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APPLICATION NUMBER:

21-393 & 21-394

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-393

Submission Date: 11-17-2005

Drug Name and Strength: Advil PM Liqui-Gels® (Ibuprofen 200mg/Diphenhydramine HCl 25mg)

Formulation: Soft Gelatin Capsule

Sponsor: Wyeth Consumer Healthcare
Madison, NJ

Type of Submission: Amendment to NDA: Response to Discipline Review Letter

Reviewer: Chandra S. Chaurasia, Ph. D.

Team Leader: Suresh Doddapaneni, Ph.D.

I. BACKGROUND:

Wyeth originally submitted NDA 21-393 seeking approval of the combination product Advil PM Liqui-Gels® (ibuprofen 200 mg/diphenhydramine hydrochloride 25 mg) on October 16, 2001. This product is indicated for nighttime pain relief and sleep-aid. On August 07, 2002 the Agency requested the Sponsor to address dissolution-related Biopharmaceutics and CMC deficiencies. On June 30, 2003 the Sponsor submitted supplemental documentation on the dissolution method and associated specification. On December 18, 2003, the Agency issued an approvable letter outlining information needed to resolve the remaining issues in this application.

On June 27, 2005 the Sponsor provided dissolution data for — samples of Advil® PM Liqui-Gels® using a rotational speed of 100 rpm and 150 rpm per Agency's recommendation in the Dec 18, 2003 approvable letter.

On Oct 18, 2005 the Agency issued FDA Discipline Letter with the following recommendation to be incorporated as the final dissolution method and specification into the manufacturing control stability program of the test product Advil PM Liqui-Gels:

- Method: Apparatus USP 1 (Basket) in 900ml phosphate buffer, 200mM, pH 7.2, rotational speed 100 rpm
- Specifications: $Q = \text{---}$ at 30 minutes for both active components – ibuprofen and diphenhydramine HCl

II. SPONSOR'S RESPONSE:

In the current submission, Wyeth agreed to accept the Agency's recommendation to incorporate the recommended dissolution method and specification into the manufacturing control stability program of Advil PM Liquigels. Wyeth will continue to monitor the stability of the test product and will re-evaluate the dissolution method and specification after more data is available.

III. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS RECOMMENDATION:

From the Clinical Pharmacology and Biopharmaceutics perspective, Wyeth's response with respect to dissolution method and specification of Advil PM Liqui-Gels® (Ibuprofen 200mg/Diphenhydramine HCl 25mg) is acceptable.

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/s/

Chandra S. Chaurasia
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Suresh Doddapaneni
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BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-393

Submission Date: 06-27-2005

Drug Name and Strength: Advil PM Liqui-Gels® (Ibuprofen 200mg/Diphenhydramine HCl 25mg)

Formulation: Soft Gelatin Capsule

Sponsor: Wyeth Consumer Healthcare

Type of Submission: Amendment Response to Approvable Letter

Reviewer: Chandra S. Chaurasia, Ph. D.

Team Leader: E. Dennis Bashaw, Pharm. D.

I. INTRODUCTION:

Wyeth originally submitted two formulations of the combination products Advil PM Liqui-Gels® (ibuprofen 200 mg/diphenhydramine hydrochloride 25 mg; NDA 21-393) and Advil PM Caplets (ibuprofen 200 mg/diphenhydramine citrate 38 mg; NDA 21-394) on October 16, 2001. The combination products are indicated for nighttime pain relief and sleep-aid. On August 07, 2002 the Agency requested the Sponsor to address dissolution-related Biopharmaceutics and CMC concerns among others. On June 30, 2003 the Sponsor re-submitted supplemental documentation on the dissolution method and specification. On December 18, 2003, the Agency issued an approvable letter outlining information needed to resolve the remaining issues in this application. From the Clinical Pharmacology and Biopharmaceutics perspective, the Agency had recommended the following regarding the dissolution of the combination product:

“Based on the results of dissolution study, the dissolution method using Apparatus USP I (Basket) in phosphate buffer, 200 mM, pH 7.2 is acceptable. Using a rotational speed of 150 rpm is acceptable as an interim provided the firm makes a commitment of providing dissolution testing results of — s old samples at a rotational speed of 100 rpm. The firm’s proposed dissolution specification of $Q=$ — at 45 minutes is not acceptable. The Division recommends an interim specification of $Q=$ — at 45 minutes for both active components—Ibuprofen and Diphenhydramine HCl—until more data is available on stability of the test product.”

This submission is the Sponsor’s response on dissolution method and specifications, among others to the Agency’s approvable letter dated Dec 18, 2003.

Sponsor’s Response:

The Sponsor has provided dissolution data for — , samples of Advil® PM Liqui-Gels® using a rotational speed of 100 rpm and 150 rpm. These are summarized in the Table 1 below. Figure 1 (Appendix) presents the mean dissolution profiles for samples at — using rotational speeds of 100 rpm and 150 rpm. Additionally, dissolution data for — -old samples at 100 rpm and 150 rpm are given in Table 2 (Appendix).

The Sponsor states that the rate at which complete dissolution of Advil PM Liquid-Gels approaches asymptote is lower and more variable at 100 rpm than at 150 rpm for both the old samples stored at 25 C/60%RH. Based on this observation, the Sponsor suggests that dissolution testing will pass the FDA requested specification of Q in 45 minutes; however, the 150 rpm rotational speed is needed, particularly for product age and beyond. The Sponsor thus argues that an increase in Q from in 45 minutes, as requested by the FDA in the Dec 18, 2003 letter, is acceptable if the dissolution rotational speed remains at 150 rpm.

Reviewer's Comments on Dissolution Specifications:

The data presented show an individual dissolution release of for each of the active ingredients – ibuprofen and diphenhydramine - of the old capsules (N=12) at either of the rotational speed (i.e., 100 or 150 rpm) at 30-minute and 45-minute sampling time. Furthermore, the mean dissolution release for each of the active ingredients is ≥95% in each case. Clearly, asymptote is reached at 30 minute with 100 rpm rotational speed for a old sample stored at ambient storage conditions 25 °C/60% RH. These data suggest that dissolution testing will pass a specification of C in 30 minutes for product old. It is noted that the FDA suggested specification of Q in 45 minutes was interim in nature based on the old samples provided at that time. The dissolution characteristics of the old samples were not presented at that time. It is further apparent from the data that there is a marked deterioration in the dissolution performance of the dosage form between

Based on the results provided, even if one uses the sponsors proposed dissolution specification at 150rpm, S2 testing would be required for the lot of drug product submitted in this amendment due to their poor performance at . The Agency recommends that the Sponsor incorporates the following dissolution method and specification into the manufacturing control and stability program of the test product Advil PM Liqui-Gels® (Ibuprofen 200mg/Diphenhydramine HCl 25mg):

- Method: Apparatus USP I (Basket) in 900 mL phosphate buffer, 200 mM, pH 7.2, rotational speed 100 rpm.
- Specification Q= at 30 minutes for both active components—Ibuprofen and Diphenhydramine HCl.

IV. RECOMMENDATIONS:

It is the recommendation of the Office of Clinical Pharmacology and Biopharmaceutics that the final in vitro dissolution test and specification be set as follows:

- Method: Apparatus USP I (Basket) in 900 mL phosphate buffer, 200 mM, pH 7.2, rotational speed 100 rpm.
- Specification: Q= at 30 minutes for both active components—Ibuprofen and Diphenhydramine HCl.

Chandra S. Chaurasia, Ph.D. _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

Date: _____

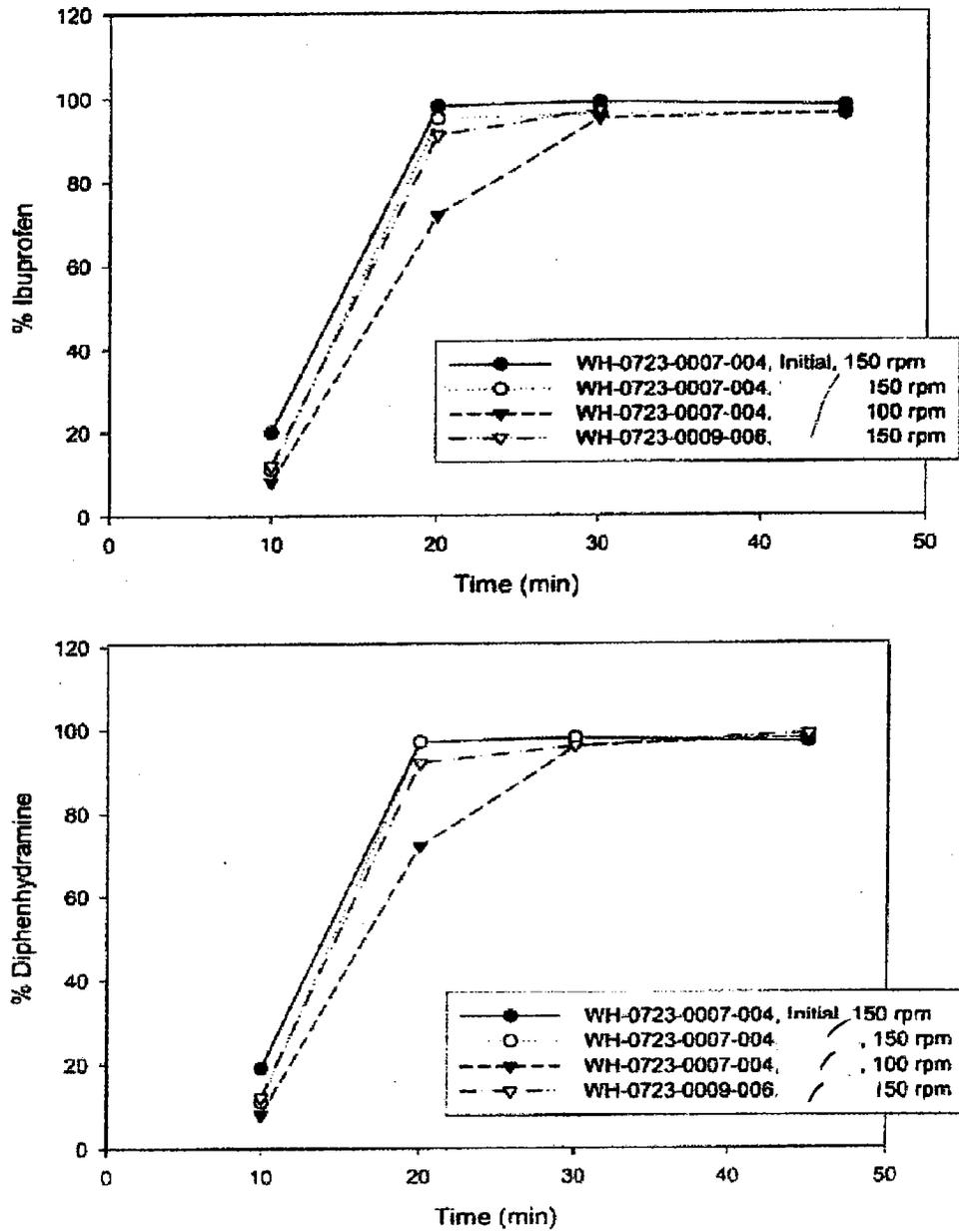
RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____
Team Leader, Clinical Pharmacology and Biopharmaceutics

Date: _____

cc: NDA 21-394 HFD-560 (Div. File), HFD 550 CSO (Dean), HFD-560 CSO (Cutter), HFD-880 (J. Lazor, A. Selen, E.D. Bashaw, C. Chaurasia, A. Noory)

APPENDIX

Figure 1
Mean Percent Dissolved
at 25°C / 60% RH
Apparatus I at 100 rpm and 150 rpm



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/s/

Chandra S. Chaurasia
9/19/2005 05:07:24 PM
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Dennis Bashaw
9/19/2005 05:46:07 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-393

Submission Date: 06-30-2003

Drug Name, Dose and Formulation: Advil PM Liquigels Ibuprofen 200mg/Diphenhydramine HCl 25mg

Sponsor: Wyeth Consumer Healthcare

Type of Submission: Amendment Response to Approvable Letter

Reviewer: Chandra S. Chaurasia, Ph. D.

Team Leader: E. Dennis Bashaw, Pharm. D.

I. INTRODUCTION:

Wyeth originally submitted the NDA 21-393 dated October 16, 2001 under section 505(b) for Advil PM (ibuprofen/diphenhydramine hydrochloride) Liquigels. The combination product is a liquid-filled gelatin capsule, and is indicated for nighttime pain relief and sleep-aid. On August 07, 2002, the Agency issued an approvable status to this application, and requested the sponsor to address dissolution-related Biopharmaceutics and CMC concerns among others.

II. SYNOPSIS

The Clinical Pharmacology and Biopharmaceutics section of this submission contained 3 pharmacokinetic studies, which were originally reviewed by Dr. Jang-Ik Lee in 2002. Additionally, the sponsor also provided in vitro dissolution data on this combination product. The firm's proposed dissolution method and specifications were as follow:

Apparatus: USP Apparatus I (basket) at 150 rpm

Medium: 900 mL of 200 mM, pH 7.2 phosphate buffer

Specification: $Q = 75\%$ at 45 minutes for both active components-Ibuprofen and Diphenhydramine HCl.

It is noted that the pharmacokinetic studies were found acceptable from the Clinical Pharmacology and Biopharmaceutics perspective, however, with regard to dissolution testing both the Clinical Pharmacology and Biopharm and CMC reviewers requested the sponsor to provide more detailed information with data on the proposed dissolution method and specification.

In the current submission, Wyeth has provided its response to FDA's Information Request Letter dated Aug 07, 2002.

III. REVIEW OF THE SUBMITTED INFORMATION ON DISSOLUTION:

Agency's Comments (on dissolution specifications):

3a. Dissolution profiles, submitted in the section for Investigational Formulations, showed that the rates of dissolution for both actives approached asymptote at the 20-minute time interval. Please provide justification for the proposed acceptance criterion of $Q = 75\%$ in 45 minutes for both of the actives, ibuprofen and diphenhydramine hydrochloride.

Firm's Response:

Wyeth believes that the originally proposed dissolution specification ($Q = \text{---}$ in 45 minutes) can be justified based on several considerations:

- Updated stability results generated subsequent to the original NDA submission show that dissolution profiles for certain --- samples do not approach asymptote until 45 minutes for both ibuprofen and diphenhydramine hydrochloride.
- A review of stability results indicate that a specification of $Q = \text{---}$ in 45 minutes is discriminating with a significant amount of samples requiring Tier 2 dissolution testing.
- The approach used to determine the originally proposed dissolution specification for Advil PM Liquegels is consistent with compendial/regulatory guidelines for establishing dissolution acceptance criteria.

Additionally, the firm has considered the following information to determine the proposed specification of $Q = \text{---}$ at 45 min (details provided in Report 02GTR058.00 pages 1-26):

- Compendial/regulatory guidelines for setting dissolution specifications. In particular the sponsor has cited the following USP guidelines:
- The test time is generally 30 to 60 minutes, with a single time point specification.
- To allow for typical disintegration times, test times of less than 30 minutes should be based on demonstrated need.
- Dissolution test times and specifications usually are established on the basis to an evaluation of dissolution profile data.
- Typical specifications for the amount of active ingredient dissolved, expressed as a percentage of the labeled content (Q), are in the range of 70% to 80% Q dissolved.
- A Q value in excess of 80% is not generally used, as allowance needs to be made for assay and content uniformity ranges.

The firm has conducted dissolution testing on --- of the Advil PM Liquegels that were subjected to varying stability conditions (25-40 °C, 60-75% relative humidity, and --- stability periods). Dissolution was carried out at 150 rpm for 45-minutes, with sampling at 10, 20, 30 and 45 minutes.

The firm states that a rotational speed of 150 rpm was chosen for historical reasons as the physical parameter (basket at 150 rpm) was used in for NDA 20-402 stability data in the submission of the single entity liqigel product, Advil Liquegels. Since second component in PM Liquegels, Diphenhydramine HCl, is readily soluble at pH 7.2, the firm anticipated that ibuprofen in fact would be the rate-limiting component.

The firm states that the reported stability data show a high percent of samples that require Tier 2 testing even at the current specification of $Q = \text{---}$ at 45 minutes (Table 1 below):

Table 4 – NDA Stability Batches: Dissolution Testing Summary*

Time (minutes)	Q = — (Q + 5 = —)	Q = — (Q + 5 = —)
10	100% Tier 2	100% Tier 2
20	36% Tier 2 3% Tier 1 - Stage 3 8% Tier 1 - Stage 2	39% Tier 2 6% Tier 1 - Stage 2
30	31% Tier 2	33% Tier 2 6% Tier 1 - Stage 2
45	28% Tier 2	28% Tier 2

* Batches 001 – 006 unless otherwise specified: ~~—~~ @ 25°C/60%RH, ~~—~~ @ 25°C/60%RH ~~—~~
~~—~~ @ 25°C/60%RH (Batches 001 – 003 only), ~~—~~ @ 30°C/60%RH (Batches 001 – 003 only) ~~—~~
~~—~~ @ 40°C/75%RH (Batches 001 – 003 only), and ~~—~~ @ 40°C/75%RH

Reviewer’s Comments on Dissolution Specifications:

Based on the reported data in the dissolution testing of the – NDA 21-393 stability batches, dissolution results from samples at accelerated stability conditions 40 °C/75% is not very relevant considering the physical nature of gelatin capsules, and also the fact that the firm has dissolution results for ~~—~~ long-term stability samples at ambient storage conditions, e.g. 25 °C /60%RH. Examination of the data from the report 02GTR058.00 page 7 indicates that at 30- or 45-minute while only those samples that were subjected to accelerated stability 40 °C /75%RH @ ~~—~~ require Tier 2 testing, only one unit of the samples under normal stability (i.e., 25 °C/60% RH) required Tier 2 testing (see Appendix, Table A, page 6 of this review). Presumably, the elevated stability testing conditions accelerates ~~—~~ necessitating the use of Tier 2 testing.

Furthermore, while at 30-minute one unit at ~~—~~ failed at both the S1 and S2 levels, at the 45-minute each unit undergoing long term stability (~~—~~ @ 25 °C/60% RH), passes the Q ~~—~~ specification. Thus, considering a 45 minute sampling time to set the specification, the Agency recommends an interim dissolution of ~~—~~ for both active components-Ibuprofen and Diphenhydramine HCl.

Agency’s Comments (on dissolution method and rotational speed):

3b. Dissolution test was carried out in USP Type 1 (basket) apparatus with rotation speed at 150 RPM. Please provide your rationale for the selection of 150 RPM.

Firm’s response:

A rotational speed of 150 rpm for the dissolution of Advil PM Liquigels (ibuprofen and diphenhydramine hydrochloride) is based on the regulatory method for single-entity ibuprofen liquigels (approved per NDA 20-402). Additionally, the firm has also submitted formal summary (General Technical Report 02GTR061.00) of the development of the dissolution method for Advil PM Liquigels to support the proposed dissolution method in terms of the selected media and the specified testing conditions, and rotational speed. The salient features of this report are summarized below:

Apparatus: Apparatus I was used as preliminary studies with Apparatus II (Paddle)

Dissolution Media:

PH Variations: A summary of the results for ibuprofen and diphenhydramine using different pH at a rotational speed of 150 rpm are given in Appendix (Table 2, page 8 of this review)

The results of these investigations are summarized in firm's report. Briefly, the 200-mM phosphate buffer at pH 7.2 and therefore, was the medium of choice for dissolution testing.

Rotation Speeds:

The firm argues that for liqigels the burst time of the gelatin shell is often the rate-limiting step for release and complete dissolution of the active components. The firm conducted dissolution testing using a dissolution medium of phosphate buffer 200 mM, pH 7.2 on fresh and aged samples at varied speeds of 75, 100 and 150 rpm. Dissolution sampling were obtained at 10, 20, 30 and 45 minutes. An infinity time point was also collected for 100 and 75 rpm conditions by increasing the speed to 150 rpm for 15 min and 150 rpm for 30 min, respectively. Results are summarized in Tables (in the firm's submission), and also depicted graphically in the Appendix.

Based on these results, the firm states that the lower rotational speed were not predictive of the actual long-term dissolution performance of the aged samples, specifically long-term samples at 25 °C /60%RH.

Reviewer's Comments on Dissolution Method and Rotational Speeds:

Based on the results of dissolution profile, the firm's rationale of using USP Apparatus I (Basket) and dissolution media phosphate buffer 200 mM, pH 7.2 is acceptable.

With regards to the rotational speed, it is noted that the firm's long-term stability dissolution results are based on the comparative testing of the fresh and aged capsules at 75, 100 and 150 rpm. While dissolution results at 150 rpm for capsules are provided, there are no data comparing the old products at 75 and 100 rpm to the fresh products. The results at 150 rpm is acceptable at the present time provided the firm makes a commitment of providing dissolution results on the stability samples at 100 rpm.

IV. RECOMMENDATIONS:

Based on the results of dissolution study, the dissolution method using Apparatus USP I (Basket) in phosphate buffer, 200 mM, pH 7.2 is acceptable. Using a rotational speed of 150 rpm is acceptable as an interim provided the firm makes a commitment of providing dissolution testing results of old samples at a rotational speed of 100 rpm. The firm's proposed dissolution specification of Q= at 45 minutes is not acceptable. The Division recommends

an interim specification of Q= — at 45 minutes for both active components—Ibuprofen and Diphenhydramine HCl—until more data is available on stability of the test product.

Chandra S. Chaurasia, Ph.D. _____ Date:
Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date:

cc: NDA 19-872 HFD-560 (Div. File), HFD 550 CSO (Dean), HFD-560 CSO (Cutter), HFD-880 (Bashaw), HFD-880 (Lazor), HFD-880 (Chaurasia)

APPENDIX
Table A - NDA Stability Data (Averaged Results - 99SP063 and 00SP037)

Q = —

@ 25C/60RH										@ 30C/60RH									
Discharge curve - C1										Discharge curve H1									
Time (min)	A	B	C	D	E	F	G	H	I	Time (min)	A	B	C	D	E	F	G	H	I
10	95	90	85	80	75	70	65	60	55	10	N/A								
20	95	90	85	80	75	70	65	60	55	20	97	91	84	77	70	63	56	49	42
30	97	90	80	70	60	50	40	30	20	30	93	84	75	66	57	48	39	30	21
45	95	80	70	60	50	40	30	20	10	45	95	89	82	75	68	61	54	47	40
Impedance										Impedance									
Time (min)	A	B	C	D	E	F	G	H	I	Time (min)	A	B	C	D	E	F	G	H	I
10	95	90	85	80	75	70	65	60	55	10	N/A								
20	94	87	80	72	64	56	48	40	32	20	95	88	81	74	67	60	53	46	39
30	95	88	80	72	64	56	48	40	32	30	93	86	78	70	62	54	46	38	30
45	97	93	85	77	69	61	53	45	37	45	95	89	82	75	68	61	54	47	40
@ 25C/60RH										@ 40C/75RH									
Discharge curve - C1										Discharge curve H1									
Time (min)	A	B	C	D	E	F	G	H	I	Time (min)	A	B	C	D	E	F	G	H	I
10	95	90	85	80	75	70	65	60	55	10	N/A								
20	95	90	85	80	75	70	65	60	55	20	95	88	80	72	64	56	48	40	32
30	95	90	85	80	75	70	65	60	55	30	92	85	77	69	61	53	45	37	29
45	100	99	90	80	70	60	50	40	30	45	93	86	78	70	62	54	46	38	30
Impedance										Impedance									
Time (min)	A	B	C	D	E	F	G	H	I	Time (min)	A	B	C	D	E	F	G	H	I
10	95	90	85	80	75	70	65	60	55	10	N/A								
20	95	90	85	80	75	70	65	60	55	20	95	88	80	72	64	56	48	40	32
30	97	90	85	80	75	70	65	60	55	30	94	87	79	71	63	55	47	39	31
45	95	90	85	80	75	70	65	60	55	45	95	89	82	75	68	61	54	47	40
@ 25C/60RH										@ 40C/75RH									
Discharge curve - C1										Discharge curve H1									
Time (min)	A	B	C	D	E	F	G	H	I	Time (min)	A	B	C	D	E	F	G	H	I
10	95	90	85	80	75	70	65	60	55	10	N/A								
20	95	90	85	80	75	70	65	60	55	20	95	88	80	72	64	56	48	40	32
30	95	90	85	80	75	70	65	60	55	30	95	88	80	72	64	56	48	40	32
45	100	100	101	N/A	N/A	N/A	N/A	N/A	N/A	45	95	89	82	75	68	61	54	47	40
Impedance										Impedance									
Time (min)	A	B	C	D	E	F	G	H	I	Time (min)	A	B	C	D	E	F	G	H	I
10	95	90	85	80	75	70	65	60	55	10	95	88	80	72	64	56	48	40	32
20	95	85	75	N/A	N/A	N/A	N/A	N/A	N/A	20	95	88	80	72	64	56	48	40	32
30	95	85	75	N/A	N/A	N/A	N/A	N/A	N/A	30	95	88	80	72	64	56	48	40	32
45	97	90	82	N/A	N/A	N/A	N/A	N/A	N/A	45	95	89	82	75	68	61	54	47	40

for Q = Q+ indicates Stage 2 testing required if Q = A 001-157-01 D 004-111-01 G 005-157-01
 <Q-15> 73 indicates Stage 3 testing required if Q = R 002-157-01 F 002-157-01 H 006-111-01
 <Q-20> 12 indicates Stage 2 testing required if Q = C 003-157-01 E 003-111-01 I 005-157-01

Figure 1 – Dissolution Profile of WH-0723-0009-001-157-01

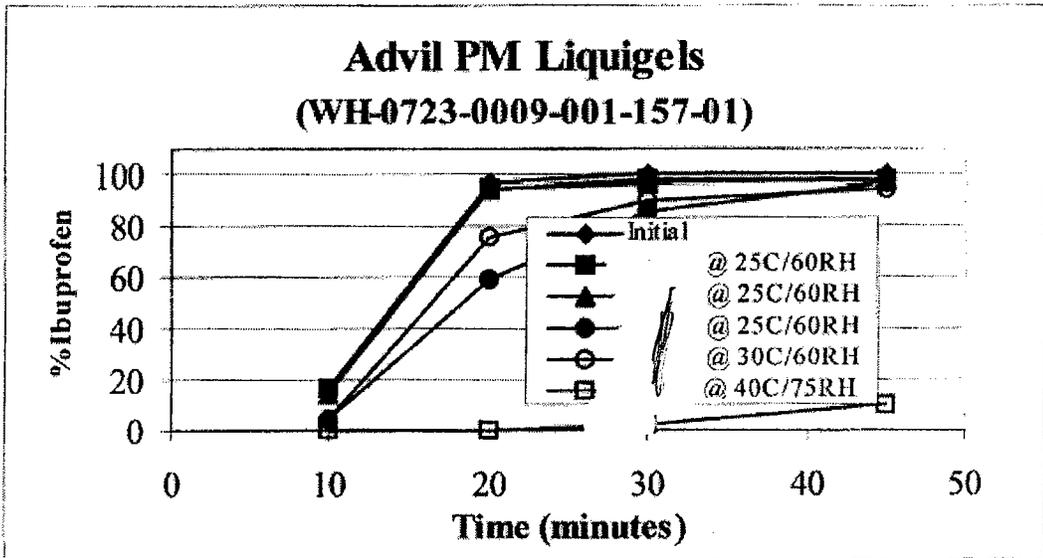
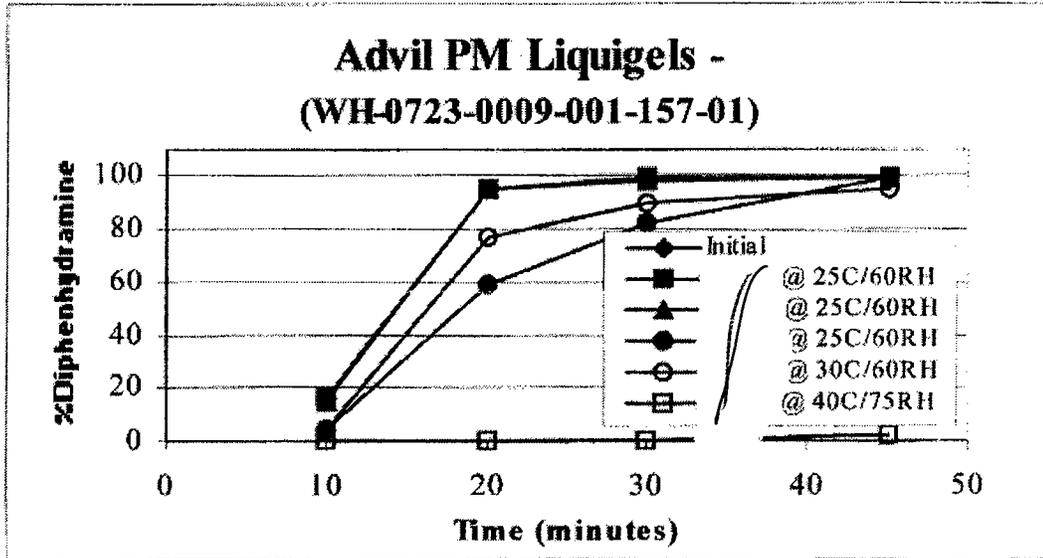


Table 2 – Average % Dissolved as a Function of pH at 150 rpm

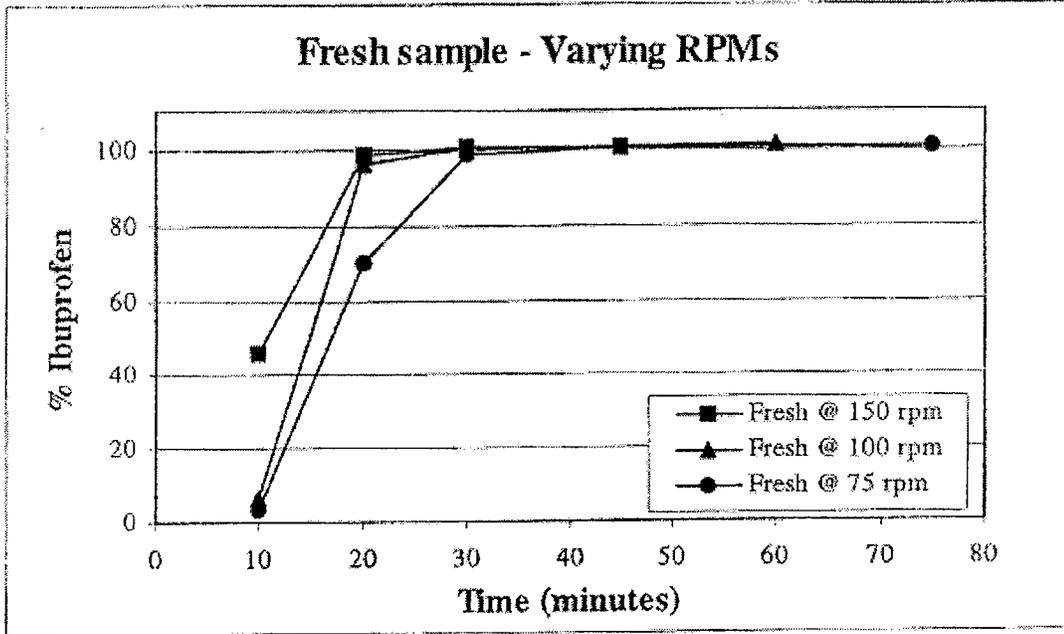
Time (min)	IBU			DPH		
	pH 6.5	pH 6.8	pH 7.2	pH 6.5	pH 6.8	pH 7.2
10	33	40	63	24	33	55
20	92	94	99	80	86	96
30	93	97	100	86	93	98
40	-	-	100	-	-	98
45	94	95	-	87	92	-
50	-	-	99	-	-	97
60	93	94	97	86	93	95

- Time point not collected

Table 5 – Advil PM Liquigels Used for RPM Study

Sample ID	Storage Conditions	RPM Studied
Fresh SF201696	N/A	75, 100, 150
Fresh SF201698	N/A	100, 150
WH-0723-0009-005-111-01	@ 25°C/60%RH	150
WH-0723-0009-001-157-01	@ 25°C/60%RH	75, 100, 150
WH-0723-0009-002-157-01	@ 25°C/60%RH	100, 150
WH-0723-0009-003-157-01	@ 25°C/60%RH	100, 150

Figure 2 - Fresh Sample (Batch # SF201696)
Apparatus I at 75, 100, and 150 rpm



200-mM pH 7.2 phosphate buffer

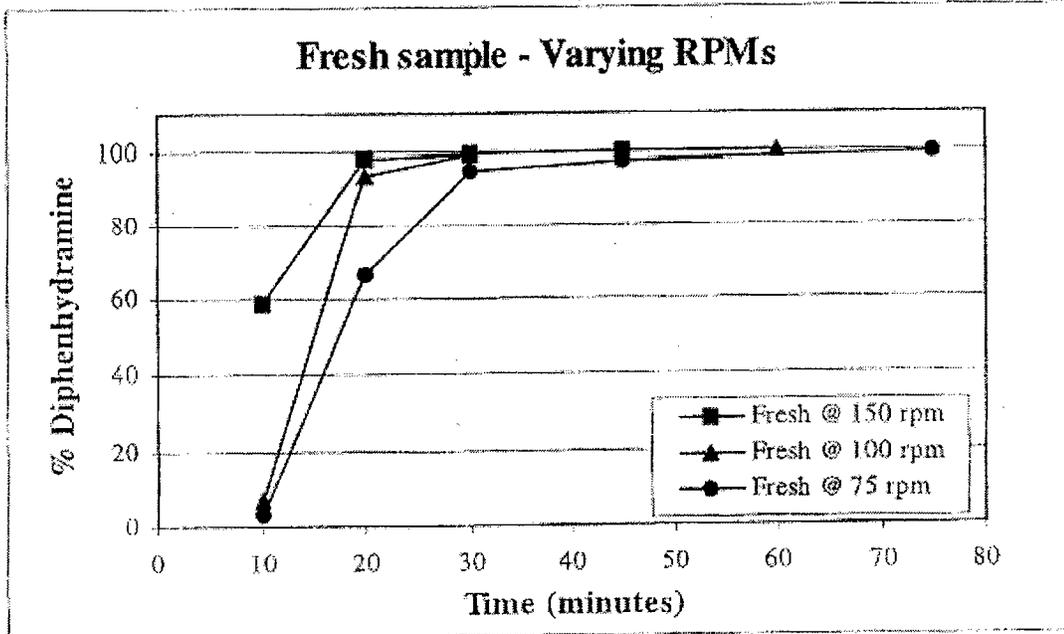


Figure 3 - Aged Sample @ 25°C/60%RH)
Apparatus I at 75, 100, and 150 rpm, 200-mM pH 7.2 phosphate buffer
WH-0723-0009-001-157-01

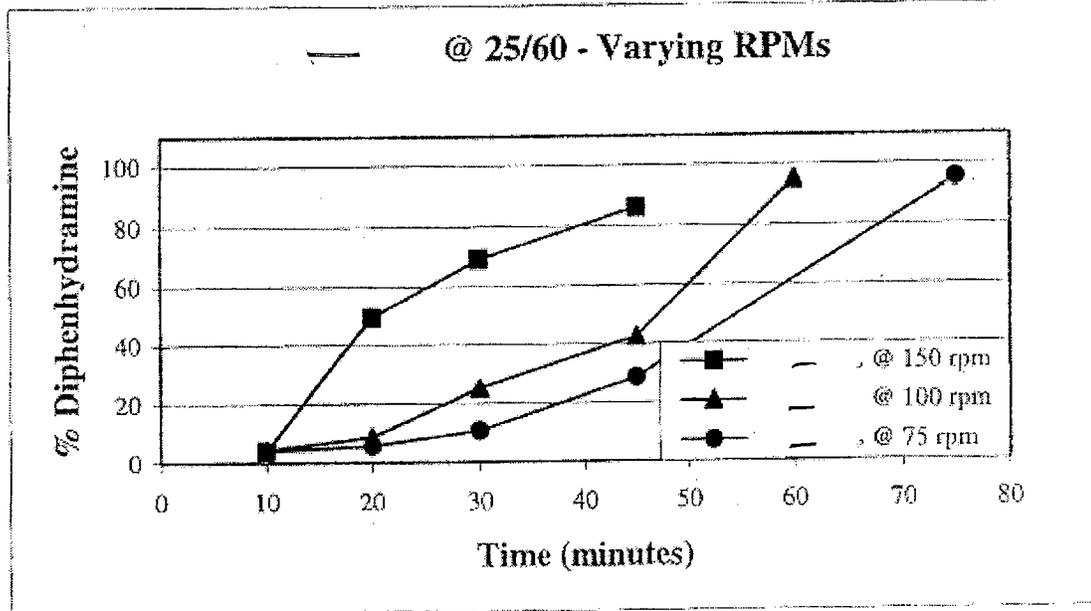
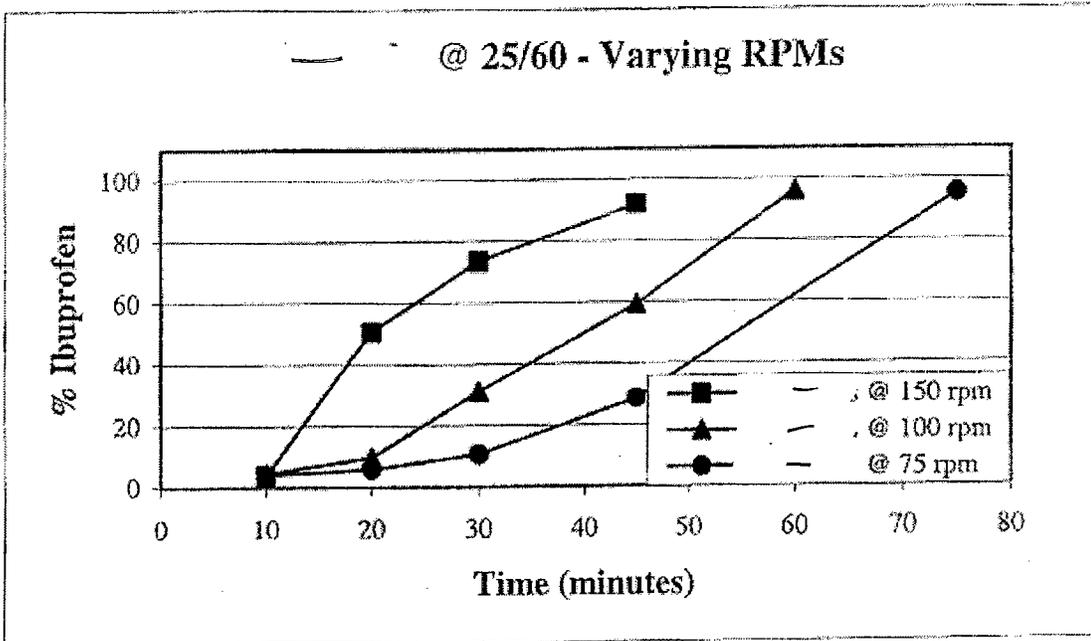


Figure 4 - Fresh and Aged Samples
Apparatus I at 150 rpm, 200-mM pH 7.2 phosphate buffer

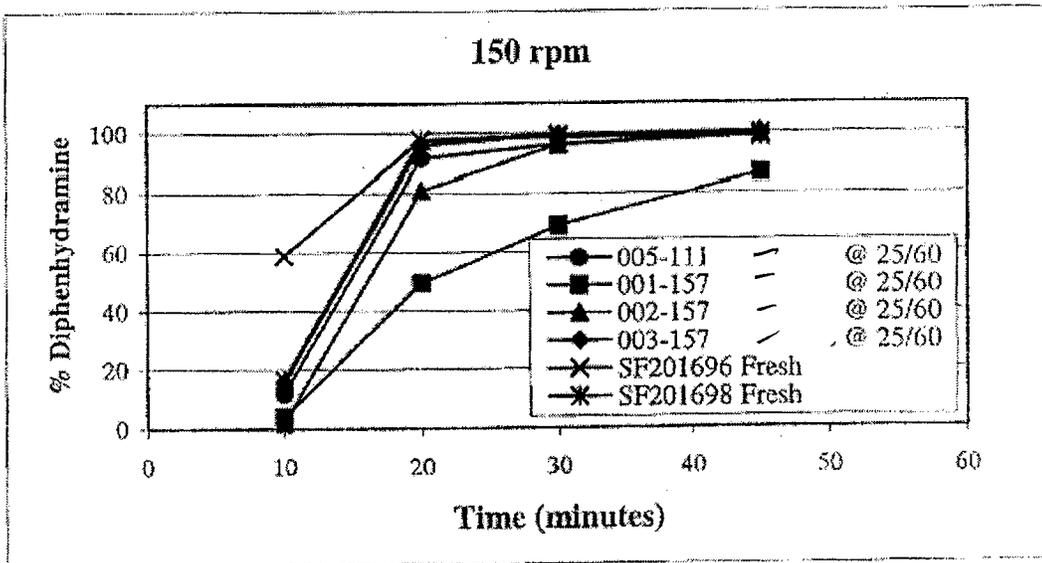
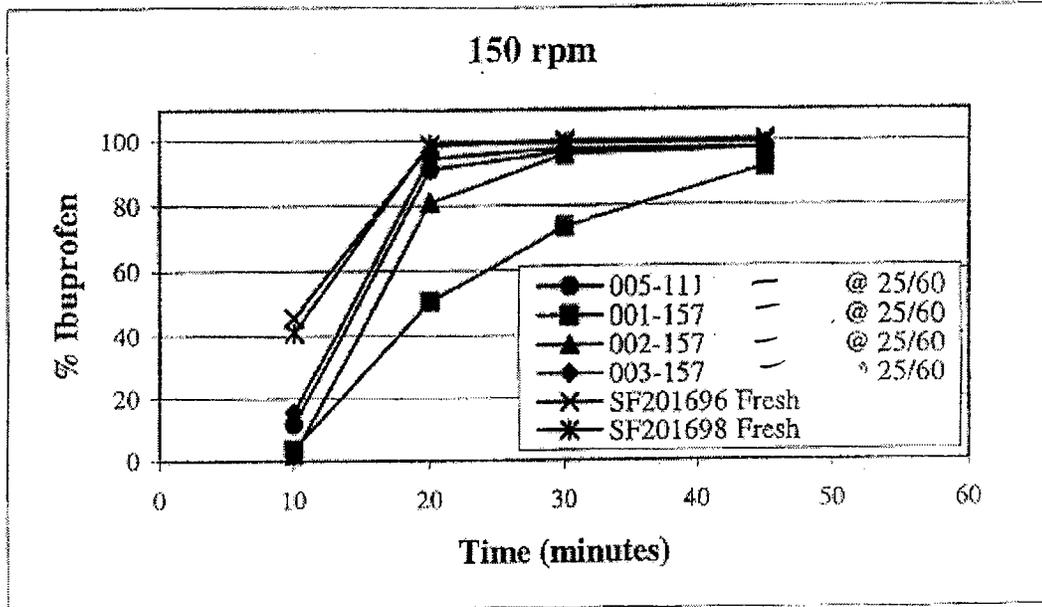
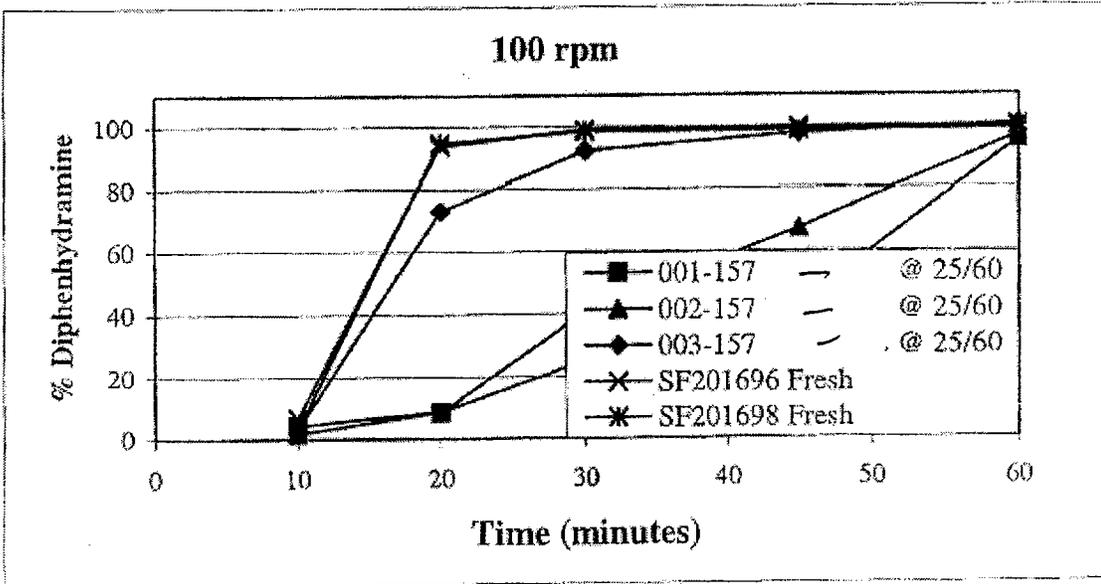
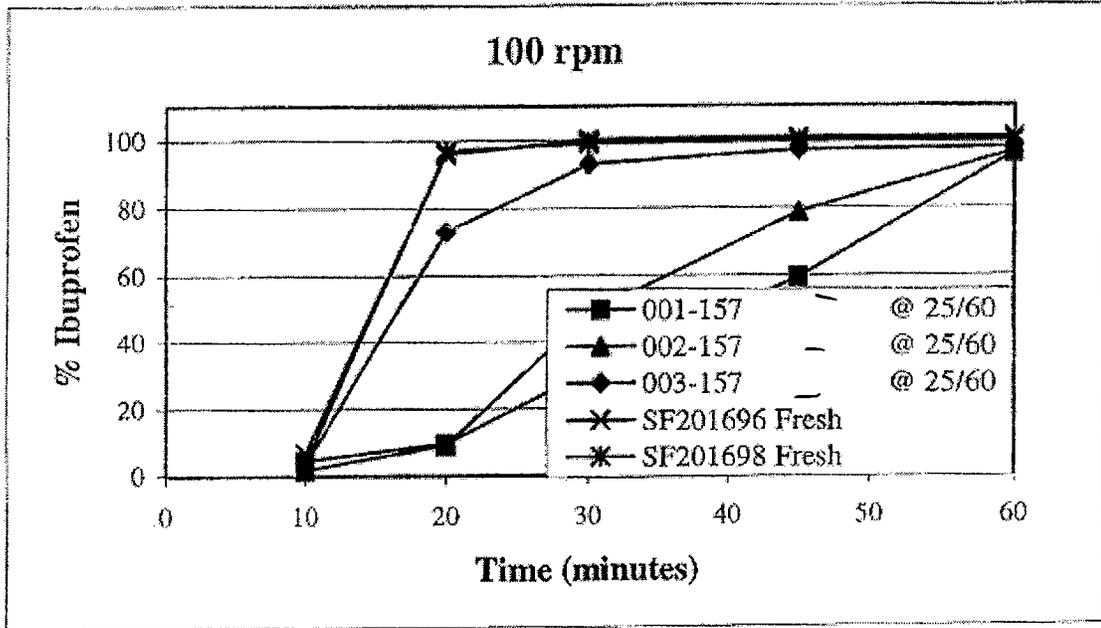


Figure 5 – Fresh and Aged Samples
 Apparatus I at 100 rpm, 200-mM pH 7.2 phosphate buffer



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19 to 7 pages. OTC PM Cutter,L added
on CC list

Dennis Bashaw
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BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-393	Submission Date(s): 10/16/01
Brand Name	Advil PM Liquigels
Generic Name	Ibuprofen / Diphenhydramine HCl
Reviewer	Jang-Ik Lee, Pharm.D., Ph.D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
OND division	ODE V (HFD-550)
Sponsor	Wyeth Consumer Healthcare
Relevant IND(s)	56,521; 44,767
Submission Type; Code	4S
Formulation; Strength(s)	Liquid-filled capsules, Ibuprofen 200 mg / Diphenhydramine HCl 25 mg
Indication	Analgesic / nighttime sleep-aid

1. EXECUTIVE SUMMARY

Ibuprofen, a propionic acid derivative, is an NSAID with analgesic and antipyretic properties. Diphenhydramine is an H₁ receptor antagonist of the ethanolamine class that has been used as a sedative and antihistaminic agent. Ibuprofen and diphenhydramine have been studied extensively and their pharmacokinetic and pharmacodynamic properties are well known. Advil PM Liquigels are a combination of these two drugs. The combination may reduce the need for pain medication and provide longer duration of sleep and, therefore, be indicated for nighttime pain relief and sleep-aid. Even though both ibuprofen and diphenhydramine are available over the counter, their combination has not been approved in the United States or elsewhere in the world. The dosage form in this submission is a liquid-filled gelatin capsule (liquigels). The sponsor also filed a separate NDA (N21-394) for a solid caplet dosage form that Dr. Abi Adebawale has reviewed. There may be an Advisory Committee meeting to address unresolved clinical issues.

The sponsor reported 3 pharmacokinetic studies (Table I) consisting of 14 volumes in this NDA submission. Study WM-716 is the first study designed to determine whether there is any pharmacokinetic interaction between ibuprofen and diphenhydramine when administered simultaneously. The study used solid-filled capsules containing ibuprofen 200mg and solid-filled capsules containing diphenhydramine citrate 38 mg alone or together. Study AE-97-02 was conducted subsequently upon the development of Advil PM Liquigels. The study compared the rate and extent of absorption of ibuprofen and diphenhydramine from Advil PM Liquigels

administered under fasted conditions with those from Advil PM Liquigels given under fed conditions (food effect), and with those from the single ingredient liquigels of ibuprofen and diphenhydramine administered simultaneously under fasted conditions (formulation effect). Then, the sponsor conducted Study AE-97-09 according to the Agency's recommendation during a meeting to discuss the designs and results of Study WM-716 and Study AE-97-02. This study compared Advil PM Liquigels with single ingredient marketed products including Advil Liquigels (ibuprofen 200 mg), Benadryl Liquigels (diphenhydramine HCl 25 mg) and Nuprin Tablets (ibuprofen 200 mg).

1.1. Recommendations

From a Clinical Pharmacology and Biopharmaceutics point of view, the pharmacokinetic studies provided in this submission are acceptable. However, it should be clarified whether a fast speed of agitation (150 rpm) is required to assure proper dissolution in spite of the finding that the dissolution of all clinical and to-be-marketed batches was almost 90% or higher within 20 minutes for both ibuprofen and diphenhydramine. This needs to be communicated with the sponsor.

1.2. Phase IV Commitments

None

1.3. Comments to the Sponsor

The reviewer requests the sponsor to provide more detailed information with data on the proposed dissolution method and specification. The information should include the rationale for selecting the speed of agitation as 150 rpm even though the data submitted in this NDA showed that the dissolution of all clinical and to-be-marketed batches was almost 90% or higher within 20 minutes for both ibuprofen and diphenhydramine. The speed both in the monograph of diphenhydramine HCl capsules and in the current Agency's guidance for general dissolution test is 100 rpm using USP apparatus type I (basket).

Jang-Ik Lee, Pharm.D., Ph.D.
Pharmacokinetics Reviewer
Division of Pharmaceutical Evaluation III

Date: _____

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

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3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

There was no pharmacokinetic interaction between ibuprofen and diphenhydramine when administered simultaneously under fasted conditions. Based on the comparison of the C_{max} and AUC_{0-∞} of ibuprofen determined in Study WM-716, 2 x ibuprofen 200 mg capsules administered in combination with 2 x diphenhydramine citrate 38 mg capsules were equivalent (90% CI of mean ratio within 80 - 125%) to 2 x ibuprofen capsules administered alone. Similarly, 2 x diphenhydramine capsules administered simultaneously with 2 x ibuprofen capsules were equivalent to 2 x diphenhydramine capsules administered alone. The values in mean T_{max} for ibuprofen and diphenhydramine when administered simultaneously were not different ($p > 0.05$) from those when given separately.

The rate (but not the extent) of ibuprofen absorption from Advil PM Liquigels containing ibuprofen 200 mg + diphenhydramine HCl 25 mg was slower than that from single ingredient liquigels containing the same amount of ibuprofen. Study AE-97-02 showed that the mean C_{max} and T_{max} of ibuprofen from 2 x Advil PM Liquigels were lower by 21.3% (mean ratio 127%; 90% CI, 115.7 - 139.5%) and slower by 0.4 hour (1.01 vs 0.61 hr, $p = 0.0102$), respectively, than those from 2 x ibuprofen liquigels coadministered with 2 x diphenhydramine liquigels. The extent of absorption (AUC_{0-∞}) was not different (90% CI of mean ratio, 97.0 - 105.4%). Similarly, Study AE-97-09 demonstrated that the mean C_{max} of ibuprofen from 2 x Advil PM Liquigels were lower by 28.6% (mean ratio, 71.4%; 90% CI, 76.2 - 96.8%) than that from 2 x Advil Liquigels (Whitehall-Robins, ibuprofen 200 mg), the currently marketed single ingredient liquigels. There may be formulation and/or other unknown differences between formulations tested in these studies on the rate of ibuprofen absorption although all liquigels used contained essentially the same ingredients and were produced under the similar manufacturing process.

In contrast, the rate and extent of diphenhydramine absorption were not different (90% CI of mean ratio within 80 - 125%) between Advil PM Liquigels containing ibuprofen 200 mg + diphenhydramine HCl 25 mg and single ingredient liquigels containing the same amount of diphenhydramine.

The rate and extent of absorption of ibuprofen and diphenhydramine from Advil PM Liquigels were altered under fed conditions (Study AE-97-02). For ibuprofen absorption, food decreased C_{max} by 18.5% (mean ratio, 81.5%; 90% CI, 72.4 - 89.4 %) without affecting T_{max} and AUC_{0-∞}. For diphenhydramine absorption, in contrast, food shortened T_{max} by 0.86 hour (2.48 vs. 3.34 hr, $p = 0.0029$), increased C_{max} by 25.0% (mean ratio, 125.0%; 90% CI, 115.5 - 132.2%), and increased AUC_{0-∞} by 20.6% (mean ratio, 120.6%; 90% CI, 114.8 - 126.6%). The food effect may not be clinically important, considering the magnitude of changes in pharmacokinetic values (25% at maximum in C_{max}) as compared with the wide safety and efficacy margin of ibuprofen and diphenhydramine.

There was a gender difference in food effect on the absorption of ibuprofen and diphenhydramine from Advil PM Liquigels (Study AE-97-02). Male subjects showed no difference between fasted and fed conditions in terms of the AUC_{0-∞} of ibuprofen (mean ratio, 92.1%; 90% CI, 87.3 - 97.1%) and diphenhydramine (mean ratio, 116.3%; 90% CI, 108.9 -

124.2%). In contrast, female subjects demonstrated differences in the $AUC_{0-\infty}$ of ibuprofen (mean ratio, 78.7%; 90% CI, 73.3 - 84.6%) and diphenhydramine (mean ratio, 125.3%; 90% CI, 115.6 - 135.9%). The gender difference may not be clinically important considering the quantitative difference in pharmacokinetic values between genders (13.4% at maximum). The gender differences observed from Study WM-716 and Study AE-97-09 do not appear meaningful. Table I shows a brief summary of all 3 pharmacokinetic studies submitted.

Table I: Pharmacokinetic Studies for Advil PM Liquigels

	Objective	Study Design / Treatments	Subjects N (M/F) Age range	Results
WM-716 (Canada)	To investigate interactions between IBU and DPH when administered simultaneously under fasted conditions	Single dose, 3-way crossover, fasted A: 2 x DPH citrate 38mg capsules B: 2 x IBU 200mg capsules C: 2 x IBU 200mg capsules + 2 x DPH citrate 38mg capsules	healthy volunteers 23 (11/12) 20 - 45 yo	No pharmacokinetic interaction between IBU and DPH when administered simultaneously
AE-97-02 (US)	1) To determine food effect on the rate and extent of absorption of IBU and DPH from Advil PM Liquigels 2) To determine the equivalence between Advil PM Liquigels and single entity IBU or DPH liquigels administered simultaneously under fasted conditions	Single dose, 3-way crossover A: 2 x Advil PM Liquigels (IBU 200mg / DPH HCl 25mg), fasted B: 2 x Advil PM Liquigels, fed C: 2 x IBU 200mg liquigels + 2 x DPH HCl 25mg liquigels, fasted	healthy volunteers 25 (13/12) 18 - 36 yo	1) Food slightly decreased IBU Cmax but slightly increased the rate and extent of DPH absorption from Advil PM Liquigels 2) Advil PM Liquigels were bioequivalent to DPH liquigels but not to IBU liquigels (lower in the rate of IBU absorption)
AE-97-09 (US)	To determine bioequivalence between Advil PM Liquigels and single entity marketed products containing IBU or DPH	Single dose, 4-way crossover, fasted A: 2 x Advil PM Liquigels B: 2 x Advil Liquigels (IBU 200mg) C: 2 x Benadryl Liquigels (DPH HCl 25mg) D: 2 x Nuprin Tablets (IBU 200mg)	healthy volunteers 23 (12/11) 20 - 43 yo	Advil PM Liquigels showed equivalent extent but lower Cmax of IBU absorption as compared with single entity marketed products (equivalent in DPH absorption)

IBU, ibuprofen; DPH, diphenhydramine

The sponsor proposed the dissolution specification of Advil PM Liquigels as $Q = \text{---}$ (NLT) in 45 minutes using USP apparatus I (basket) with a rotation speed of 150 rpm. This appears too loose as compared with those in the monograph for diphenhydramine capsules and in the Agency's guidance for general dissolution test for capsules (100 rpm).

4. QUESTION-BASED REVIEW

4.1. General Attributes

What are the highlights of the formulation of the drug product? What is the proposed dosage and route of administration?

Chemical Names:

Ibuprofen: 2-(4-isobutylphenyl)-propionic acid (MW 206.3, pKa 5.4)

Diphenhydramine HCl: 2-(diphenylmethoxy)-N-diethylamine hydrochloride (MW 291.8)

Formulation: liquid-filled gelatin capsules (liquigels)

Table II. Ingredients in clinical and to-be-marketed formulations of Advil PM Liquigels

Ingredients	Weight (mg/liquigels)			
	WH-0723-0001 (Study AE-97-02)	WH-0723-0005 (Study AE-97-09)	WH-0723-0007 (Study AE-97-08)	WH-0723-0009 (To-Be-Marketed)
<i>Fill Material</i>				
Ibuprofen, USP	200	200	200	200
Diphenhydramine HCl, USP	25.0	25.0	25.0	25.0
Polyethylene Glycol				
Potassium Hydroxide, NF				
Purified Water, USP				
Total Fill Weight (dried)				
<i>Gelatin Shell</i>				
Gelatin, NF				
FD & C Blue No. 1				
D & C Red No. 33				
Fractionated Coconut Oil, EP				
Lecithin NF				
Total Shell Weight				
Total Liquigel Weight	887	887	887	887

Remark: Ibuprofen presents as free acid and potassium salt

Indication: nighttime pain relief and sleep-aid

Dosage and Administration: 2 liquigels orally at bedtime

What is the rationale for the combination of ibuprofen and diphenhydramine?

The combination of ibuprofen and diphenhydramine is based on their pharmacodynamic (PD) characteristics (Table III). Conditions such as muscle soreness, sprains, strains, arthritis,

headaches, and outpatient surgical procedures are typical painful episodes that interfere with normal sleep. An ideal analgesic/sleep-aid combination should quickly relieve pain, induce sleep, and maintain its effect throughout the night. Upon awakening, patients should have minimal pain, feel like they had a good night's sleep, and feel refreshed with no hangover effects.

Table III. Pharmacokinetic and pharmacodynamic characteristics of ibuprofen and diphenhydramine (adapted from the sponsor's summary in NDA 21-393)

	Ibuprofen 400 mg	Diphenhydramine 50 mg
Pharmacokinetic Characteristics		
C _{max}	35 - 40 µg/mL	65 - 75 ng/mL
T _{max}	0.75 - 2 hrs	3 - 4 hrs
Half-Life	2 hrs	9 - 10 hrs
Pharmacodynamic Characteristics		
Time to Onset of Effect	15 - 30 min post dose	1 - 2 hrs post dose
Duration of Effect	up to 6 hrs post dose	up to 8 hrs post dose
Minimum Effective Plasma Concentration	6 - 10 µg/mL	30 - 50 ng/mL

Patients can expect that faster pain relief would shorten latency time to falling asleep and improve sleep quality. The pharmacodynamic profile of ibuprofen is indicative of effective pain relief (Table III). Ibuprofen is known as a stronger analgesic relative to acetaminophen, the most commonly found analgesic in marketed analgesic/sleep-aids. Diphenhydramine is considered one of the most sedating OTC antihistamines. Based on pharmacodynamic profile of diphenhydramine (Table III), its addition to ibuprofen can be a beneficial combination by allowing patients to sleep longer, have less need for analgesic during sleeping, and have a better night's sleep.

4.2. General Clinical Pharmacology

Is there any pharmacokinetic interaction between ibuprofen and diphenhydramine when administered simultaneously?

There was no pharmacokinetic interaction between ibuprofen and diphenhydramine. In Study WM-716, the rate and extent of absorption of ibuprofen and diphenhydramine when two capsules containing ibuprofen 200 mg per capsule and two capsules containing diphenhydramine citrate 38 mg per capsule were administered simultaneously were compared with those when the two drugs with same doses were administered separately. Based on C_{max} and AUC_{0-∞}, ibuprofen capsules administered in combination with diphenhydramine capsules were bioequivalent (90% CI of mean ratio within 80 - 125%) to ibuprofen capsules administered alone. Similarly, diphenhydramine capsules administered simultaneously with ibuprofen capsules were bioequivalent to diphenhydramine capsules administered alone. The mean ratios of C_{max} and AUC_{0-∞} for ibuprofen were 101.2% and 96.5%, respectively. Their 90% CIs were 94.8 - 108.2% and 92.6 - 100.6%, respectively. The mean T_{max}'s for ibuprofen were not significantly different (1.35 vs. 1.42 hr, p > 0.05). The mean ratios of C_{max} and AUC_{0-∞} of diphenhydramine were 107.4% and 101.4%, respectively. Their 90% CIs were 99.7 - 115.7% and 95.9 - 107.3%,

respectively. The mean Tmax's for diphenhydramine were not significantly different (2.76 vs. 2.95 hr, $p > 0.05$).

Are the rate and extent of absorption of ibuprofen and diphenhydramine observed from Advil PM Liquigels equivalent to those from single ingredient products (formulation effect)?

There may be formulation and/or other unknown differences between Advil PM and ibuprofen liquigels although the composition in inactive ingredients and manufacturing process were essentially the same (Advil PM contains — polyethylene glycol — than ibuprofen liquigels in inactive ingredients). The difference affected only the rate of ibuprofen absorption. In Study AE-97-02, the rate and extent of absorption of ibuprofen and diphenhydramine from proposed market formulation (Advil PM Liquigels; ibuprofen 200 mg + diphenhydramine HCl 25 mg) were compared with those from ibuprofen liquigels (ibuprofen 200 mg) and diphenhydramine liquigels (diphenhydramine HCl 25 mg) administered simultaneously. Even though 2 x Advil PM Liquigels showed an equivalent extent of ibuprofen absorption to 2 x ibuprofen liquigels (mean ratio in $AUC_{0-\infty}$, 98.9%; 90% CI, 94.9 - 103.1%), the Cmax and Tmax of ibuprofen from Advil PM Liquigels were lower by 21.3% (mean ratio, 78.7%; 90% CI, 71.7 - 86.4%) and slower by 0.4 hour (1.01 ± 0.54 vs 0.61 ± 0.17 hr, $p = 0.0102$), respectively. For diphenhydramine absorption, in contrast, 2 x Advil PM Liquigels were bioequivalent to 2 x diphenhydramine liquigels in $AUC_{0-\infty}$ (mean ratio, 100.5%; 90% CI, 95.6 - 105.6%), Cmax (mean ratio, 98.9%; 90% CI, 91.2 - 107.1%), and Tmax (3.34 vs 3.26 hr, $p > 0.05$).

Study AE-97-09 confirmed the results obtained from Study AE-97-02 using Advil PM Liquigels and corresponding single ingredient marketed references (Advil Liquigels, ibuprofen 200 mg; Benadryl Liquigels, diphenhydramine HCl 25 mg). The mean Cmax of ibuprofen obtained from Advil PM Liquigels was lower by 28.6% than that from Advil Liquigels (mean ratio, 71.4%; 90% CI, 63.4 - 80.4%). The mean Tmax of ibuprofen from Advil PM Liquigels was insignificantly longer than that from Advil Liquigels (0.91 ± 0.58 vs 0.75 ± 0.36 hr, $p = 0.145$). As expected, 2 x Advil PM Liquigels were equivalent in the extent of ibuprofen absorption to 2 x Advil Liquigels (mean ratio in $AUC_{0-\infty}$, 99.3%; 90% CI, 95.3 - 103.4%). In terms of the extent of diphenhydramine absorption, Advil PM Liquigels and Benadryl Liquigels were bioequivalent (mean ratio in $AUC_{0-\infty}$, 97.2%; 90% CI, 91.0 - 103.9%). The difference seen initially in diphenhydramine Cmax disappeared by deleting an outlier (least-squares mean ratio, 87.0%; 90% CI, 81.4 - 92.3%). In addition, Advil PM Liquigels were not bioequivalent to Nuprin Tablets (ibuprofen 200 mg). Even though the extent of ibuprofen absorption was the same (mean ratio for $AUC_{0-\infty}$, 94.5%; 90% CI, 90.7 - 98.4%), the Cmax and Tmax obtained from Advil PM Liquigels were lower by 14.1% (mean ratio, 85.9%; 90% CI, 76.2 - 96.8%) and shorter by 0.56 hour (0.91 ± 0.58 vs 1.48 ± 0.58 hr, $p < 0.001$), respectively, than those from Nuprin Tablets.

What are the characteristics of the exposure-response relationships for efficacy and safety?

The sponsor summarized that the ibuprofen concentrations of approximately 6 µg/mL in plasma were associated with the onset of pain relief (Table III). Following an oral dose of ibuprofen 400 mg, these levels typically reached within 15 - 30 minutes and concentrations remained above the levels of 6 µg/mL for 4 - 6 hours post dosing. The diphenhydramine concentrations of 30 - 50 ng/mL in plasma were associated with the onset of sedative effects (Table III). Following single

oral doses of diphenhydramine HCl 50 mg, therapeutic concentrations were typically reached between 1.5 - 2 hours after dosing, and concentrations remained above the levels of 30 ng/mL for 3 - 8 hours post dosing. Toxic concentrations .

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4.3. Intrinsic Factors

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on dosage regimen adjustments?

Gender: a gender difference was seen only in the determination of food effect on the extent of absorption of ibuprofen and diphenhydramine from Advil PM Liquigels (Study AE-97-02). Male subjects showed no difference between fasted and fed conditions in terms of the $AUC_{0-\infty}$ of ibuprofen (mean ratio, 92.1%; 90% CI, 87.3 - 97.1%) and diphenhydramine (mean ratio, 116.3%; 90% CI, 108.9 - 124.2%). In contrast, female subjects demonstrated differences in ibuprofen (mean ratio, 78.7%; 90% CI, 73.3 - 84.6%) and diphenhydramine (mean ratio, 125.3%; 90% CI, 115.6 - 135.9%). In case of C_{max} , the result in each gender was consistent with the overall result. The cause of this gender difference is not known. It may be due to larger variability in the pharmacokinetic parameters in female subjects. There was a trend that female subjects have larger standard deviation in almost all pharmacokinetic parameters within treatments and larger differences in mean values between treatments. The difference may also be partly attributable to weight difference between male and female subjects. However, the gender effect in clearance and volume of distribution remained significant even after adjusting for body weight. At any rate, this gender difference may not be clinically important considering the quantitative difference in pharmacokinetic values between genders (13.4% at maximum in C_{max}).

Gender differences observed in other pharmacokinetic studies do not appear meaningful. In Study WM-716 for the comparison of diphenhydramine pharmacokinetic parameters with and without ibuprofen coadministration, only the upper boundary of the 90% CI in the ratio of mean C_{max} for females (125.9%) exceeds the upper bioequivalence boundary (125%); all other 90% CIs were within 80 - 125% limits. In Study AE-97-09 for the comparison of the rate and extent of diphenhydramine absorption between Advil PM Liquigels and Benadryl Liquigels, gender differences disappeared after deleting an extreme outlier and adjusting for body weight. Therefore, dosage adjustment based on gender is not required for Advil PM Liquigels.

4.4. Extrinsic Factors

N/A

4.5. General Biopharmaceutics

What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The rate and extent of absorption of ibuprofen and diphenhydramine from Advil PM Liquegels were altered under fed conditions that provide a total of 648 calories including 240 calories (37%) as fat. Food lowered the mean C_{max} of ibuprofen by 18.5% (mean ratio, 81.5%; 90% CI, 74.3 - 89.4 %) without significantly affecting mean T_{max} (1.26 ± 0.49 vs 1.01 ± 0.54 hr, p = 0.0927). The effect of food on the extent of ibuprofen absorption was negligible (90% CI of mean ratio for AUC_{0-∞}, 81.5 - 88.5%). Food shortened the mean T_{max} of diphenhydramine absorption (2.48 ± 0.81 vs 3.34 ± 0.90 hr, p < 0.0029), and increased mean C_{max} by 25.0% (mean ratio, 125%; 90% CI, 115.5 - 135.2%) and mean AUC_{0-∞} by 20.6% (mean ratio, 120.6%; 90% CI, 114.8 - 126.6%). The food effect determined in this study may not be clinically important, considering that the magnitude of the effect is small (maximum 25%) as compared with the wide safety and efficacy margin of ibuprofen and diphenhydramine, and that patients are to take Advil Liquegels at bedtime with light snack rather than full high fat meal.

How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The sponsor provided a brief report on dissolution method and specification, and comparative dissolution profiles between manufactured batches for Advil PM Liquegels. There was no remarkable batch-to-batch variation between clinical and to-be-marketed formulations (Figure 1). However, the sponsor used a dissolution method and specification that are too liberal. The reviewer needs more detailed information with data from the sponsor to make a decision. Particularly, it needs to be clarified whether a fast speed of agitation (150 rpm) is required to assure proper dissolution although the dissolution of all clinical and to-be-marketed batches was almost 90% or higher within 20 minutes for both ibuprofen and diphenhydramine (Figure 1). The speed both in the monograph of diphenhydramine HCl capsules and in the current Agency's guidance for dissolution test is 100 rpm using USP type I (basket). If the dissolution method provided is reasonable, its specification may be modified to Q = — in 30 min for a better quality control of the product.

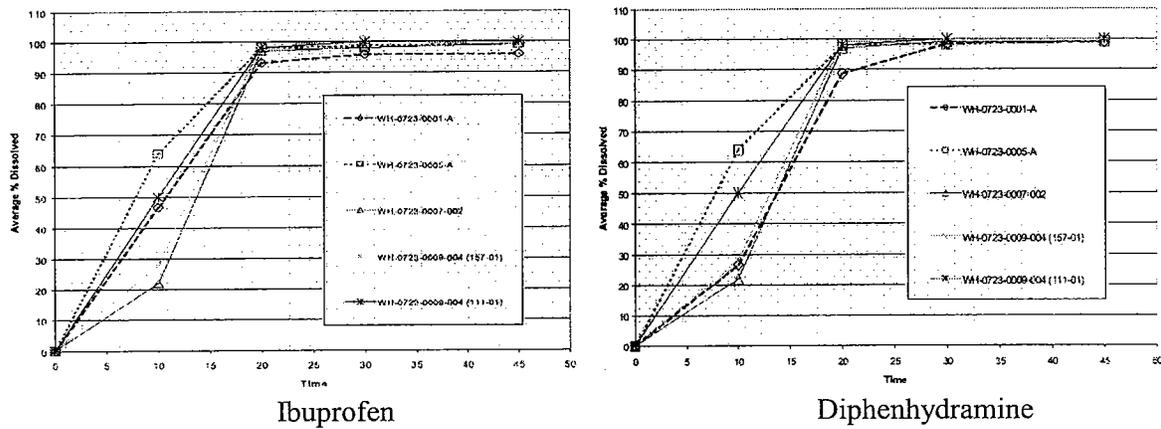
Proposed Dissolution Method

Apparatus: USP apparatus type I (basket)
Media: 200 mM phosphate buffer, pH 7.2
Volume: 900 mL per sample
Speed of Agitation: 150 rpm
Sampling Time: within 45 min (10, 20, 30, and 45 min)
Temperature: 37 ± 2 °C
Analytical Method: HPLC

Proposed Specification

Q = — in 45 min
Stage 1 NLT — (Q + 5%) dissolved in 45 min
Stage 2 and 3 if appropriate
Tier 2 testing with pancreatin added to media, per USP, if required.

Figure 1. Comparative dissolution profiles of clinical and to-be-marketed batches of Advil PM Liquigels



Are any other studies required to demonstrate an equivalence between clinical and to-be-marketed formulations?

The sponsor developed three clinical and one to-be-marketed Advil PM Liquigels formulations for pharmacokinetic, clinical, and stability studies. Differences in ingredients (Table III) and manufacturing processes between the formulations are minute (Table IV). The sponsor provided comparative dissolution profiles between manufactured batches (see previous question). Bioequivalence studies are not required between clinical and to-be-marketed formulations.

Table IV. Summary in formulation development for Advil PM Liquigels

Study Number/ Batch Significance	DRUG FORMULATION DEVELOPMENT SUMMARY				
	Formulation/ Lot Number	Dosage Form and Strength	Batch Size*/ Manufacturing Site	Formulation or Significant Manufacturing Change and Reason for Change	Effect of Change
AE-97-02 Clinical Batch	WH-0723-0001 Batch A	Soft Gelatin Capsule: Ibuprofen 200 mg, Diphenhydramine HCl 25 mg			N/A
AE-97-09 Clinical Batch	WH-0723-0005 Batch A	Soft Gelatin Capsule: Ibuprofen 200 mg, Diphenhydramine HCl 25 mg			None***
AE-97-08 Clinical Batch	WH-0723-0007 Batch 002	Soft Gelatin Capsule: Ibuprofen 200 mg, Diphenhydramine HCl 25 mg			None***
N/A (NDA stability & proposed market formula)	WH-0723-0009 All batches	Soft Gelatin Capsule: Ibuprofen 200 mg, Diphenhydramine HCl 25 mg			None***

4.6. Analytical

What bioanalytical methods are used to assess the plasma concentrations of ibuprofen and diphenhydramine?

For the determination of the plasma concentrations of racemic ibuprofen, a reverse-phase high performance liquid chromatographic (HPLC) method coupled with ultraviolet absorbance detection at 224 nm was used. The analyte was prepared by a liquid-liquid extraction technique. Fenoprofen was used as an internal standard. In a validation study using 0.3 mL of plasma, the lower limit of quantitation was 0.10 µg/mL and the method was linear ($r \geq 0.998$) through 125 µg/mL when the calibration curve was constructed with a set of 8 non-zero standards. The intra-assay accuracy as determined by % recovered from the quality controls of 0.1, 0.3, 20, 40, and 100 µg/ml, ranged from 92.5% to 99.8% and the precision as indicated by coefficient of variation (CV, %) varied from 1.3% to 10.7%. The inter-assay accuracy ranged from 94.8% to 98.5%, and the precision from 1.3% to 15.7%. Plasma samples were stable at a nominal temperature of -22°C and 22°C for 105 days and 5.5 hours, respectively.

For diphenhydramine assay, a reverse-phase HPLC method coupled with ultraviolet absorbance detection at 205 nm was used. The analyte was prepared by a liquid-liquid extraction followed by back extraction. Desipramine HCl was used as an internal standard. In a validation study using 1.0 mL of plasma, the lower limit of quantitation was 2 ng/mL and the method was linear ($r \geq 0.997$) through 150 ng/mL when the calibration curve was constructed with a set of 8 non-zero standards. The intra-assay accuracy as determined from the quality controls of 2, 6, 60, and 120 ng/ml, ranged from 92.1% to 110.1% and the precision (CV, %) varied from 3.2% to 7.7%. The inter-assay accuracy ranged from 96.1% to 113.5%, and the precision from 5.0% to 10.0%. Plasma samples were stable at a nominal temperature of -22°C and 22°C for 83 days and 6 hours, respectively.

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5. DETAILED LABELING RECOMMENDATIONS

The proposed labeling by the sponsor needs to be consistent with the Agency's policy on NSAID labeling. Detailed labeling recommendations are deferred until clinical issues are resolved. This is based on the discussion with the OTC labeling team leader (Ms Marina Chang).

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2 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

6.2. Individual Study Reviews

Study WM-716

SINGLE DOSE, OPEN LABEL, RANDOMIZED, 3-WAY CROSSOVER PHARMACOKINETIC INTERACTION STUDY COMPARING AN IBUPROFEN/DIPHENHYDRAMINE COMBINATION TO INDIVIDUAL DOSES OF IBUPROFEN AND DIPHENHYDRAMINE

Objectives:

To compare the rate and extent of absorption of ibuprofen (IBU) and diphenhydramine (DPH) administered simultaneously to those of each drug individually

Study Design:

This is a randomized, open-label, three-way crossover, bioequivalence-type study. Healthy volunteers received a single oral dose of each of the following treatments under fasted conditions.

Treatment A: 2 x DPH capsules (DPH citrate 38 mg/capsule, equivalent to DPH HCl 25 mg/capsule; Whitehall Robins Lot #, WH-552-5)

Treatment B: 2 x IBU capsules (IBU 200 mg/capsule; Whitehall Robins Lot #, WH-435-26A)

Treatment C: 2 x DPH capsules (DPH citrate 38 mg/capsule, Whitehall Robins Lot # WH-552-5) + 2 x IBU capsules (IBU 200 mg/capsule, Whitehall Robins Lot #, WH-435-26A), administered simultaneously

All formulations used in this study were solid-filled capsules and, therefore, different from the proposed market formulation (Advil PM Liquigels). Each treatment was separated by a 7-day washout period. Each dose was administered with 240 mL of water in the morning after overnight fast for 10 hours. During the treatment periods of A and C, 20 blood samples (7 mL each) were collected pre-dose and at 15, 30, 45, 60, 75, and 90 minutes, and 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours post-dose. During the treatment period of B, 16 blood samples (7 mL each) were collected pre-dose and at 15, 30, 45, 60, 75, and 90 minutes, and 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hours post-dose. Plasma was obtained from the blood samples, stored at -20°C and subsequently analyzed for racemic IBU or for DPH using reverse-phase high performance liquid chromatographic (HPLC) methods coupled with ultraviolet absorbance detection.

Analyses of variance (ANOVA) were performed on the untransformed and log-transformed pharmacokinetic parameters including AUC_{0-t} (data not shown in this review), $AUC_{0-\infty}$ (AUCI) and C_{max} . The ANOVA model included sequence, subjects nested within sequence, period and drug formulation as factors. The significance of sequence effect was tested using subject nested within sequence as error term. Each ANOVA included calculation of least-squares means, adjusted differences between formulation means and the standard error associated with these differences. The statistical analyses were done using a SAS GLM procedure. Ratios of means and their 90% confidence intervals (90% CI) were calculated for AUC_{0-t} , AUCI and C_{max} using log-transformed data. To test for bioequivalence, the 90% confidence interval for the ratio was

performed on log-transformed data, and observed whether the interval was contained within 80% and 125%.

Inclusion/Exclusion: Normal, healthy, volunteers aged between 18 and 45 years old were eligible for this study. Pregnant or lactating females, illicit drug users and subjects who took any drugs within the past 14 days before the study were excluded. Subjects were asked to refrain from ingesting any medications, caffeine and alcohol for 24 hours prior to and throughout each study period, and smoking from 1 hour before dosing and until 4 hours after dosing. Other inclusion and exclusion criteria appear to be relevant to this study.

Results:

All clinical investigations, and drug and data analyses were conducted at _____ Canada. A total of 23 subjects aged 20 - 45 years old (mean 30.8 ± 8.21) completed the study. There were 11 males and 12 females consisting of all Caucasians. All three treatments were well tolerated.

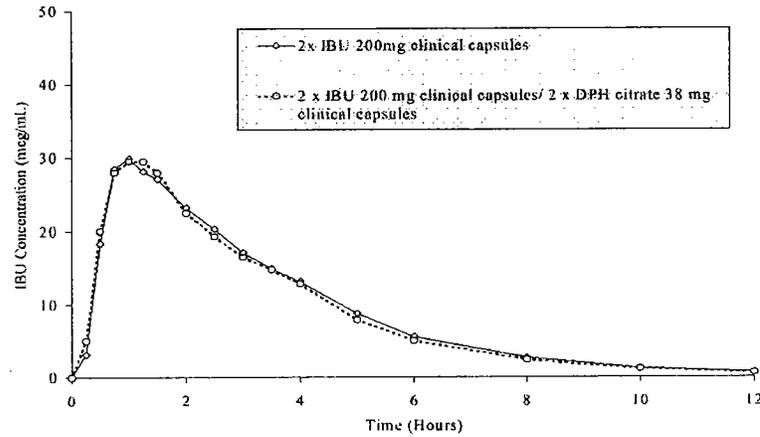
The concentrations of DPH and racemic IBU in plasma were analyzed by validated HPLC methods (see 4.6. Analytical). For IBU assay, the correlation coefficient (r) of standard curve was 0.993 or larger. Inter-assay accuracy ranged from 93.9% to 98.1%, and precision varied from 1.3% to 4.0%. For DPH assay, the correlation coefficient (r) of standard curve was 0.997 or larger. Inter-assay accuracy ranged from 99.3% to 102.0%, and precision varied from 6.5% to 7.7%.

Based on log-transformed C_{max} and AUCI, 2 x IBU 200 mg capsules administered in combination with 2 x DPH citrate 38 mg capsules were bioequivalent to 2 x IBU capsules administered alone. Similarly, 2 x DPH capsules administered simultaneously with 2 x IBU capsules was bioequivalent to 2 x DPH capsules administered alone. When the PK parameters of IBU were compared between Treatments C and B, the ratios of least-squares means for the log-transformed C_{max} and AUCI were 101.2% and 96.5%, respectively (Table 1-1). Their 90% CIs were 94.8 - 108.2% and 92.6 - 100.6%, respectively. The mean T_{max}'s for IBU were 1.35 and 1.42 hours for Treatments C and B, respectively. The mean concentration-time profiles of IBU were similar between Treatments C and B (Figure 1-1).

Table 1-1. Study WM-716, Pharmacokinetic parameters for ibuprofen (Mean ± SD)

Treatment (sample size)	C _{max} (mcg/mL)	AUCI (mcg-hr/mL)	T _{max} (hr)	t _{1/2} (hr)	Kel (1/hr)
IBU 400 mg (B) (n=23)	36.1 ± 7.4	112.7 ± 24.9	1.42 ± 1.13	1.83 ± 0.30	0.39 ± 0.06
DPH citrate 76 mg + IBU 400 mg (C) (n=23)	36.4 ± 7.0	109.5 ± 27.6	1.35 ± 0.99	1.82 ± 0.29	0.39 ± 0.06
C/B Ratio [†]	101.2%	96.5%	--	--	--
C/B 90% CI [†]	94.8 - 108.2%	92.6 - 100.6%	--	--	--

Figure 1-1. Study WM-716, Mean concentrations of ibuprofen over time (N=23)

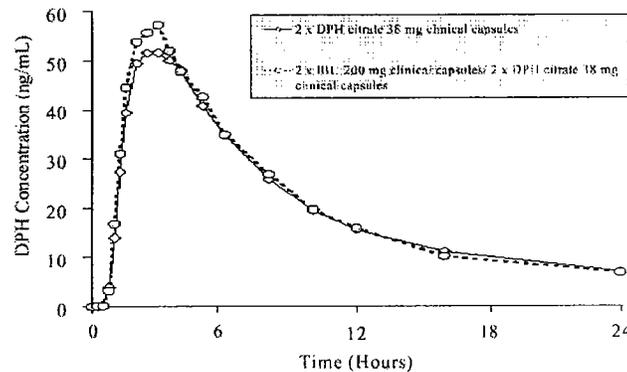


When the PK parameters of DPH were compared between Treatments C and A, the ratios of least-squares means for the log-transformed C_{max} and AUCI were 107.4% and 101.4%, respectively (Table 1-2). Their 90% CIs were 99.7-115.7% and 95.9-107.3%, respectively. The mean T_{max} for DPH were 2.76 and 2.95 hours for Treatments C and A, respectively. The mean concentration-time profiles of DPH were similar between Treatments C and A (Figure 1-2).

Table 1-2. Study WM-716, Pharmacokinetic parameters for diphenhydramine (Mean ± SD)

Treatment (sample size)	C _{max} (ng/mL)	AUCI (ng-hr/mL)	T _{max} (hr)	t _{1/2} (hr)	Kel (1/hr)
DPH citrate 76 mg (A) (n=23)	56.3 ± 15.9	598.8 ± 199.0	2.95 ± 1.00	9.64 ± 2.08	0.08 ± 0.02
DPH citrate 76 mg + IBU 400 mg (C) (n=23)	61.7 ± 23.9	608.7 ± 211.9	2.76 ± 0.69	10.10 ± 2.36	0.07 ± 0.02
C/A Ratio [†]	107.4%	101.4%	--	--	--
C/A 90% CI [†]	99.7 - 115.7%	95.9 - 107.3%	--	--	--

Figure 1-2. Study WM-716, Mean concentrations of diphenhydramine over time (N=23)



The original protocol for this study was not designed to determine a gender effect. In order to be consistent with subsequent studies, the sponsor reanalyzed the data for a gender effect. Even though the ratios of mean values in pharmacokinetic parameters for DPH were generally higher in females than in males, the contribution of the gender effect to the overall result is negligible (Table 1-3). The upper boundary of the 90% CI in the ratio of mean C_{max} of diphenhydramine for females (125.9%) was the only value slightly outside 80 - 125% bioequivalence boundary.

Table 1-3. Study WM-716, Pharmacokinetic parameters for diphenhydramine stratified by gender (Mean ± SD)

Treatment	C _{max} (ng/mL)		AUCI (ng-hr/mL)		T _{max} (hr)	
	Males (n=11)	Females (n=12)	Males (n=11)	Females (n=12)	Males (n=11)	Females (n=12)
DPH (A)	55.6 ± 17.5	57.0 ± 15.1	617.0 ± 230.1	581.9 ± 174.4	3.1 ± 1.3	2.8 ± 0.7
DPH + IBU (C)	54.0 ± 17.5	68.9 ± 27.5	577.1 ± 213.9	637.8 ± 215.2	3.0 ± 0.8	2.5 ± 0.5
C/A ratio (%) [†]	94.8	116.2	92.7	108.0	--	--
C/A 90% CI [†]	84.7 -106.1	107.3 - 125.9	86.4 - 99.5	101.4 -115.0	--	--

Conclusions:

- The rate and extent of ibuprofen absorption from ibuprofen capsules when administered in combination with diphenhydramine citrate capsules were equivalent to those when administered alone.
- Similarly, the rate and extent of diphenhydramine absorption from diphenhydramine citrate capsules when administered simultaneously with ibuprofen capsules were equivalent to those when administered alone.

Reviewer's Comment:

- Based on the result of this study, there is no pharmacokinetic interaction between ibuprofen and diphenhydramine.
- The gender difference in diphenhydramine pharmacokinetics shown in this study does not seem to be meaningful. Only the upper boundary of the 90% confidence interval in the ratio of diphenhydramine C_{max} for females (125.9%) slightly exceeds upper bioequivalence boundary (125%).

Study AE-97-02

ADVIL PM LIQUIGELS BIOEQUIVALENCE/ FOOD EFFECTS STUDY

Objectives:

1. To determine the effect of food on the rate and extent of absorption of ibuprofen (IBU) and diphenhydramine (DPH) from the proposed market formulation of Advil PM Liquigels
2. To compare the rate and extent of absorption of IBU and DPH from Advil PM Liquigels with those from coadministered single entity IBU liquigels and DPH liquigels under fasted conditions

Study Design:

This was a randomized, open-label, three-way crossover, bioequivalence-type study. Healthy male and non-pregnant female volunteers received a single oral dose of each of the following treatments under fasted (for 10 hours overnight before dose) or fed conditions (10 minutes after a standardized breakfast).

Treatment A: 2 x Advil PM Liquigels (IBU 200mg + DPH HCl 25mg / liquigel; Batch #, WH-0723-0001A), fasted

Treatment B: 2 x Advil PM Liquigels, fed

Treatment C: 2 x IBU liquigels (IBU 200mg/liquigel; Batch #, WH-0693-0003A) plus 2 x DPH liquigels (DPH HCl 25mg/liquigel; Batch #, WH-0722-0001A), administered simultaneously, fasted

The composition of inactive ingredients in Advil PM Liquigels was very similar to that in ibuprofen liquigels and diphenhydramine liquigels. Each treatment was separated by a 7-day washout period. Each dose in treatment A and C was administered with 240 mL of water while each dose in treatment B was given with 240 mL of whole milk. The standardized breakfast with milk provided a total of 648 calories including 240 calories (37%) as fat. During each treatment period, 19 blood samples (7 mL) were collected pre-dose and at 15, 30, 45, 60, 75, and 90 minutes, and 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-dose. Plasma was obtained from the blood samples, stored at -20°C and subsequently analyzed for racemic IBU or for DPH using reverse-phase high performance liquid chromatographic (HPLC) methods coupled with ultraviolet absorbance detection.

The treatment groups were compared for untransformed AUC_{0-t} , $AUC_{0-\infty}$ (AUCI), C_{max} , T_{max} and half-life, and for log-transformed AUC_{0-t} , AUCI and C_{max} by means of the analysis of variance (ANOVA) appropriate for a multiple-crossover design, stratified by gender. Statistical significance was declared if the resulting p value ≤ 0.05 . The effect of gender or treatment-by-gender interaction was considered significant if $p \leq 0.15$. If the gender or treatment-by-gender interaction was significant for the pharmacokinetic parameters, the volume of distribution and clearance divided by body weight were calculated and analyzed for gender or treatment-by-gender interaction. The statistical analyses were done using a SAS GLM procedure. The ratio for each parameter was calculated by dividing the least-squares means of test treatment by those

of reference treatment calculated from the ANOVA. To test for bioequivalence, it was determined whether the 90% confidence interval (90% CI) computed for the ratio with log-transformed data was contained within 80% and 125%.

Inclusion/Exclusion: Normal, healthy, non-smoking volunteers aged between 18 and 45 years old were eligible for this study. Pregnant or lactating females, and subjects who took any investigational drugs within the past 30 days before the study were excluded. Subjects were asked to refrain from ingesting any medications except oral contraceptives for 14 days, caffeine for 24 hours, and alcohol for 3 days prior to and during each study period. These and other inclusion and exclusion criteria were appropriate for this study.

Results:

Clinical investigations were conducted at _____

A total of 25 subjects aged 18 - 36 years old completed the study. There were 13 males and 12 females consisting of 20 whites and 5 blacks. All three treatments were well tolerated.

Drug and data analyses were conducted at _____

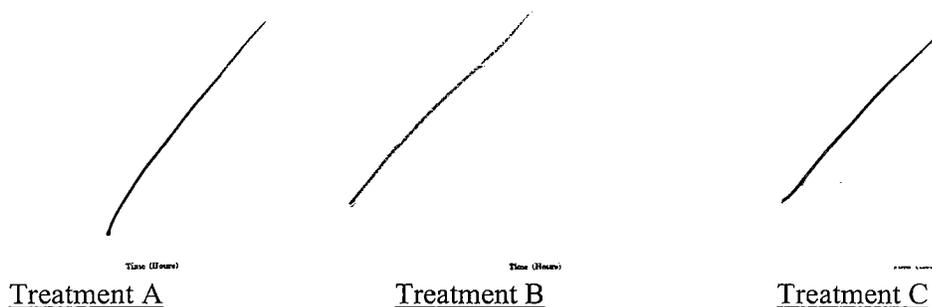
The plasma concentrations of DPH and racemic IBU were analyzed by validated HPLC methods (see 4.6. Analytical). For IBU assay, the correlation coefficient (r) of standard curve was 0.998 or larger. Inter-assay accuracy ranged from 100.4% to 104.7%, and precision varied from 2.2% to 4.5%. For DPH assay, the correlation coefficient (r) of standard curve was 0.996 or larger. Inter-assay precision varied from 4.8% to 9.6%.

The rate of IBU absorption from Advil PM Liquigels was altered under fed conditions. Food lowered the mean C_{max} of IBU by 18.5% (least-squares mean ratio, 81.5%; 90% CI, 74.3 - 89.4 %) without significantly affecting T_{max} (1.26 ± 0.49 vs 1.01 ± 0.54 hr, p < 0.0927) (Table 2-1). The effect of food on the extent of IBU absorption was negligible (90% CI of least-squares mean ratio for AUCI, 81.5 - 88.5%). The spaghetti plots for IBU concentrations in each treatment over time are shown in Figure 2-1.

Table 2-1. Study AE-97-02, Pharmacokinetic parameters for ibuprofen (mean ± SD)

Treatment (sample size)	C _{max} (mcg/mL)	AUCI (mcg-hr/mL)	T _{max} (hr)	t _{1/2} (hr)	Kel (1/hr)
Advil PM fast (A) (n=25)	38.3 ± 12.3	127.9 ± 40.3	1.01 ± 0.54	2.21 ± 0.33	0.32 ± 0.04
Advil PM fed (B) (n=25)	31.8 ± 9.5	107.6 ± 23.8	1.26 ± 0.49	2.13 ± 0.29	0.33 ± 0.04
IBU/DPH fast (C) (n=25)	47.7 ± 13.2	130.2 ± 40.4	0.61 ± 0.17	2.11 ± 0.23	0.33 ± 0.04
B/A Ratio [†]	81.5%	85.0%	--	--	--
C/A Ratio [†]	127.0%	101.1%	--	--	--
B/A 90% CI [†]	74.3 - 89.4%	81.5 - 88.5%	--	--	--
C/A 90% CI [†]	115.7 - 139.5%	97.0 - 105.4%	--	--	--

Figure 2-1. Study AE-97-02, Spaghetti plots for ibuprofen concentrations over time.



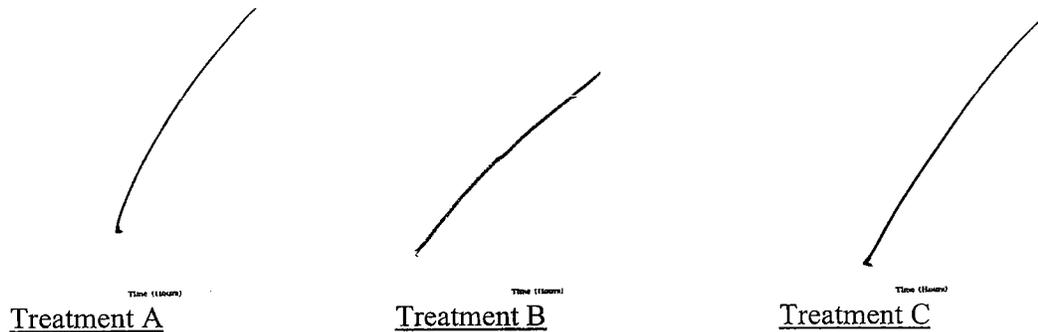
Advil PM Liquegels were not equivalent in the rate of IBU absorption to IBU liquegels coadministered with DPH liquegels under fasted conditions. Even though the difference between the two formulations in the AUCI was negligible (least-squares mean ratio, 101.1%; 90% CI, 97.0 - 105.4%), the C_{max} and T_{max} after administration of Advil PM Liquegels were lower by 21.3% (least-squares mean ratio 127%; 90% CI, 115.7 - 139.5%) and slower by 0.4 hour (0.61 ± 0.17 vs 1.01 ± 0.54 hr, $p = 0.0102$), respectively (Table 2-1). The therapeutic plasma concentrations of IBU ($\geq 6 \mu\text{g/mL}$) were reached within 30 minutes after the administration of Advil PM Liquegels or IBU liquegels with DPH liquegels under fasted conditions, but slightly delayed under fed conditions.

The rate and extent of DPH absorption from Advil PM Liquegels was altered under fed conditions. Food shortened DPH T_{max} by 0.86 hour (2.48 ± 0.81 vs 3.34 ± 0.90 hr, $p < 0.0029$), and increased C_{max} by 25.0% (least-squares mean ratio, 125%; 90% CI, 115.5 - 135.2%) and AUCI by 20.6% (least-squares mean ratio, 120.6%; 90% CI, 114.8 - 126.6%; Table 2-2). The spaghetti plots for DPH concentrations in each treatment over time are shown in Figure 2-2.

Table 2-2. Study AE-97-02, Pharmacokinetic parameters for diphenhydramine (mean \pm SD)

Treatment (sample size)	C_{max} (ng/mL)	AUCI (ng-hr/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)
Advil PM fast (A) (n=25)	71.6 \pm 22.5	761.1 \pm 278.0	3.34 \pm 0.90	9.88 \pm 1.69	0.07 \pm 0.01
Advil PM fed (B) (n=25)	90.2 \pm 23.7	900.3 \pm 298.8	2.48 \pm 0.81	9.98 \pm 1.69	0.07 \pm 0.01
IBU/DPH fast (C) (n=25)	70.2 \pm 19.9	756.9 \pm 267.0	3.26 \pm 0.71	10.19 \pm 2.31	0.07 \pm 0.02
B/A Ratio [†]	125.0%	120.6%	--	--	--
C/A Ratio [†]	101.1%	99.5%	--	--	--
B/A 90% CI [†]	115.5 - 135.2%	114.8 - 126.6%	--	--	--
C/A 90% CI [†]	93.4 - 109.6%	94.7 - 104.6%	--	--	--

Figure 2-2. Study AE-97-02, Spaghetti plots for diphenhydramine concentrations over time.



Under fasted conditions, Advil PM Liquigels were bioequivalent in diphenhydramine absorption to DPH liquigels coadministered with IBU liquigels. All 90% CIs in least-squares mean ratios for C_{max} and AUCI were within 80 - 125% (Table 2-2). Therapeutic plasma concentrations of DPH (≥ 30 ng/mL) were reached within 1.5 hours after the administration of Advil PM Liquigels or DPH liquigels with IBU liquigels under fasted or conditions.

Based on the sponsor's criteria ($p \leq 0.15$), there were significant gender effects with or without treatment-by-gender interactions in statistical tests using ANOVA for almost all ibuprofen pharmacokinetic parameters. This analysis is not appropriate because there is no consensus on the criteria. Therefore, the reviewer examined a difference between genders in a least-squares mean ratio of a pharmacokinetic parameter using a 90% CI approach.

Based on the 90% CI approach, the gender effect was seen in the determination of food effect on the extent of absorption of IBU and DPH from Advil PM Liquigels. Male subjects showed no difference between fast and fed conditions in terms of the AUCI of IBU (least-squares mean ratio, 92.1%; 90% CI, 87.3 - 97.1%; Table 2-3) and DPH (least-squares mean ratio, 116.3%; 90% CI, 108.9 - 124.2%; Table 2-4). In contrast, female subjects demonstrated differences in the AUCI of IBU (least-square mean ratio, 78.7%; 90% CI, 73.3 - 84.6%; Table 2-3) and DPH (least-squares mean ratio, 125.3%; 90% CI, 115.6 - 135.9%; Table 2-4). In case of C_{max}, the result in each gender was consistent with overall result.

The cause of the gender difference is not clearly known. It may be due to larger variability in pharmacokinetic parameters in female subjects. There was a trend that female subjects have larger standard deviation in almost all pharmacokinetic parameters within treatments and larger differences in mean values between treatments (Tables 2-3 and 2-4). Similar to Study AE-97-09, the difference may also be partly attributable to weight difference between male and female subjects. However, the gender effect in clearance and volume of distribution remained significant in this study even after adjusting body weight (data not shown in this review).

Table 2-3. Study 97-02, Pharmacokinetic parameters for ibuprofen stratified by gender (mean ± SD).

Treatment	C _{max} (mcg/mL)		AUCI (mcg-hr/mL)		T _{max} (hr)	
	Males (n=13)	Females (n=12)	Males (n=13)	Females (n=12)	Males (n=13)	Females (n=12)
Advil PM Liqui-Gel fasted (A)	32.8 ± 6.3	44.3 ± 14.5	111.3 ± 16.5	145.9 ± 50.7	1.2 ± 0.7	0.8 ± 0.2
Advil PM Liqui-Gel fed (B)	28.2 ± 6.3	35.7 ± 11.1	102.8 ± 16.3	112.7 ± 29.7	1.3 ± 0.4	1.3 ± 0.6
IBU/DPH (C)	41.3 ± 7.2	54.6 ± 15.0	114.8 ± 19.4	146.8 ± 50.8	0.6 ± 0.1	0.6 ± 0.2
B/A ratio ⁺	87.0	77.0	92.1	78.7	--	--
C/A ratio ⁺	130.0	127.8	101.9	100.9	--	--
B/A 90% CI ⁺	74.6-101.4	68.4-86.6	87.3-97.1	73.3-84.6	--	--
C/A 90% CI ⁺	111.3-151.8	113.2-144.5	96.5 - 107.5	93.7 - 108.7	--	--

Table 2-4. Study 97-02, Pharmacokinetic parameters for diphenhydramine stratified by gender (mean ± SD).

Treatment	C _{max} (ng/mL)		AUCI (ng-hr/mL)		T _{max} (hr)	
	Males (n=13)	Females (n=12)	Males (n=13)	Females (n=12)	Males (n=13)	Females (n=12)
Advil PM Liqui-Gel-fasted (A)	68.0 ± 10.2	75.5 ± 31.0	749.0 ± 199.2	774.2 ± 353.4	3.4 ± 0.7	3.3 ± 1.1
Advil PM Liqui-Gel-fed (B)	85.2 ± 16.4	95.6 ± 29.5	873.2 ± 243.9	929.6 ± 357.9	2.5 ± 0.8	2.4 ± 0.9
IBU/DPH - fasted (C)	67.1 ± 13.0	73.5 ± 25.6	748.1 ± 198.1	766.3 ± 335.5	3.4 ± 0.7	3.1 ± 0.8
B/A ratio (%) ⁺	120.8	129.2	116.3	125.3	--	--
C/A ratio (%) ⁺	97.7	104.5	99.7	98.9	--	--
B/A 90% CI ⁺	109.0-133.9	112.7-148.1	108.9-124.2	115.6-135.9	--	--
C/A 90% CI ⁺	88.1-108.5	90.8-120.4	93.3-106.5	90.9-107.5	--	--

Conclusions:

- The administration of Advil PM Liquigels under fed conditions resulted in slight decrease in ibuprofen C_{max} (by 18.5%). In contrast, food slightly increased in the rate and extent of diphenhydramine absorption (shortened T_{max} by 0.86 hour, increased C_{max} by 25.0%, increased AUC_{0-∞} by 20.6%).
- Advil PM Liquigels demonstrated an equivalent extent, but a slower rate of ibuprofen absorption relative to ibuprofen liquigels coadministered with diphenhydramine liquigels under fasted conditions (lower C_{max} by 21.3%, longer T_{max} by 0.4 hours).
- The rate and extent of diphenhydramine absorption from Advil PM Liquigels were equivalent to those from diphenhydramine liquigels coadministered with ibuprofen liquigels under fasted conditions.
- There was a gender difference in food effect on the absorption of ibuprofen and diphenhydramine from Advil PM Liquigels. Females but not male subjects demonstrated the food effect; lower extent in ibuprofen but larger extent in diphenhydramine absorption.

Reviewer's Comment:

- The food effect observed in this study does not appear to be clinically important, considering the magnitude of the food effect (25% at maximum in pharmacokinetic values) as compared with the wide safety and efficacy margin of ibuprofen and diphenhydramine.
- In the fed study (Treatment B), total calorie intake and calories as fat (648 calories, 37%, respectively) were lower than those in the Agency's guidance for a food effect study with high fat meal (1000 calories, 50%, respectively). This is acceptable since it is likely for a patient to take Advil PM Liquigels at bedtime with light snack rather than high fat meal.
- It is not known why the rate of ibuprofen absorption was different between Treatments A (Advil PM Liquigels) and C (ibuprofen liquigels + diphenhydramine liquigels) although their formulations were essentially the same (only difference is — PEG content by — . Study AE-97-09 showed similar results.
- The gender difference observed in this study does not appear to be clinically important considering the quantitative difference between genders (13.4% at maximum in pharmacokinetic values).

**APPEARS THIS WAY
ON ORIGINAL**

Study AE-97-09

ADVIL PM LIQUIGELS RELATIVE BIOAVAILABILITY STUDY

Objectives:

To compare the rate and extent of absorption of ibuprofen (IBU) and diphenhydramine (DPH) from the proposed market formulation of Advil PM Liquigels with those from the currently marketed single ingredient products

Study Design:

This is a randomized, open-label, four-way crossover, bioequivalence-type study. Volunteers received a single oral dose of each of the following treatments under fasted conditions.

Treatment A: 2 x Advil PM Liquigels (IBU 200mg + DPH HCl 25mg / liquigel; Whitehall-Robins Batch #, WH-0723-0005A)

Treatment B: 2 x Advil Liquigels (IBU 200 mg/liquigel; Whitehall-Robins Batch #, WH-0693-0001)

Treatment C: 2 x Benadryl Liquigels (DPH HCl 25 mg/liquigel; Warner Lambert Batch #, 10268C)

Treatment D: 2 x Nuprin Tablets (IBU 200 mg/tablet; Bristol-Myers Squibb Batch #, 805507)

Advil PM Liquigels was very similar to Advil Liquigels in formulation but not to Benadryl Liquigels or Nuprin Tablets. Each treatment was separated by a 7-day washout period. Each dose was administered with 240 mL of water after overnight fast for 10 hours. During Treatments A and C, 15 blood samples (7 mL) were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 8, 12, 24, and 36 hours post-dose. During Treatments B and D, blood sampling at 24 and 36 hours post-dose were omitted. Plasma was obtained from the blood samples, stored at -20°C and subsequently analyzed for racemic IBU or for DPH using reverse-phase high performance liquid chromatographic (HPLC) methods coupled with ultraviolet absorbance detection.

The treatment groups were compared for original AUC_{0-t} , $AUC_{0-\infty}$ (AUCI), C_{max} , T_{max} and half-life, and for log-transformed AUC_{0-t} , AUCI and C_{max} by means of the analysis of variance (ANOVA) appropriate for a multiple-crossover design, stratified by gender. Statistical significance was declared if the resulting p value was ≤ 0.05 . The effect of gender or treatment-by-gender interaction was considered significant if $p \leq 0.15$. If a gender effect or treatment-by-gender interaction was significant for the pharmacokinetic parameters, the volume of distribution and clearance divided by body weight were calculated and analyzed for the gender effect or treatment-by-gender interaction. The statistical analyses were done using a SAS GLM procedure. The ratio for each parameter was calculated by dividing the least-squares means of test treatment by those of reference treatment calculated from the ANOVA. To test for bioequivalence, it was determined whether the 90% confidence interval (90% CI) computed for the ratio with log-transformed data was contained within 80% and 125%.

Inclusion/Exclusion: Normal, healthy, non-smoking volunteers aged between 18 and 45 years old were eligible for this study. Pregnant or lactating females, and subjects who took any investigational drugs within the past 30 days before the study were excluded. Subjects were asked to refrain from ingesting any medications except oral contraceptives for 14 days, caffeine for 24 hours, and alcohol for 3 days prior to and during each study period. These and other inclusion and exclusion criteria appears to be relevant to this study.

Results:

Clinical investigations were conducted at _____

A total of 24 subjects aged 20 - 43 years old completed the study. One subject was excluded from data analysis due to protocol violation (pre-exposure to DPH). There were 12 males and 11 females consisting of 10 Caucasians, 12 blacks and 1 Hispanic. All four treatments were well tolerated.

Drug assay was conducted at _____

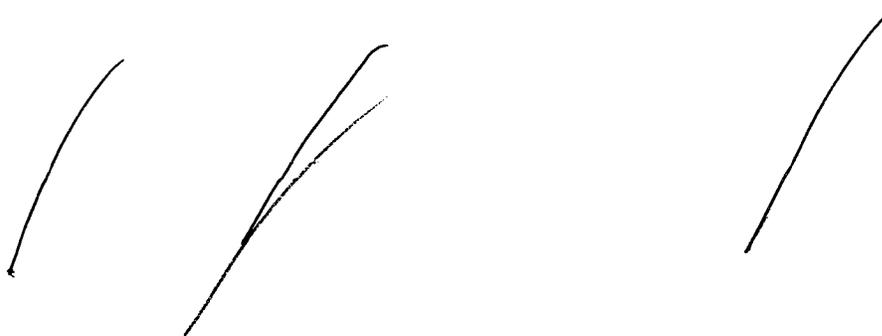
The plasma concentrations of DPH and racemic IBU were analyzed by validated HPLC methods (see 4.6. Analytical). For IBU assay, the correlation coefficient (r) of standard curve was 0.999 or larger. Inter-assay accuracy ranged from 100.5% to 101.6%, and precision varied from 2.6% to 6.5%. For DPH assay, the correlation coefficient (r) of standard curve was 0.997 or larger. Inter-assay accuracy ranged from 96.8% to 99.5%, and precision varied from 5.0% to 5.4%.

In terms of the extent of IBU absorption, Advil PM Liquigels, Advil Liquigels, and Nuprin Tablets were equivalent (90% CI of least-squares mean ratio, 80 - 125%; Table 3-1). However, the C_{max} of IBU obtained from Advil PM Liquigels was lower by 28.6% (least-squares mean ratio, 71.4%; 90% CI, 63.4 - 80.4%) or by 14.1% (least-squares mean ratio, 85.9%; 90% CI, 76.2 - 96.8%) than that from Advil Liquigels or Nuprin Tablets, respectively (Table 3-1). The T_{max} of IBU obtained from Advil PM Liquigels was shorter by 0.56 hour than that from Nuprin Tablets (0.91 ± 0.58 vs 1.47 ± 0.58 hr, $p < 0.001$; Table 3-1). Therapeutic plasma concentrations of IBU (≥ 10 $\mu\text{g/mL}$) were maintained from 0.5 through 4 hours after the administration of Advil PM Liquigels. Similar results were seen with the single ingredient marketed products of Advil Liquigels and Nuprin Tablets. The spaghetti plots for IBU concentrations over time are shown in Figure 3-1.

Table 3-1. Study AE-97-09, Pharmacokinetic parameters for ibuprofen (mean ± SD)

Treatment (sample size)	C _{max} (mcg/mL)	AUCI (mcg-hr/mL)	T _{max} (hr)	t _{1/2} (hr)	Kel (1/hr)
Advil PM Liqui-Gels (A) (n=23)	33.7 ± 11.1	131.2 ± 28.0	0.91 ± 0.58	2.87 ± 1.17	0.27 ± 0.07
Advil Liqui-Gels (B) (n=23)	45.4 ± 10.1	132.5 ± 30.1	0.75 ± 0.36	2.15 ± 0.31	0.33 ± 0.06
Nuprin Tablets (D) (n=23)	38.0 ± 9.0	138.8 ± 28.8	1.47 ± 0.58	2.07 ± 0.34	0.34 ± 0.06
A/B Ratio [†]	71.4%	99.3%	--	--	--
A/D Ratio [†]	85.9%	94.5%	--	--	--
A/B 90% CI [†]	63.4 - 80.4%	95.3 - 103.4%	--	--	--
A/D 90% CI [†]	76.2 - 96.8%	90.7 - 98.4%	--	--	--

Figure 3-1. Study AE-97-09, Spaghetti plots for ibuprofen concentrations over time



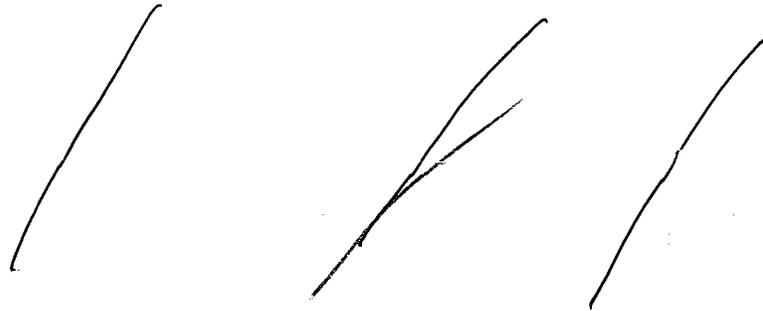
In terms of the extent of DPH absorption, Advil PM Liquigels and Benadryl Liquigels were equivalent (90% CI of least-squares mean ratio, 80 - 125%; Table 3-2). Even though the C_{max} from Advil PM Liquigels was lower by 17.0% (least-squares mean ratio, 83.0%; 90% CI, 76.4 - 89.3%) than Benadryl Liquigels, this difference disappeared (least-squares mean ratio, 87.0%; 90% CI, 81.4 - 92.3%) by deleting an outlier (subject No. 51, Figure 3-2 Treatment C).

Therapeutic plasma concentrations of DPH (≥ 30 ng/mL) were maintained from 1.5 through 8 hours after the administration of Advil PM Liquigels. Similar results were seen with the single ingredient market product, Benadryl Liquigels. The spaghetti plots for DPH concentrations over time are shown in Figure 3-2.

Table 3-2. Study AE-97-09, Pharmacokinetic parameters for diphenhydramine (mean ± SD)

Treatment (sample size)	C _{max} (ng/mL)	AUCI (ng-hr/mL)	T _{max} (hr)	t _{1/2} (hr)	Kel (1/hr)
Advil PM Liqui-Gels (A) (n=23)	54.7 ± 21.0	691.7 ± 273.0	3.48 ± 1.95	9.74 ± 2.61	0.08 ± 0.02
Benadryl Liqui-Gels (C) (n=23)	67.6 ± 40.7	713.4 ± 367.1	2.87 ± 0.68	9.77 ± 2.66	0.08 ± 0.02
A/C Ratio [†]	83.0%	97.2%	--	--	--
A/C 90% CI [†]	76.4 - 89.3%	91.0 - 103.9%	--	--	--

Figure 3-2. Study AE-97-09, Spaghetti plots for diphenhydramine concentrations over time.



Based on the sponsor's criteria ($p \leq 0.15$), there were significant gender effects with or without treatment-by-gender interactions in statistical tests using ANOVA for both IBU and DPH pharmacokinetic parameters. This analysis is not acceptable because there is no consensus on the criteria. Therefore, the reviewer examined a difference between genders in a least-squares mean ratio of a pharmacokinetic parameter using a 90% CI approach.

Based on the 90% CI approach, the gender difference was not meaningful. For IBU absorption, the results in both male and female subjects (Table 3-3) were consistent with the overall results (Table 3-1) although differences between treatments were mostly larger in female than male subjects. Even though Advil PM Liquigels did not appear bioequivalent to Benadryl Liquigels as determined in female subjects (Table 3-4), this is due to a notable female outlier (subject No. 51, Figure 3-2 Treatment C); the gender difference was virtually gone by deleting the outlier. In addition, the gender difference may also be attributable to body weight difference between male and female subjects since the gender effect in clearance and volume of distribution disappeared with weight adjustment.

Table 3-3. Study 97-09, Pharmacokinetic parameters for ibuprofen stratified by gender (mean \pm SD).

Treatment	C_{max} (mcg/mL)		AUCI (mcg•hr/mL)		T_{max} (hr)	
	Males (n=12)	Females (n=11)	Males (n=12)	Females (n=11)	Males (n=12)	Females (n=11)
Advil PM Liqui-Gel (A)	32.0 \pm 9.9	35.6 \pm 12.5	124.0 \pm 19.3	139.2 \pm 34.4	1.0 \pm 0.7	0.8 \pm 0.4
Advil Liqui-Gel (B)	39.8 \pm 6.9	51.4 \pm 9.8	122.9 \pm 24.4	143.1 \pm 33.2	0.8 \pm 0.5	0.7 \pm 0.2
Nuprin Tablet (D)	35.1 \pm 6.6	41.2 \pm 10.4	134.0 \pm 24.2	144.0 \pm 33.5	1.4 \pm 0.6	1.5 \pm 0.6
A/B ratio [†]	75.4	65.3	102.8	96.5	--	--
A/B 90% CI [†]	63.2 - 89.9	55.9 - 76.3	97.3 - 108.7	90.0 - 103.4	--	--
A/D ratio [†]	85.3	83.1	92.5	96.8	--	--
A/D 90% CI [†]	71.5 - 101.7	71.1 - 97.1	87.5 - 97.8	90.4 - 103.7	--	--

Table 3-4. Study 97-09, Pharmacokinetic parameters for diphenhydramine stratified by gender (mean \pm SD).

Treatment	C _{max} (ng/mL)		AUCI (ng-hr/mL)		T _{max} (hr)	
	Males (n=12)	Females (n=11)	Males (n=12)	Females (n=11)	Males (n=12)	Females (n=11)
Advil PM	51.7 \pm	57.9 \pm	623.4 \pm	759.9 \pm	3.5 \pm	3.5 \pm
Liqui-Gel (A)	17.6	24.8	177.7	338.6	2.3	1.7
Benadryl	52.8 \pm	83.8 \pm	568.5 \pm	871.6 \pm	2.9 \pm	2.9 \pm
Liqui-Gel (C)	12.7	54.1	190.0	451.6	0.8	0.5
A/C ratio (%) ⁺	95.3	69.8	106.1	87.1	--	--
A/C 90% CI ⁺	83.5 -108.7	63.4 -76.8	95.4 - 117.9	78.8 - 96.4	--	--

Conclusions:

- Advil PM Liquigels demonstrated equivalent extent, but lower C_{max} (by 28.6%) of absorption of ibuprofen relative to the single entity marketed liquigels containing ibuprofen (Advil Liquigels).
- Advil PM Liquigels showed an equivalent extent, but earlier T_{max} (0.91 vs 1.47 hr) and lower C_{max} (by 14.1%) of ibuprofen absorption as compared with single entity marketed tablets containing ibuprofen (Nuprin Tablets).
- Advil PM Liquigels demonstrated bioequivalence relative to the single entity marketed liquigels containing diphenhydramine (Benadryl Liquigels).

Reviewer's Comments:

- The sponsor conducted this study according to the Agency's recommendation during the sponsor-FDA meeting of June 23, 1997.
- It is not known why the C_{max} of ibuprofen with Advil PM Liquigels (combination) was lower than that with currently marketed Advil Liquigels (ibuprofen only) although Study WM-716 showed no pharmacokinetic interactions between ibuprofen and diphenhydramine and the formulations used were essentially the same (only difference is more PEG content by 33%). Study AE-97-02 showed similar results.
- The gender difference in bioequivalence detected in this study does not appear meaningful since the difference disappeared after deleting an outlier and adjusting for body weight.

6.3. OCPB Filing / Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-393	Brand Name	Advil PM Liquigels	
OCPB Division (I, II, III)	III	Generic Name	Ibuprofen / Diphenhydramine HCl	
Medical Division	HFD-550	Drug Class	Analgesic/Antihistamine	
OCPB Reviewer	Jang-Ik Lee	Indication(s)	Analgesic / nighttime sleep-aid	
OCPB Team Leader	E. Dennis Bashaw	Dosage Form	Capsules (liquid filled)	
		Dosing Regimen	2 capsules at bedtime	
Date of Submission	10/16/01	Route of Administration	Oral	
Estimated Due Date of OCPB Review	01/15/02	Sponsor	Wyeth Consumer Healthcare	
PDUFA Due Date	08/15/02	Priority Classification	4S	
Division Due Date	04/15/02			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) - Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	(X)*	(3)*	(3)*	
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	(X)**	(2)**	(2)**	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		3	3	
Filability and QBR comments				
	"X" if yes	Comments		
Application fileable ?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1. What are the highlights of the formulation of the drug product? What is the proposed dosage and route of administration? 2. What is the rationale for the combination of ibuprofen and diphenhydramine? 3. Is there any pharmacokinetic interaction between ibuprofen and diphenhydramine when administered simultaneously? 4. Are the rate and extent of absorption of ibuprofen and diphenhydramine observed from Advil PM Liquigels equivalent to those from single ingredient products (formulation effect)? 5. What are the characteristics of the exposure-response relationships for efficacy and safety? 6. What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on dosage regimen adjustments? 7. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types? 8. How do the dissolution conditions and specifications assure in vivo performance and quality of the product? 9. Is any study required to demonstrate an equivalence between clinical and to-be-marketed formulations? 10. What bioanalytical methods are used to assess the plasma concentrations of ibuprofen and diphenhydramine? 		
Other comments or information not included above		* PK data stratified by gender ** not a true bioequivalence study (single entity vs. combo)		
Primary reviewer Signature and Date	Jang-ik Lee	April 24, 2002		
Secondary reviewer Signature and Date				

CC: NDA 21-393, HFD-850 (P. Lee), HFD-860 (M. Mehta), HFD-550(CSO), HFD-880 (TL, DD, DDD), CDR

End of Document

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jang-Ik Lee
4/24/02 04:31:16 PM
BIOPHARMACEUTICS

Changed wording in Labeling Recommendation

Dennis Bashaw
4/24/02 05:12:02 PM
BIOPHARMACEUTICS