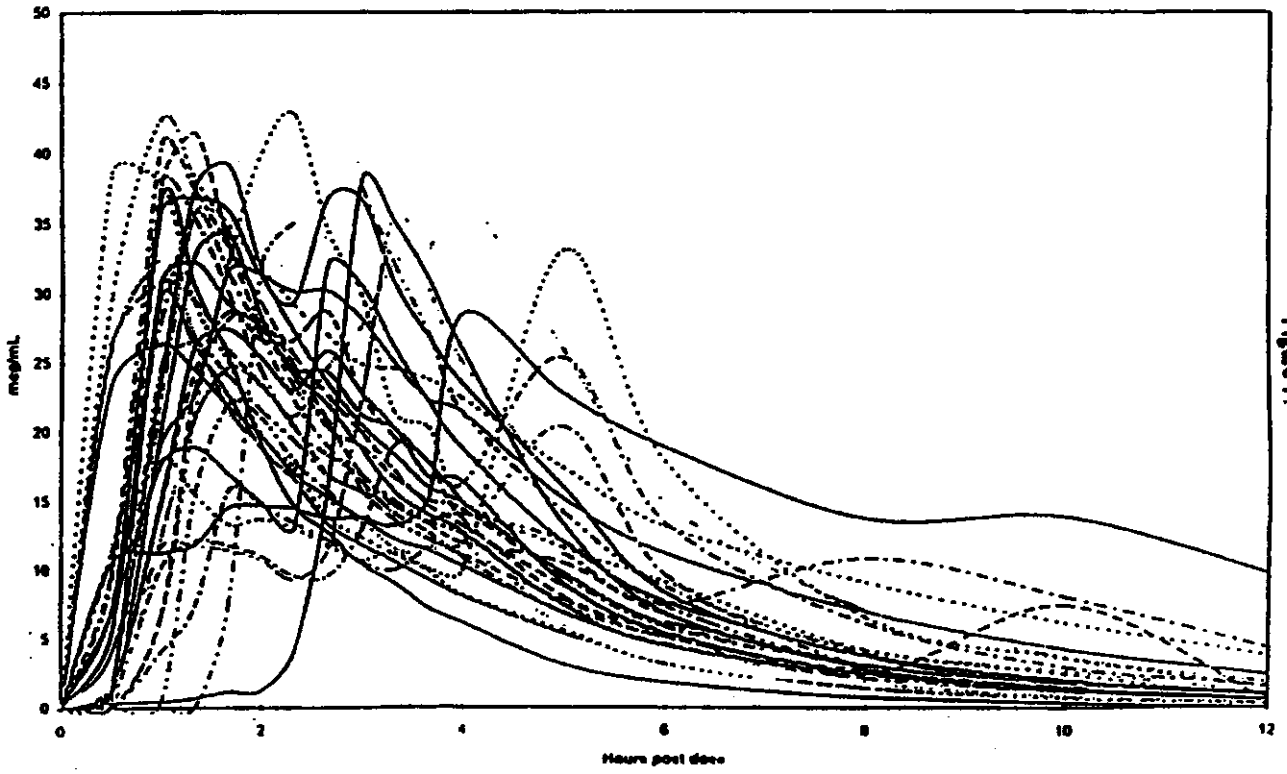


Figure 17