CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-402/SCM-001/S-002/S-003/S-004/S-005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW DEC 13 1999

NDA:	20-402 (SE1-005)	**Submission Date:**	9/8/99
Product:	Advil Liquigels© (Ibuprofen, 200 mg)		
Sponsor:	Whitehall-Robins Madison, NJ 07940	**Reviewer:**	Abimbola Adebowale Ph.D.

Review of an Amendment to a Supplemental Application

I. Background and Amendment Overview

This amendment is a response to the FDA letter dated August 6th, 1999 to the sponsor which offered preliminary comments on pending supplement S-005 to NDA 20-402. The agency noticed that all clinical trials supporting S-005 were conducted using the currently marketed green oblong liqui-gels® and not the to be marketed brown oval liqui-gels®. The division also explained that although both formulations (green and brown liqui-gels®) were tested against the same reference product (i.e. ibuprofen suspension) in two different bioequivalence studies, a direct comparison of the two formulations was still necessary to support bioequivalence. The agency also requested clarification as to whether the sponsor intended to market the brown oval Liqui-gels® as Advil Migraine®, while continuing to market the green oblong product as Advil Liqui-gels®.

The agency recommended in the letter that the sponsor should conduct *in vitro* dissolution testing using both the green and the brown liqui-gels® products using the approved dissolution media and apparatus described in their original dissolution testing protocol. The sponsor should then generate individual capsule dissolution profiles over the first 30 min. using the following time-points. 0, 5, 10, 15, 20, 25, and 30. These dissolution profiles were then to be compared using the difference factor [redacted] and the similarity factor [redacted] The rationale being that the *in vitro* dissolution testing would be sufficient to detect the presence or absence of any significant change in *in vivo* behavior, given the formulation change being made and the magnitude of the change.

In this amendment, the sponsor has submitted *in vitro* dissolution data previously submitted to the agency as general correspondence (NDA 20402 on 12/9/96) except that, the data are now presented with corresponding profile comparison calculation results [redacted] An expert report by [redacted] which discusses how the pharmacokinetic results for the 2 bioequivalence studies previously submitted (PV-96-02 and PV-96-08) relate to the in vitro dissolution data to support the conclusion of bioequivalency between the brown and green liqui-gels [redacted]

The sponsor also provided confirmation of their intention to market the "brown oval liqui-gels®" product as Advil® Migraine, while continuing to market the "green oblong liqui-gels®" product as Advil® liqui-gels®.

II. Dissolution

The sponsor stated that they did not have any recently manufactured "brown oval" liquigel batches available for testing at the present time. The dissolution data submitted are for batches of the "green oblong" and "brown oval" Liqui-gels® manufactured in 1996 which were previously submitted to the agency as general correspondence to NDA 20-402 on 12/9/96. Dr. Dennis Bashaw reviewed this general correspondence and was concerned with the more rapid dissolution profile observed for the brown/oval product, which could have a potential impact on both the bioequivalence and the adverse event profile of the product. The agency then concluded that the acceptance of the reduced gelatin content brown/oval product could not be granted without a demonstration of in vivo bioequivalence between an appropriate reference product and the brown/oval product. Batch details for the submitted dissolution data are reproduced in the table below:

[redacted]

[redacted] the main difference being that the [redacted] time point was extrapolated, since this time point was not tested for in 1996. These dissolution data demonstrate the difference in dissolution profiles that were of concern in 1996 between the two formulations.

[redacted]

This portion of the document contains information that will not be included in the redacted portion of the document for the public to obtain.

III. Consultant Report

Objective: To critically review the evidence supporting bioequivalence of the two Liqui-gel capsule® products, particularly with respect to the in vitro data.

Methods: Comparison of the Tmax data of the previously submitted two bioavailability studies (PV-96-02 and PV-96-08) to determine if bursting is a rate-limiting step for absorption.

Results: The consultant compared the Tmax of the suspension that was the reference product used in both studies against the Tmax of the Liqui-gels®. A copy of the individual Tmax data and the plot of the Tmax of the Liqui-gels® against the Tmax of the suspension for each subject Reproduced below is a table of the summary statistics of the Tmax data:

Table 3: Mean Tmax (SD) from Bioavailability studies PV-96-02 and PV-96-08

Study	Liquigel Mean (SD)	Suspension Mean (SD)	P-value
PV-96-02	0.70 (0.25)	0.81 (0.50)	0.18
PV 96-08	0.81 (0.39)	0.74 (0.49)	0.43
Mean	0.75	0.78	

On evaluation of the data it appears that the difference between the Tmax values for the Liqui-gel® and the suspension were not statistically significant suggesting that the time of bursting had no effect on the overall rate of absorption.

Conclusions: The conclusions derived from this comparison evaluation by the consultant were that the time of bursting had no effect on the overall rate of absorption. The [redacted] time point was regarded as introducing "noise" in the in vitro evaluation rather than providing relevant information. [redacted]

IV. Recommendation

[redacted]

/S/

12/13/99

Abimbola O. Adebowale Ph.D.
Office of Clinical Pharmacology /Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Dennis Bashaw, Pharm.D. /S/ 12/12/99

CC:
NDA 20-402 (Supplement, Amendment)
HFD-560 (Div. File)
HFD-560 (CSO/Rothschild)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Adebowale)
HFD-340 (Viswanathan)
CDR: ATTN: Barbara Murphy

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CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

DEC 1 8 1999

NDA:	20-402 (SE1-005)	**Submission Date:**	5/14/99
Product:	Advil® Liquigels® (Ibuprofen, 200 mg)		
Sponsor:	Whitehall-Robins Madison, NJ 07940	**Reviewer:**	Abimbola Adebowale Ph.D.

Review of a Supplemental NDA

I. Background and Supplement Overview

This SNDA under review is a supplemental new drug application for a brown, oval liquigel® dosage form containing 200 mg of solubilized ibuprofen under the name Advil ® Migraine, for treating mild to moderate migraine headaches in adults and children age 12 years and older. The sponsor has included one new study report (PV-96-08), and, an overview of the human pharmacokinetics/bioavailability report in the human pharmacokinetics and bioavailability section.

Sandoz Pharmaceutical Corporation originally received the approval for NDA 20-402 from the FDA (April 25, 1995) and then transferred the NDA to Whitehall-Robins (April 22, 1996). Whitehall-Robins Healthcare currently markets a 200mg green oblong, liquigel containing 200mg of solubilized potassium ibuprofen under approved NDA No. 20-402 for OTC as an analgesic/antipyretic. The sponsor also included the synopsis for two bioequivalence studies [redacted] that evaluated the original green oblong liquigels. Study [redacted] (submitted 12/10/96) that evaluated the original green oblong liquigels was approved by the agency as part of supplemental NDA 20-402 (S002) (reviewed by Dennis Bashaw Pharm D). The main focus of this review will be study [redacted] with any other studies being supportive information wherever applicable.

II. Formulation

[redacted]

Table 1: Comparison of the green oblong and the brown oval liquigel formulations

	Formulation (mg/unit)

III. PK and Bioavailability Studies

Report (Study dates March 7 – 14, 1997; Report date July 7 1997)

Study Title: A Randomized, Single-Dose, Two-way Crossover. Bioequivalence Study Comparing Advil® 200 mg Liquigel Capsules to Children's Advil® 20mg/mL Suspension.

Study Investigator:

Study Site:

Analytical Site:

Objective:

To compare the rate and extent of absorption of Ibuprofen from Advil® 200 mg brown, oval liquigel capsules and Children's Advil® 20 mg/mL suspension administered under fasting conditions.

Methods:

Study Population: A total of 24 healthy adult male (75%) and female (25%) were enrolled in the study. The mean age was 31.83 ± 6.75 years (range: 19-41). The mean height was 68.46 ± 3.01 inches (range: 63 to 73 inches), mean weight was 157.92 ± 26.56 pounds (range 109 to 210 pounds). Eighteen (75%) subjects were caucasian, 5 (21%) were black, and 1 (4%) was asian (in the appendix page 2 is a summary of the demographic data). Twenty-three subjects completed the study. Subject No. 24 voluntarily withdrew from the study after completing period 1 dosing.

Test product:

Reference Product:

Treatment Regimens:

Treatment A: 2 x 200 mg Advil® brown oval Liquigel Capsules administered with 240 mL of water after a 10 hr overnight fast

Treatment B: 20 ml of Children's Advil® 20 mg/ml Suspension administered with 240 mL of water after a 10 hr overnight fast

Treatments were assigned to the subjects according to a computer-generated randomization Schedule

Pk and Statistical analysis:

Analytical Method:

Validation Report:

Specificity:

These chromatograms indicate the specificity of the method in that there was no interference at the retention time of ibuprofen and the internal standard.

Linearity: For the validation of the method 5 standard curves were constructed and, 17 were constructed throughout the analysis of the samples. Thus a total of 22 standard curves were constructed throughout the analysis phase of the study.

Table 2. Mean back calculated concentrations for the 5 standard curves used for the pre-study validation of the method

	Back Calculated Calibration Curve Standard Concentrations in mcg/ml									
	0.10	0.20	2.504	7.511	25.037	38.057	45.067	50.075	90.134	125.187
Mean	0.1008	0.1924	0.2.4995	7.1436	25.4583	42.0250	44.0745	49.3392	89.4696	123.4941
SD	0.00127	0.00530	0.05261	0.13616	0.64064	1.99461	0.92107	3.34709	0.80403	0.62657
%CV	1.3	2.8	2.1	1.9	2.5	4.7	2.1	6.8	0.9	0.5
N	5	4	5	4	5	5	5	5	5	5
% Nominal	100.8	96.2	99.8	95.1	101.7	110.4	97.8	98.5	99.3	98.6

Table 3. Mean back calculated concentrations for the 17 standard curves used for the analysis (in study validation)

	Back Calculated Calibration Curve Standard Concentrations in mcg/ml									
	0.10	0.20	2.51	7.52	25.05	38.08	45.09	50.11	100.21	125.26
Mean	0.100	0.206	2.476	7.633	24.652	37.195	45.001	50.195	101.241	125.431
SD	0.007	0.011	0.0745	0.1675	0.4753	0.6366	1.0938	0.7863	1.8204	2.5074
%CV	7.0	5.4	3.0	2.2	1.9	1.7	2.4	1.6	1.8	2.0
N	17	15	16	17	17	17	17	17	17	17
% Nominal	100.1	102.8	98.6	101.5	98.4	97.7	99.8	100.2	101.0	100.1

Linear regression with weighting of 1/concentration equation was judged adequate to represent the concentration/response relationship.

Accuracy and Precision: The in-study precision and accuracy was demonstrated by the analysis of quality control (QC) samples of Ibuprofen in human plasma prepared at

Table 4. Quality Control Sample Data (Between-Batch Precision and Accuracy) for In-study validation

	Low	Medium	Medium	High
Target (mcg/ml)	0.30	20.29	40.58	91.31
Mean (mcg/ml)	0.315	19.884	40.211	91.825
SD	0.0207	0.3959	1.1361	1.8546
%CV	6.6	2.0	2.8	2.0
N	32	33	34	33
% Nominal	105.1	98.0	99.1	100.6

The HPLC assay had a precision (%CV) between batches of [redacted] as shown in the table above. Analysis of the results of the quality control samples indicates that the assay was both accurate and, precise during the analysis of the study samples. The sponsor did not include any data on within batch precision obtained during the analysis of the samples. The within batch precision during the study analysis of [redacted] could probably be deduced from the back calculated concentrations for the in study standard curves.

Sensitivity: The limit of reliable quantitation was set at the concentration of the [redacted] for Ibuprofen. The between-batch CV for samples at this concentration was [redacted] which, was < the acceptance criteria of = 20% specified in the SOP. Thus based on the results from the back-calculated standard curve and quality control samples, this was an appropriate lower limit of quantitation (LOQ). Concentrations below LOQ were reported as below limit of quantitation (BLQ).

Stability: The sponsor reported and documented the Long term. short term. freeze-thaw and stock solution stability of ibuprofen carried out in the pre-study validation only in 1994. Ibuprofen was found to be stable at:

1) [redacted]
2)
3)
4)
5)

The stability data met the criteria specified in the SOP indicating that Ibuprofen was stable during analysis and during storage before analysis.

Analytical Conclusions:

The analytical procedures used by the applicant were reproducible and were fully documented in the study report. From a biopharmaceutic standpoint the assay was fully validated suggesting that the procedures used were sufficient to maintain control of the assay.

Results:

Subject 24 was excluded from the pharmacokinetic analysis, however period 1 data obtained from Subject 24 was presented for informational purposes in the analytical report. Reproduced below is a summary table of the mean (± SD) pharmacokinetic parameters and confidence intervals for Ibuprofen 400 mg obtained:

Table 5: A Summary of the Pharmacokinetic Parameters (Mean (%CV) and CI for Ibuprofen 400 mg from Study PV-96-08 (N = 23)

Treatment	**Cmax (mcg/ml)**	**AUCinf (mcg.hr/ml)**	**AUC 0-t (mcg.hr/ml)**	**Tmax (hr)**	**$T_{1/2}$ (hr)**	**MRT (hr)**	**Kel**
Brown, oval liquigels Fasted (A)	40.13 (25.5)	115.52 (29.4)	112.51 (28.7)	0.81 (49.0)	2.36 (12.3)	3.27 (21.6)	0.30 (14.3)
Children's Advil® 20 mg/ml Suspension Fasted (B)	37.38 (18.1)	109.00 (28.4)	106.25 (27.6)	0.74 (53.0)	2.36 (13.4)	3.16 (16)	0.30 (17.0)
Ratio of least-square means (A/B) %	107.1	105.9					
90% CI (A/B)	100-115%	102 – 110%	101.6 110.2%	-	-	-	-

- = Not done

From the results in the above table the following observations were made:
An evaluation of the confidence limits for the log transformed AUC inf (102 –110 %) and Cmax (110 – 115 %) for the comparison of the Advil® Liquigel fasted vs. Children's Advil® 20 mg/ml Suspension were within the 80 – 125 % FDA acceptance criteria

Exclusion of data from subject 11:

A statistically significant sequence effect ($p<0.1$) was observed for the untransformed and log-transformed AUC 0-t, AUC inf and C max. Detectable pre-dose plasma levels were observed in both periods 1 and 2 for subject No.11 and, thus does not meet the criteria for acceptability of studies with sequence effects listed in the division of Bioequivalence guidance on statistical procedures. Additional statistical analysis was performed excluding subject 11's data from both formulations. summary tables of the mean pharmacokinetic parameters and 90% CI excluding data from subject 11. Reproduced below is a summary table of the mean (± SD) pharmacokinetic parameters and confidence intervals for Ibuprofen 400 mg excluding subject 11.

Table 6: A Summary of the Pharmacokinetic Parameters (Mean (%CV) and CI for Ibuprofen 400 mg from Study PV-96-08 (N = 22)

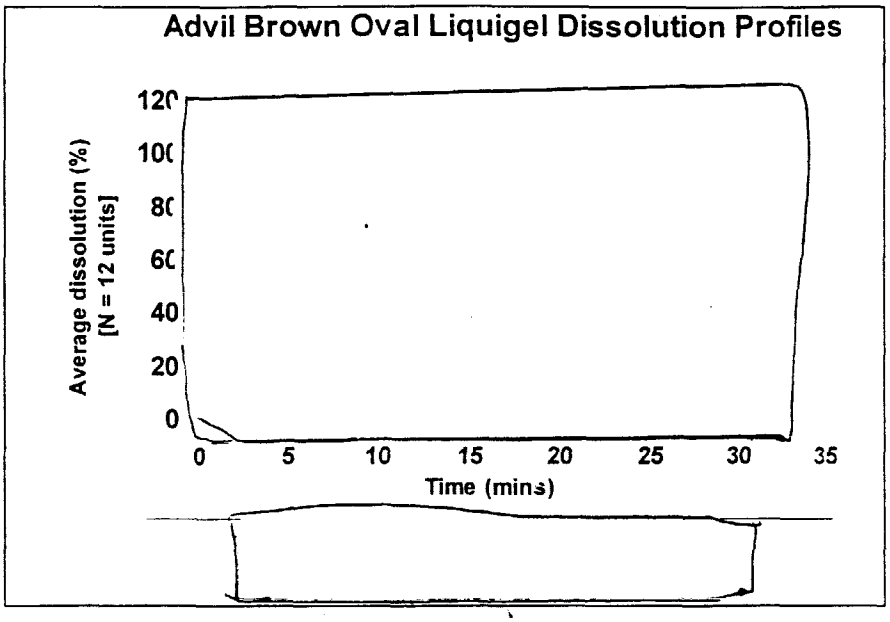
Treatment	**Cmax (mcg/ml)**	**Tmax (hr)**	**$T_{1/2}$ (hr)**	**MRT (hr)**	**AUCinf (mcg.hr/mL)**	**Kel**
Brown, oval liquigels Fasted (A)	40.16 (26.1)	0.77 (48.1)	2.35 (12.5)	3.24 (21.7)	113.63 (28.9)	0.30 (14.4)
Children's Advil® 20 mg/ml Suspension Fasted (B)	37.37 (18.51)	0.71 (53.7)	2.35 (13.7)	3.14 (16.2)	107.92 (28.6)	0.30 (17.2)
Ratio of least-square means (A/B) %	107.5				105.3	
90% CI (A/B)	100-116%	-	-	-	101 – 110%	-

- = Not done

The above table shows that statistical analysis of the data excluding subject 11 resulted in log transformed AUCinf, and Cmax whose ratios of least - squares means and confidence intervals also met FDA bioequivalence acceptance criteria. Inclusion or exclusion of subject 11 does not appear to affect the determination of bioequivalence.

Conclusions: The confidence intervals and ratios of least-squares means for the Log-transformed AUCinf and Cmax parameters for ibuprofen in plasma were within the 80 – 125 % range bioequivalence criteria accepted by the FDA. Therefore, based on these results the sponsor has shown that Whitehall-Robins 200 mg Advil® brown oval Liquigels are bioequivalent to Children's Advil® 20 mg/ml suspension under fasting conditions

IV. Dissolution:



Examination of the attached dissolution data suggests that > than 80% of the brown liquigels are in solution at the [redacted] time point. At the proposed specification time of [redacted] the mean % dissolved for all batches was > than 95 %. Based on this data it appears that a method that used a specification of [redacted] instead of [redacted] would be adequate to show lot to lot consistency of the product. However after consulting with the review chemist the current specification of [redacted] was found acceptable since this was still within the USP tolerance [redacted] for the dissolution of ibuprofen tablets and suspensions.

V. Comments:

In the summary table for the study under the section labeled overview, the data reported was not consistent. The sponsor included the untransformed data for the PK parameters and the 90% CI for the log transformed data in the same table. The sponsor is advised that in future studies the agency standard is to use the log transformed data for the analysis of data in bioequivalence studies as this achieves the general comparison based on ratio rather than difference.

VI. Recommendation

The information contained in this supplement demonstrates that Whitehall-Robins 200-mg Advil® brown Liquigels are bioequivalent to Children's Advil® Suspension under fasting conditions. From the biopharmaceutical point of view the firm has met the requirement of in vivo bioequivalency with an appropriate reference product. Based on

concurrence with the review chemist the proposed dissolution specifications were also acceptable. From the biopharmaceutical point of view the application is acceptable.

/S/

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RD/FT signed by Dennis Bashaw, Pharm.D. /S/ 12/8/99

CC:
NDA 20-402
HFD-560 (Div. File)
HFD-560 (CSO/Rothschild)
HFD-880 (Bashaw)
HFD-880 (Lazor)
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