CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-128

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-128	**Submission Date:**	10/1/99
Product:	Children's Motrin® Cold Suspension Ibuprofen (100 mg/5 ml) and Pseudoephedrine HCl (15 mg/5ml)		
Sponsor:	McNeil Consumer Healthcare, Fort Washington, PA	**Reviewer:**	Abimbola Adebowale Ph.D

Review of an NDA

I. Background and Introduction

Children's Motrin® Cold Suspension is a combination of Ibuprofen 100 mg/5ml (anti-inflammatory, analgesic and antipyretic) and, Pseudoephedrine HCl 15 mg/5ml (a decongestant), to be marketed OTC for children 2-11 years old. Ibuprofen and Pseudoephedrine are currently marketed OTC as single ingredient products for children and adults, and as a combination product for adults (Motrin IB ® Sinus). The proposed indications for Children's Motrin® Cold Suspension include the indications of 1) the temporary relief of symptoms associated with the common cold, flu, or sinusitis, including nasal and sinus congestion, stuffy nose, headache, sore throat, body aches and pains 2) temporary reduction of fever.

The applicant has included reports of two Phase 1 studies: a multiple dose pharmacokinetic study in children (97-024) and, a bioequivalence study in adults (98-057) in the human pharmacokinetics and bioavailability section of this NDA. In addition the applicant included supporting pharmacokinetics Literature and data (from previous McNeil studies) for ibuprofen and pseudoephedrine in the human pharmacokinetics and bioavailability section.

II. Recommendation

The information submitted did not indicate any systemic interactions between Ibuprofen and Pseudoephedrine that were of any clinical significance after multiple dose administration of Children's Motrin® Cold Suspension to children spanning the age range 4-11 years old. Based on the data submitted, the applicant has met the requirements outlined in 21CFR 320 and their application is acceptable from a clinical pharmacology and biopharmaceutics perspective. However, the applicant should adequately address the comment on page 22.

Question Based Review of Children's Motrin® Cold Suspension (Ibuprofen (100mg/5ml) and Pseudoephedrine (5mg/5ml)

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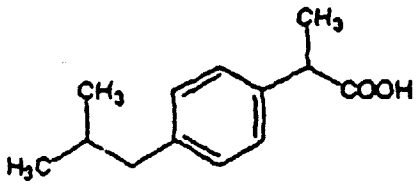
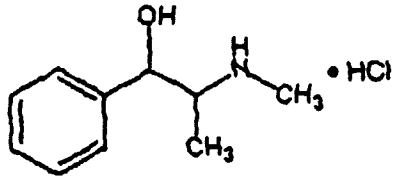
III. Physiochemical Properties, Dosage Administration and Indication(s)

What is Children's Motrin® Cold Suspension?

Children's Motrin® Cold Suspension is a combination of Ibuprofen 100 mg/5ml (anti-inflammatory, analgesic and antipyretic) and, Pseudoephedrine HCl 15 mg/5ml (a decongestant), to be marketed OTC for children 2-11 years old.

1. ***Physiochemical Properties:*** The physiochemical properties of Ibuprofen and Pseudoephedrine are as follows:





Drug Name	Ibuprofen	Pseudoephedrine HCl
Chemical Name	(±)-2-(p-isobutylphenyl) propionic acid	Benzenemethanol, α-[1 (methylamino) ethyl]-,[S-(R*, R*)]-,hydrochloride
Molecular formula	$C_{13}H_{18}O_2$	$C_{10}H_{16}NO.HCl$
Molecular weight	206.28	201.70
pKa	5.4 (weak acid)	9.22 (weak base)
pH	Between 3.6 and 4.6	4.6 –6.0 in a solution (1in 20)

2. ***Dosage Administration and Indication(s):***

The dosing schedule for the proposed OTC pediatric combination suspension product containing Ibuprofen and Pseudoephedrine is shown in the table below

Weight Range (lb)	Age (y)	Dose[a] (teaspoon)	Ibuprofen Dose[a] (mg)	Pseudoephedrine Dose[a] (mg)
Under 24	Under 2	Consult Doctor	Consult Doctor	Consult Doctor
24 - 35	2 - 3	1	100	15
36 - 47	4 - 5	1 ½	150	22.5
48 - 59	6 - 8	2	200	30
60 - 71	9 - 10	2 ½	250	37.5
72 - 95	11	3	300	45

a: Dosage may be repeated every six to eight hours, but not more than four times a day.

The proposed indications for Children's Motrin® Cold Suspension include the indications of 1) the temporary relief of symptoms associated with the common cold, flu, or sinusitis, including nasal and sinus congestion, stuffy nose, headache, sore throat, body aches and pains and, 2) temporary reduction of fever. Ibuprofen is a nonsteroidal anti-inflammatory drug with both analgesic and antipyretic properties considered to be related to prostaglandin synthetase inhibition. Pseudoephedrine is a sympathomimetic amine, with decongestant properties, through stimulation of alpha-adrenergic receptors, which constrict blood vessels throughout the body.

IV. Formulation

Was the formulation used in each biostudy the to be marketed formulation?

The applicant stated that two formulations of Children's Motrin® Cold Suspension are the to-be-marketed formulations (TBMF). The only difference between the two formulations is the flavoring, berry (deep orange color) and grape (purple color) flavored. The TBMF grape flavored, ibuprofen-pseudoephedrine suspension (Batch C-846-3C) was used as the clinical supplies for the human pharmacokinetic and bioavailability studies submitted. A copy of the composition of the formulations (showing that they differ only in flavoring) is inserted below:

Ingredients	Unit Weight (mg)
Both Formulations	
Glycerin USP	
Xanthan Gum NF	
Starch,	
Sucrose NF	
Pseudophedrine HCl USP	15.0
Ibuprofen USP	100
Acesulfame	
Sodium Benzoate NF	
Citric Acid USP	
Berry flavored formulation only	
FD&C Red No. 40	
D&C Yellow No. 10	
Polysorbate 80 NF	
Grape flavored formulation only	
FD&C Red No. 40 Certified	
D&C Red No. 33 Certified	
FD&C Blue No. 1 Certified	
Polysorbate 80 NF	
Both formulations	
Purified Water USP	
Total Volume	5 mL

V. Analytical Methods and Validation

Were the assay methods used for the determination of Ibuprofen and Pseudoephedrine in biological fluids validated?

The applicant stated that [redacted] conducted the analysis of Ibuprofen and Pseudoephedrine in human plasma. [redacted] A summary of the results of the assay methods validation for Ibuprofen and Pseudoepherine in human plasma, submitted by the applicant are reproduced below:

1. ***Results:*** ***Assay Validation Parameters in Human Plasma***

		Ibuprofen	Pseudoephedrine
Accuracy:	*Within-day:*		
	Between-day:		
Precision:	*Within-day*		
	Between-day		
Linearity:			
Sensitivity (LOQ):			
Recovery:			
Stability:			

2. ***Conclusions***

From the clinical pharmacology and biopharmaceutics perspective, the data submitted indicate that the analytical methods developed and validated for the determination of Ibuprofen and Pseudoephedrine in human plasma are reproducible and accurate and, are acceptable.

VI. Summary of Bio/PK Characteristics

A. Is there any systemic interaction between Ibuprofen and Pseudoephedrine when both drugs are administered in combination as a suspension?

On March 18th, 1998, McNeil CPC submitted, for FDA review, draft protocols for studies to support approval of Ibuprofen/Pseudoephedrine [redacted] combination products for OTC use in children. The draft protocol consisted of a 2-study program with one blood draw in children. On July 1st, 1998, The FDA responded, via fascimile to the applicant with pharmacokinetic comments regarding their pediatric

ibuprofen/pseudoephedrine protocol. The recommendation in the fascimile for the study design and interpretation by the FDA is inserted below:

Study Design

FDA recommends that McNeil conduct a multiple dose pk study in children (N=20) with your to-be-marketed formulation with pk sampling on day 2 (assuming 4 q6hr doses of product). At a minimum,sufficient plasma sampling to describe the steady state interval (6hrs) should be incorporated into the trial.

Study Interpretation

The results of this trial would be compared to data from the published literature and your NDA files dealing with the single entity administration of these components. The determination as to whether or not sufficient published/NDA data exists to make such a comparison should be researched and agreed to prior to study initiation.

A teleconference was then held on July 15th, 1998 to discuss the following objectives:

1. Understand the objective of the proposed pediatric PK study, and determine the primary endpoints for the study.

FDA responded that the study is needed to define the pharmacokinetics of the combination and assess, in pediatrics, any potential for interaction. FDA also stated that 1 plasma sample is inadequate. If McNeil has proof of principle that 1 sampling time is adequate, please submit data and FDA will review.

2. Confirm that the proposed FDA pediatric study is not crossover in design

FDA stated that the study could be done as a cross-over or a parallel design study.

3. Confirm that adult pharmacokinetic study is no longer required.

FDA stated the adult pharmacokinetic study is not required.

McNeil had questions with regards to the multi-dose study proposed by FDA. McNeil stated it is difficult to conduct a multi-dose study at home. FDA will review any proposals from McNeil. FDA suggested submitting a summary of any ibuprofen database and a rationale for the protocol. FDA emphasized that this is a pk study, not a bioequivalency study.

Based on the fascimile and the teleconference McNeil agreed to move forward with the protocol as recommended by FDA in their Fax on July 1, 1998. The protocol (No. 97-024) for a multiple dose pharmacokinetic study of an Ibuprofen-Pseudoephedrine HCl suspension in children was submitted by the applicant on October 22nd, 1998 and reviewed by Dr. V. Tandon and found acceptable. The results of this study are included in this submission as the pivotal study to assess the potential for drug-drug interaction in pediatrics and are discussed below:

Study # 97-024

This was an open-label, multiple-dose, single center pharmacokinetic study of Children's Cold Motrin in 24 (16 male and 8 female) healthy children aged 4-11 years, who had previously experienced symptomatic rhinitis. The treatment regimen consisted of one dose (~7.5 mg/kg of ibuprofen and ~1.125 mg/kg of pseudoephedrine HCl) of ibuprofen–pseudoephedrine suspension given every six hours for five doses. The objectives of this study were to determine the multiple-dose pharmacokinetics of ibuprofen and pseudoephedrine when administered concurrently and then, to assess the potential for a drug-drug pharmacokinetic interaction by comparing the results of this study with those from previous single-ingredient studies in children.

The applicant stated that a direct comparison with the results from the multiple dose studies could not be made due to differences in doses. However, since the doses in the published literature and the McNeil sponsored studies encompass the 7.5 mg/kg dose an indirect comparison was made. A detailed description of the study design, subject enrollment, and results are contained in the study abstract sheet and data sheets attached in the Appendix pages 1-6. Summary of the results are reproduced below:

Ibuprofen: Reproduced in the table below is a summary of the comparison of the PK data for ibuprofen administered as liquids from 3 published [1-3] and 2 McNeil sponsored studies (Study # 86-642 submitted to NDA 19-842, Motrin suspension in 1989 and 91-113 submitted to NDA 20-135 in 1994, Motrin chewable tablets)) [4-5] in children and ibuprofen administered as liquid in combination with Pseudoephedrine in study 97-024.

Table 2: Cross Comparison of PK parameters of Ibuprofen

PK Parameters	Mean (SD)								
Reference No[a] /or Study #.	1	1	2	2	3	4	4	5	97-024
N	17	26	9	8	38	19	22	18	24
Age Range (years)	2.5-12	2.5-12	3-10	3-10	0.25 –10.4	2.5-11.7	2.4-11.8	1-11.5	4-11.7
Dose (mg/kg)	5	10	5	10	8	5	10	6	7.5
Dosing (single or multiple)	SD	SD	SD	SD	SD	SD	SD	SD	MD
$AUC_{inf\ or\ \tau}$ (μg.h/ml)	88.3 (43.6)	126.0 (35.1)	NR[b]	NR	102.3 (35.2)	88.9 (25.0)	154.4 (35.0)	90.6 (25.9)	99.3 (21.1)
Cl/F (ml/h/kg)	67 (28)	86 (25)	72 (24)	84 (30)	NR	64 (18.0)	68.1 (13.2)	70.5 (20.6)	78 (16)
$T_{1/2}$ (h)	NR	NR	1.6 (0.6)	1.6 (0.5)	1.6 (0.7)	2.2 (1.3)	2.1 (1.28)	1.9 (1.0)	1.3 (0.3)
Vd/F (ml/Kg)	0.13 (0.05)	0.19 (0.16)	NR	NR	NR	0.20 (0.1)	0.20 (0.1)	0.20 (0.15)	0.15 (0.04)
$Cmax_{1\ or\ ss}$ (μg/ml)	NR	NR	28.4 (7.5)	43.6 (18.6)	35.8 (16.7)	28.8 (9.4)	53.8 (13.1)	30.9 (11.6)	32 (6.7)
$Tmax_{1\ or\ ss}$ (h)	NR	NR	1.1 (0.3)	1.2 (0.6)	0.7 (0.5)	1.0 (0.47)	0.99 (0.53)	0.87 (0.42)	0.97 (0.31)

[a] References

1. Brown RD et al. Single dose pharmacokinetics of Ibuprofen and acetaminophen in febrile children, J Clin Pharmacol 1992;32:231-241.
2. Nahata NC et al. Pharmacokinetics of Ibuprofen in febrile children. Ur J Clin Pharmacol 1991: 40:427-428.
3. Kauffman RE, Nelson MV: Effect of age on ibuprofen pharmacokinetics and antipyretic response
4. McNeil Study # 91-113 Efficacy and pharmacokinetic/pharmacodynamic profile of ibuprofen chewable tablets versus ibuprofen suspension in febrile children
5. McNeil Study # 86-642 Correlation of antipyretic effect with blood levels of ibuprofen in febrile children.

[b] NR = Not reported

1. The cross comparison as shown in the table above indicate that the AUC, Cmax and Tmax values for ibuprofen (7.5 mg/kg) administered as a combination with pseudoephedrine were within those for the 5-10 mg /kg dose administration of ibuprofen alone.
    a) This suggests that the rate and extent of absorption of Ibuprofen from the combination suspension is similar to that from the Motrin® suspension alone in children aged 4-11.7 years old.
    b) This also suggests that Pseudoephedrine does not effect the rate and extent of absorption of Ibuprofen when both are administered concurrently as a combination to children aged 4-11.7years old.
    c) The data from the comparison suggested that the rate and extent of absorption of Ibuprofen in febrile children aged 0.25 – 12 years old were comparable to that of healthy children aged 4-11 years old.
2. In most cases the oral clearance (Cl/F) for the 7.5mg/kg multiple dosing of ibuprofen in combination with pseudoephedrine were within the range of values obtained after administration of the single dose 5-10 mg/kg ibuprofen studies (only exception was data from reference no. 4).
3. The Volume of distribution Vd/F for the 7.5mg/kg multiple dosing of ibuprofen in combination with pseudoephedrine was within the range of values obtained with only reference 1 and in all other cases was lower. The half- life ($t_{1/2}$) was lower than the values obtained in all cases.
4. The cross comparison evaluation although highly suggestive of a lack of interaction in terms of the rate and extent of absorption and oral clearance between ibuprofen and pseudoephedrine when administered as a combination is limited in terms of the volume of distribution and half life.
5. The results in the above table also indicated that there appears to be a nonlinear relationship of AUCinf with higher ibuprofen doses in the results obtained with reference # 1, however, this does not appear to be the case with the results obtained in reference # 4 (Mcneil study).
    a) This difference could be due to the differences seen in Cl/F between the two doses used in reference 1 (i.e. 67 and 86 ml/h/kg) and, between it and the rest of the studies. Also a difference suggests possible differences in study population, possibly due to the use of febrile children and should be viewed carefully.
    b) The "suggestion" of a dose dependent kinetics for ibuprofen would confound the comparison of pharmacokinetic data across different studies with different doses.
    c) However, since this is not consistent with the data provided and the other parameters evaluated across the other studies it could not be confirmed.

Pseudoephedrine: Reproduced in the table below is a summary of the comparison of the PK data for Pseudoephedrine administered as liquids from 1 publication and, the above multiple dose study 97-024. There were no pharmacokinetic data from previous Mcneil single-dose studies submitted for Pseudoephedrine. The sponsor also included limited results of another publication by *Auritt et.al: Pharmacokinetics of pseudoephedrine in children. Ann Allergy 1981; 47: 139,* but this was only submitted as an abstract and not reviewed since the full publication which would give the relevant details of the study was not included.

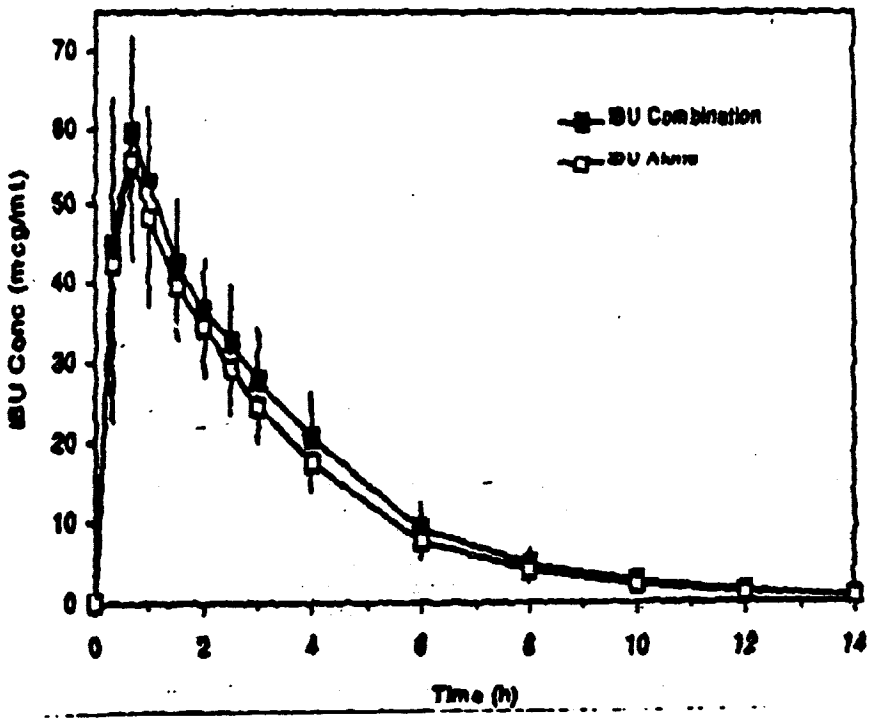
5. The applicant stated that difference in Cl/F and t ½ was attributable to differences in the urine pH between the two studies, with an increased pH resulting in a decrease in clearance.
6. The cross comparison evaluation for pseudoephedrine is highly suggestive of a lack of interaction in terms of the extent of absorption and volume of distribution between ibuprofen and pseudoephedrine when administered as a combination. The effects on the rate of absorption (Cmax and Tmax) and elimination kinetics (Cl/F and t ½) is also suggestive of a lack of interaction, but difficult to interpret due to the limited data.

Supportive Drug Interaction Study: Also Study # 98-057 the bioequivalence study conducted in adults, although not in the target population and, technically not a drug interaction study is supportive of the presence or lack of an interaction and the results are discussed below:

Study # 98-057

This was a single-dose, open-label, three-treatment, crossover, bioequivalence study in 24 (10 men and 14 women) healthy subjects to determine the bioequivalence of Children's Motrin® Cold Suspension (Ibuprofen-Pseudoepherine combination) with currently marketed, single-ingredient children's products that contain either ibuprofen or pseudoephedrine. A detailed description of the study design, subject enrollment, and results are contained in the Appendix pages 7-12.

Ibuprofen: Inserted below is a graph of the mean plasma concentrations of ibuprofen versus time for the combination product and Motrin® suspension alone:



- The graph above indicates that the plasma concentration time profiles for Ibuprofen from the combination product and the Motrin® suspension are similar suggesting that

pseudoephedrine does not affect the pharmacokinetics of Ibuprofen when both are concurrently administered as a combination suspension.

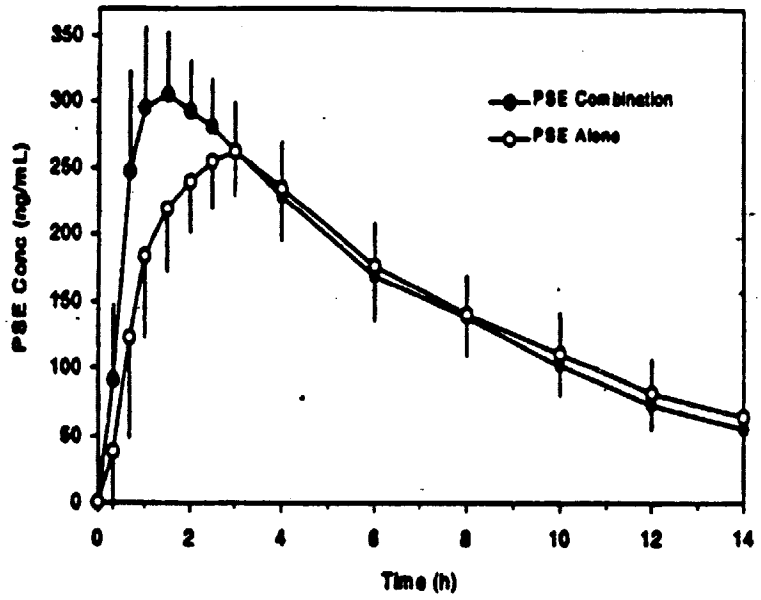
Table 4: A Summary of the Mean Primary Pharmacokinetic Parameters (Mean (%CV)) and CI for Ibuprofen from Study 98-057 (N = 24)

Treatment	Cmax (mcg/ml)	AUC (mcg.hr/ml)	AUC inf (mcg.hr/ml)	Ln Cmax (mcg/ml)	Ln AUC (mcg.hr/ml)	Ln AUCinf (mcg.hr/ml)	Tmax (hr)
Combination Suspension (A)	61.9 (20.0)	202 (19.0)	205 (19.0)	60.7	199	201	0.70 (36.0)
Motrin® Suspension (B)	60.3 (21.0)	181 (17.0)	183 (18.0)	59.0	179	181	0.74 (46.0)
Ratio of least-square means (A/B) %	102.7	111.6	111.8	102.8	111.2	111.4	94.3
90% CI (A/B)	94.6 – 110.7%	105.2 – 117.9%	105.3 – 118.3%	94.6 – 111.6%	105 – 117.7%	105.1 – 118.0%	NA
Intrasubject %CV	16	12	12	17	12	12	41
p-value A vs. B ANOVA	0.5743	0.0047	0.0048	0.5771	0.0040	0.0041	0.6254
Power A vs. B	98.1%	99.9%	99.8%	99.1%	>99.9%	>99.9%	37.1%
Statistically Significant difference	NS	A>B	A>B	NS	A>B	A>B	NS

NA= Not applicable

1. From the above table the geometric mean ratios and the corresponding 90% CI for AUC inf (111.8, (105.3 –117.9)%) and Cmax (102.7, (94.6 – 110.7) %) for the comparison of the combination suspension and Motrin®suspension were within the FDA (80 – 125 %) bioequivalence acceptance range.
    a) This also further suggests that pseudoephedrine has no effect on the rate and extent of absorption of ibuprofen when administered as a combination.
    b) The applicant stated that a statistically significant difference between means for AUC and AUCinf was observed as shown in the table above. This suggested that the extent of drug absorption of the two formulations tested were different, with the combination formulation having a greater systemic exposure (~10% higher) than the monotherapy.
    c) The clinical implications of the greater extent of absorption were discussed with the medical reviewer Dr. M. Villalba, who informed me that the safety profile for the combination product was relatively good (5 adverse events by 4 subjects, with three (dizziness, diarrhea and lightheadedness) being possibly related to the drug.
    d) This suggested that the greater extent of absorption was not clinically significant.

Pseudoephedrine: Inserted below is a graph of the mean plasma concentrations of ibuprofen versus time for the combination product and Motrin® suspension alone:



- The graph above indicates that the Cmax of pseudoephedrine from the combination product was about 15 % higher than from the Sudafed® Liquid and that the Tmax was about 1 hour earlier. These all suggest a faster rate of absorption for the combination product.

Table 5: A Summary of the Mean Primary Pharmacokinetic Parameters (Mean (%CV)) and CI for Pseudoephedrine from Study 98-057 (N = 24)

Treatment	Cmax (ng/ml)	AUC (ng.hr/ml)	AUC inf (ng.hr/ml)	Ln Cmax (ng/ml)	Ln AUC (ng.hr/ml)	Ln AUCinf (ng.hr/ml)	Tmax (hr)
Combination Suspension (A)	322 (11.0)	2223 (15.0)	2614 (19.0)	320	2199	2568	1.48 (50.0)
Sudafed® Liquid (C)	273 (10.0)	2125 (16.0)	2633 (23.0)	272	2097	2566	2.60 (27.0)
Ratio of least-square means (A/C) %	118.2	104.6	99.3	118.0	104.8	100.1	56.9
90% CI (A/C)	113.9-122.5%	101.1 – 108.1%	94.2 – 104.4%	113.3 – 122.8%	101.2 – 108.6%	95.3 – 105.1%	NA
Intrasubject %CV	8	7	10	8	12	10	26
p-value A vs. C ANOVA	0.0001	0.0343	0.8114	0.0001	0.0326	0.9788	0.0001
Power A vs. C	100 %	100%	>99.9%	100.0%	100%	100%	91.0%
Statistically Significant difference	A>C	A>C	NS	A>C	A>C	NS	A<C

NA= Not applicable

1. From the above table the geometric mean ratios and the corresponding 90% CI for AUC inf (100.1, (95.3 –105.1)%) and Cmax (118.0, (113.3 – 122.8) %) for the comparison of the combination suspension and Sudafed®Liquid were within the FDA (80 – 125 %) bioequivalence acceptance range.

a) This also further suggests that ibuprofen has no effect on the rate and extent of absorption of pseudoephedrine when administered as a combination.

2. The applicant stated that a statistically significant difference between means for AUC (<5%), Cmax (15%) and Tmax (50%) was observed in the ANOVA analysis as shown in the table above. Since there was a difference the CI was skewed to the upper limits.
   a) This suggested that the extent and especially rate of drug absorption from the two formulations tested were different.
   b) However, the combination formulation peaked within the range acceptable for equivalence to those from the Sudafed ® liquid suggesting that pseudoephedrine has no effect on the PK of ibuprofen when administered as a combination.
   c) Although there was a statistically significant difference between means for AUC, Cmax and Tmax, this difference is not significant from the regulatory perspective since the CI were still within the FDA acceptable range.
   d) Also, discussions with the Medical reviewer (Dr. M. Villalba) indicated that the higher rate and extent of absorption did not translate to any clinically significant differences in terms of safety in adults.
3. The applicant however stated that the increased pseudoephedrine absorption rate in the presence of ibuprofen appears to be related to the combination of both active ingredients in the liquid dosage form, based on comparison with data from a previous McNeil bioequivalence study (Protocol 87-744; submitted to NDA 19-899) with an Ibuprofen-pseudoephedrine tablet.

B. Are the differences observed in the AUC and Cmax for the combination product in comparison to the single ingredient products in adults due to a gender effect?

The data set from the bioequivalence study # 98-057 was evaluated for gender effect by noncompartmental analysis although this was not one of the primary objectives of the study. There were 10 male and 14 female subjects altogether. The mean weight of the men was 79.1 ± 8.2 kg and 60.3 ± 5.8 kg. Graphs and summary tables of the mean pharmacokinetic parameters of both formulations by gender are attached in the appendix pages. 13-15.

An evaluation of the data suggested that there was some gender differences for ibuprofen and pseudoephedrine.

Ibuprofen: The gender analysis suggested that the rate and extent of absorption (AUC and Cmax) of ibuprofen from the combination suspension and Motrin® suspension is about 10% higher in men than in women. The oral clearance (CL/F) is about 10-13% faster in women than in men, and the t1/2 was about 12.5% longer in the male compared to the females for both the combination and Motrin® suspension.

Pseudoephedrine: The gender analysis suggested that there is a gender difference of about 5-12% in AUC, AUCinf with these being higher in men than in women. Also the clearance of pseudoephedrine was ~9 % higher in women than in men. There did not appear to be a gender difference in the rate of absorption as reflected in the Cmax and the Tmax. Although the absorption rate from the combination suspension was much faster than from the marketed Sudafed ® Liquid as was observed in the overall mean data.

Gender Analysis Conclusion: A definitive interpretation of this gender analysis as presented is difficult as the pharmacokinetic parameters were not properly normalized for weight and body size differences and the applicant did not carry out any statistical tests to evaluate the significance of these differences. However, the overall small magnitude of the difference does not appear to be significant (i.e. all differences are < 15%) and would be lost in clinical variability in response.

C. Will dosing adjustments be required for the administration of Ibuprofen-Pseudoephedrine suspension to children?

A comparison of the PK (AUC and Cmax) data obtained in the two McNeil studies 97-024 and 98-057 indicate that there is a difference in the values of these PK parameters between adults and children. This is illustrated in the table reproduced below:

Table 7: Comparison of AUC and Cmax in Children and Adults from studies 97-024 and 98-057 following administration of Ibuprofen-Pseudoephedrine Combination Suspension

Study	Mean Weight (SD) kg	Mean Dose mg (SD) [mg/kg (SD]	AUCinf or AUCτ (μg.h/ml) (SD)	Cmax or Cmax [a] (μg/ml) (SD)
Ibuprofen				
97-024, MD, PK Children (4-11years old) N = 24 (Q 6 h)	29.4 (30)	219 (71) [7.4 (0.3)]	99.3 (21.1)	29.6 (6.2)
98-057, SD, PK Adults (20-40years old) N = 24	68.2 (17)	511 (88) [7.5 (0.2)]	205 (39.6)	61.9 (12.3)
Pseudoephedrine				
	Mean Weight (SD) kg	**Mean Dose mg (SD) [mg/kg (SD]**	**AUCinf or AUCτ (ng.h/ml)**	**Cmax or Cmax [a] (ng/ml)**
97-024, MD,PK Children (4-11years old) N = 23	29.1 (30)	33 (11) [1.108 (0.051)]	1276 (280)	218 (38)
98-057, SD, PK Adults (20-40years old) N = 24	68.2 (17)	77 (13) [1.125 (0.031)]	2614 (485)	322 (36.5)

[a] = Dose Normalized values

- The cross comparison data in the table above indicates that the similar weight-based dose of ibuprofen and pseudoephedrine resulted in different rates and extent of absorption for ibuprofen and pseudoephedrine as reflected in the AUC and Cmax, with the systemic exposure being lower (~ 50 %) in children that in adults.

Supportive Dosing Adjustment Evaluation: McNeil also included a supplement (97-024(S2)) report to Mcneil Pharamcokinetics study 97-024 to provide a sufficiently accurate estimate of any potential dosing adjustments in children for the ibuprofen-pseudoephedrine suspension by comparing oral clearance (Cl/F), half-life (t1/2), and distribution volume

(Vd/F) for children with those for adults for McNeil Bioequivalence Study 98-057: The data in this supplement is discussed below:

Primary analysis: was a one-way analysis of variance (ANOVA) by age group of pooled Cl/F $t_{1/2}$ and Vd/F normalized for body surface area (BSA) (calculated using the equation $[0.0235\ H^{0.4246}W^{0.51456})]$[1] for both Ibuprofen and pseudoephedrine from McNeil Studies 97-024 and 98-057 combination therapy reports. The applicant stated that the analysis was sufficiently powered to detect a 30% change in Cl/F, Vd/ and T1/2 between children and adults, but did not include any information on how this was achieved. Statistical significance was evaluated at the 0.05 alpha level. The scatter plots are attached in the appendix pages 16-21. The results analyzed using SAS® Version 6.12 by the applicant are reproduced in the table below:

[1].Gehan EA, George SL. Estimation of human body surface area from height and weight. Cancer Chemo Rep 1970; 19: 340-345

Table 8: Primary (One –Way ANOVA) Analysis for Ibuprofen and Pseudoephedrine

PK Parameter	LSM [a] for children	LSM for Adults	Age Group [b] % difference	P-value Children vs Adults
Ibuprofen (N =48)				
Cl/F (ml/min/m^2)	35.6 (20)	23.6 (21)	50.0	0.0001
T1/2 (h)	1.34 (25)	2.22 (12)	-39.6	0.0001
Vd/F (L/m^2)	4.06 (21)	4.45 (15)	-9.66	0.0564
Pseudoephedrine (N = 47)				
Cl/F (ml/min/m^2)	339.7 (19)	226.1 (19)	50.2	0.0001
T1/2 (h)	2.45 (27)	4.65 (20)	-47.3	0.0001
Vd/F (L/m^2)	69.0 (17)	88.8 (14)	-22.1	0.0001

[a] LSM = least square mean

[b] Percent Difference = 100 (LSM for Children-LSM for Adults)/LSM for Adults

1. The results in the above table further indicate that children were more efficient in the elimination of ibuprofen and pseudoephedrine than adults.
   a) Ibuprofen mean Cl/F was ~ 50% higher and, $t_{1/2}$ was ~ 40% shorter in children and, these differences were statistically significant ($p< 0.05$).
   b) Ibuprofen mean Vd/F was ~ 10% lower in children and this difference was not statistically significant ($p >0.05$) although it could be regarded as borderline because it was so close to 0.05.
   c) Pseudoephedrine mean Cl/F was ~ 50% higher, mean Vd/F was ~ 20% lower and, $t_{1/2}$ was ~ 47% shorter in children for pseudoephedrine and, these differences were all statistically significant ($p<0.05$).
   d) The applicant stated that these findings are in agreement with known differences in single-ingredient ibuprofen and pseudoephedrine pharmacokinetics between children and adults.
2. These findings offer a possible explanation as to why the administration of the combination suspension in children does not result in a higher plasma level of pseusdoephedrine than the single ingredient pseudoephedrine as compared with the

observation in the adults (bioequivalence Study). However, this could also be due to other factors like a formulation effect.

Secondary Analysis: A two way ANOVA which included an age group –by –gender interaction term was also conducted on the pooled data from studies 97-024 and 98-057 to examine possible gender differences in Cl/F, $t_{1/2}$, and Vd/F. The significance of the age group-by-gender interaction was evaluated at the 0.10 alpha level. Reproduced below is a tabular summary of the two-way ANOVA analysis:

Table 9: Secondary Analysis (Two-way-ANOVA) for Ibuprofen Pseudoephedrine

PK Parameter	Gender % Difference Children	Gender % Difference Adults	p-value Children vs Adults	p-value Gender	p-value Interaction
Ibuprofen (N = 48)					
Cl/F (ml/min/m^2)	3.4	-3.3	0.0001	0.8973	0.5984
T1/2 (h)	2.3	15.9	0.0001	0.0501	0.0975
Vd/F (L/m^2)	3.0	12.5	0.03338	0.1573	0.3654
Pseudoephedrine (N =47)					
Cl/F (ml/min/m^2)	13.3	1.3	0.0001	0.1997	0.2677
T1/2 (h)	-8.6	1.5	0.0001	0.7630	0.5645
Vd/F (L/m^2)	4.7	4.4	0.0001	0.3601	0.9262

[a] LSM = least square mean

[b] Percent Difference = 100 (LSM for Children-LSM for Adults)/LSM for Adults

1. The results of the two way ANOVA as shown in the table above also indicated significant differences between children and adults on all three pharmacokinetic parameters for both ibuprofen (including Vd/F) and pseudoephedrine.
2. In addition there was both a significant gender difference and group-by-gender-interaction for $t_{1/2}$ for Ibuprofen.
   a) The results suggest that this difference in $t_{1/2}$ was higher in the adults than the children. The comparison of the means indicate that this difference in children is almost negligible about 2.3% longer in males than in females, while in the adult population this indicates a 16 % longer $t_{1/2}$ in males than in females.
   b) Since this preparation is intended for the population of children aged 2-11 years old, this gender effect especially in the adult population may not be clinically relevant in this case (to be confirmed with the medical reviewer).
   c) There were no significant effects of gender or significant age-group-by-gender interaction for any of the other parameters evaluated for Ibuprofen and, for none of the parameters for pseudoephedrine.
   d) The applicant stated that this finding is consistent with the higher likelihood for adults to have gender differences in drug pharmacokinetics and metabolism than children, because of hormonal influences and/or differences in lean body mass.

Pharmacokinetic Simulations: Since there were statistically significant differences between children and adults for the 3 PK parameters evaluated (Cl/F, Vd/F and $t_{1/2}$) the applicant simulated pharmacokinetic profiles in children using the proposed weight-based, OTC dosing schedule for the Ibuprofen-pseudoephedrine suspension. This was intended to provide sufficiently accurate estimate of any dosing adjustments for the ibuprofen-pseudoephedrine suspension that may be needed in children. These results were then compared with profiles simulated in adults using the current OTC adult dosing schedule for each drug. The OTC doses used for each drug in the pharmacokinetic simulations and an estimate of the $Cmax_{ss}$ from the simulated plasma concentration time profiles is reproduced in the table below. A copy of the PK simulation graphs is included in the appendix as page 22.

Table 10: Summary of the Pharmacokinetic Simulations Results and the Doses Used

Age group	Proposed OTC label Ibuprofen Dose mg [mg/kg]	Estimated $Cmax_{ss}$ from the PK simulation graph (mcg/ml)	Proposed OTC label Pseudoephedrine Dose mg [mg/kg]	Estimated $Cmax_{ss}$ from the PK simulation graph (ng/ml)
Children	235 [8.1]	35	35 [1.108]	350
Adults	200 [3.0]	25	60 [0.905]	420
Adults	400 [6.0]	50		

1. The above table indicates that the doses of both drugs proposed for the combination suspension is higher than the proposed OTC adult doses. The applicant stated that the doses of both drugs provided by the combination suspension is appropriately higher than the adult OTC doses and, that this is consistent with children having higher drug elimination rates than adults
    a) The approximate plasma levels for ibuprofen and pseudoephedrine in children was also ~15% (ibuprofen) and 40% (pseudoephedrine) higher than would be expected in adults given the same dose.
    b) This was probably because the proposed OTC pediatric dosing schedule for the combination suspension keeps the weight and age based dosing the same as that established for single-ingredient pediatric ibuprofen products, and modifies the pseudoephedrine dose.
    c) These results imply that the applicant would need to adjust the dosing schedule for the Ibuprofen-pseudoephedrine suspension in children so as achieve comparable systemic exposure to those observed in adults.
    d) The alternative might be to base the dosing schedule on that established for single-ingredient monograph pediatric pseudoephedrine dosing, which was used in the PK studies submitted. Also through discussions with the Medical reviewer (Dr. L. Villalba) I was informed that no new data was submitted in this application to support the efficacy of pseudoephedrine (in children under 4) using this new proposed 5 "tier" dosing schedule (The adjustment in dosing schedule is currently under review by the medical review team).

D. Can the PK data obtained from the multiple dose study in children be extrapolated for ibuprofen and Pseudoephedrine down to age 2 based on an assessment of age on PK?

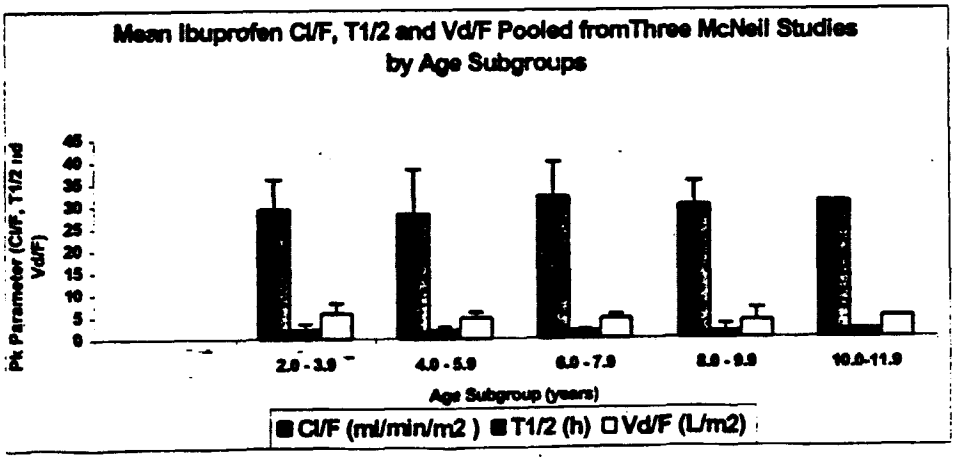
The applicant submitted a supplement (PK RPT 97-024 (S1)) to the PK 97-024 study report to support this. The Clinical phase of study 97-024 was from November 7 to 15 1998. The original protocol submitted to the FDA on October 22nd 1998 stated that the population to be studied were children aged 4 through 11 years. The applicant also submitted a Proposed pediatric study request on October 22nd 1998. The FDA issued an official Written Request for 2 studies for the Ibuprofen/Pseudoephedrine combination suspension on September 7th, 1999. One of the studies requested was the multiple dose study of Ibuprofen/Pseudoephedrine combination suspension in subjects spanning the age range 2 through 11 years, with at least one third of the subjects approximately evenly distributed below 7 years of age.

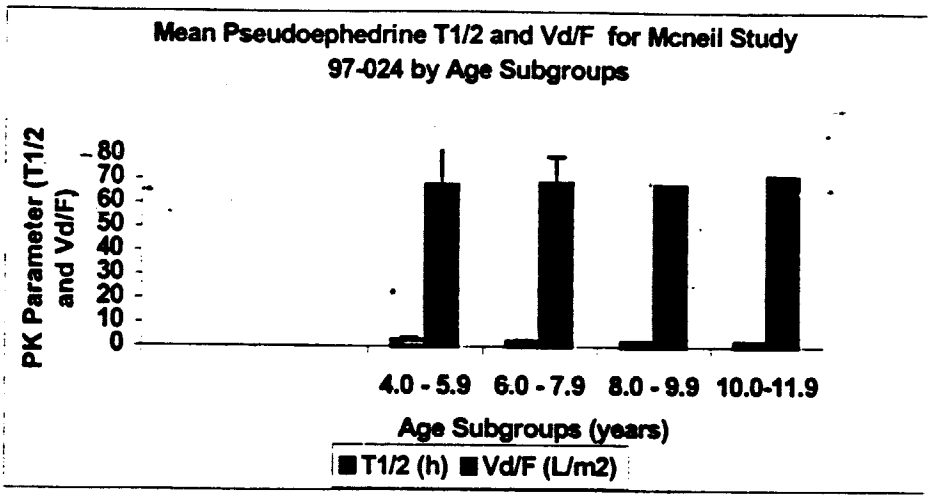
The applicant has stated in this application in Vol. 8 Sec 6 Pg. 994, that Mcneil Pharmacokinetics Study 97-024 did not plan to enroll children ages 2 and 3 years. This statement in itself although violates the requirements of the written request is in accordance with the protocol that was submitted prior to the studies being conducted. The applicant also stated that the FDA at a meeting between the Agency and Mcneil Consumer healthcare on May 10, 1999 requested the assessment of age on the PK of both ibuprofen and pseudoephedrine

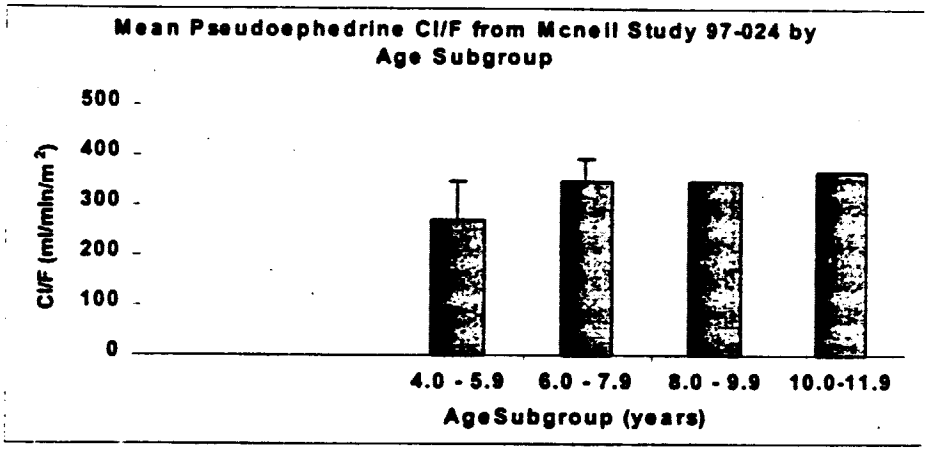
For ***Ibuprofen*** the applicant pooled the individual values of Cl/F, $t_{1/2}$ and Vd/F for all children aged ≥ 2 years (N = 82) in Mcneil pharmacokinetics Study 97-024 (healthy children) and two McNeil sponsored, single-dose ibuprofen studies (91-113 and 86-642 in febrile children). The number of subjects enrolled (% of total) across the five age groups for Ibuprofen was 2-3.9 yr. (9 (11 %), 4-5.9 yr. (22 (27 %), 6-7.9 yr. (21 (26 %), 8-9.9 yr. (18 (22 %), 10-11.9 yr. (12 (15 %). The age of the youngest child in the 2-3.9 year old group included in this analysis was 2.4 years old.

For ***Pseudoephedrine*** the applicant stated that the only data available were the data for the 23 children in Mcneil Pharmacokinetics study 97-024 in children aged 4-11 years old. The number of subjects enrolled (% of total) across the four age groups for pseudoephedrine was 4-5.9 yr. (4 (18 %), 6-7.9 yr. (7 (30 %), 8-9.9 yr. (6 (26 %), 10-11.9 yr. (6 (26 %). The age of the youngest child in the 4-5.9 yr. group included in this analysis was 4 years old.

Inserted below are plots of the mean pharmacokinetic parameters (Cl/F, $t_{1/2}$ and Vd/F) of ibuprofen and pseudoephedrine by age subgroup. Scatter plots of the 3 pharmacokinetic parameters with age are included in the appendix (pages 21-24).







1. The graphs above indicate that the pharmacokinetic parameters evaluated were fairly consistent across the age subgroups for Ibuprofen.
2. For Pseudoephedrine there was consistency across the age subgroups 6.0-7.9, 8.0-9.9 and 10.0-11.9 for all three PK parameters. For the 4.0-5.9 age subgroup the clearance was lower and the $t_{1/2}$ was slightly higher, however the Vd/F was fairly consistent. This is probably a function of the sample size (N) or trend, it is difficult to make a definitive interpretation of these findings based on the data submitted.

Linear Regression Analysis: These results were further demonstrated by the linear regression analysis conducted by the applicant. The applicant stated that each of these pharmacokinetic parameters were normalized with body surface area (BSA) and then, a linear regression analysis of each pharmacokinetic parameter with age was evaluated using SAS® Version 6.12

The results of the linear regression analysis between each BSA normalized pharmacokinetic parameter and age for Ibuprofen and Pseudoephedrine are reproduced in the table below:

Table 11: Linear Regression analysis of Ibuprofen and Pseudoephedrine Pharmacokinetics and Age

Pharmacokinetic Parameter	Slope (standard error)	Slope p-value	R	Intercept
Ibuprofen (N = 82)				
Cl/F (ml/min/m^2)	0.32 (0.32)	0.3074	0.114	27.8 (2.3)
$t_{1/2}$ (h)	-0.04 (0.04)	0.3944	0.095	2.1 (0.3)
Vd/F (L/m^2)	-0.07 (0.09)	0.4414	0.0852	5.1 (0.7)
				(p = 0.001 for all)
Pseudoephedrine (N = 23)				
Cl/F (ml/min/m^2)	12.6 (5.7)	0.0382	0.435	235 (49)
$t_{1/2}$ (h)	-0.1 (0.06)	0.1212	0.332	3.3 (0.5)
Vd/F (L/m^2)	0.6 (1.1)	0.5856	0.12	64 (9)
				(p = 0.001 for all)

1. For Ibuprofen the slope of the linear regression of the pharmacokinetic parameters with age were not significant as indicated by the p-value in the table above.
   a) This indicates that the pharmacokinetic parameters (Cl/F, $t_{1/2}$ and Vd/F) were independent of age in children aged 2.4 –11.9 years old.
   b) The R values were closer to 0 than 1, indicating that there is little if any, linear association between the PK parameters and age. This lack of a linear association also suggests that the age is not really of any value in predicting the pharmacokinetic parameters measured and so this linear model cannot be extrapolated for predictive purposes.
2. For Pseudoephedrine the slope of the regression of the $t_{1/2}$ and Vd/F with age were not significant indicating that these PK parameters were independent of age in children aged 4-11.9 years old.
   a) The slope of the linear regression of Cl/F was significant indicating that clearance was dependent upon age. An evaluation of the mean Cl/F and $t_{1/2}$ values for the four age subgroups indicated Cl/F was ~ 27 % lower and $t_{1/2}$ was ~ 25 % higher in the 4-5.9 year old subgroup as compared to the other age subgroups.
   b) The applicant stated that renal tubular function is mature by six months of age[2] and since pseudoephedrine is mainly excreted unchanged in the urine by renal tubular filtration and secretion one would not expect an effect of age on its pharmacokinetics in children aged 2-11 years of age.

[2 Glatke E. The importance of pharmacokinetics for pediatrics. Eur J Pediatr 1979; 131: 85-91.]

3. Based on the information above the pharmacokinetics data for ibuprofen in the combination suspension determined in children aged 4-11 years for ibuprofen was comparable to that of children down to 2 years old.

4. The pharmacokinetics data for pseudoephedrine in the combination suspension evaluated in children aged 4-11 years although suggestive could not really be concluded as being comparable to that of children down to 2 years old, because the data submitted was very limited.
5. Since the linear regression analysis shows that there is no linear relationship between age and the PK parameters evaluated, the data submitted cannot be extrapolated down to the lower age range for pseudoephedrine.

VII. Dissolution

Are Ibuprofen and Pseudoephedrine fully dissolved in the Liquid portion of the suspension base?

The applicant evaluated the dissolution of Ibuprofen from the grape-flavored suspension results and included the results in this submission. The applicant stated that dissolution of pseuoephedrine from the combination product was not evaluated because the salt is fully dissolved in the liquid portion of the suspension base (this was confirmed with the review chemist Dr. Bart Ho). Attached in the Appendix as pages 29-30 are graphical representations of the dissolution data for Ibuprofen for batch C-846-3C from Ibuprofen-pseudoephedrine suspension used in McNeil Pharamcokinetics study 97-024 and Mcneil bioequivalence study 98-057. In addition the applicant also determined dissolution profiles for the berry flavored, combination suspension (batch C-822-4A) and Children's Motrin® suspension (formula C-163-7 lot BME045) used in the bioequvalence study 98-057. The applicant stated that the proposed dissolution method and specifications are identical to that approved on December 18,1998 for three new formulations of Children's Motrin® Ibuprofen Suspension (grape, berry and bubble gum) that were submitted in S-003 to NDA 20-516 and are as follows:

Apparatus:
Speed:
Medium:
Specifications:
Number of units:

Reproduced in the table below is a summary of the dissolution results:

Mean Percent dissolved (% CV) (Time in Minutes) (N = 12)						
Drug Product	5	10	15	30	45	60
Ibuprofen-Pseudoephedrine Suspension (grape flavored)	99 (1)	99(1)	99(1)	100(1)	100(1)	100(1)
Ibuprofen-Pseudoephedrine Suspension (berry flavored)	99(1)	99(1)	99(1)	99(1)	99(1)	99(1)
Motrin® Suspension	98(1)	97(1)	97(1)	97(1)	97(1)	97(1)

The results as shown in the table above demonstrate that all three products evaluated passed the specifications, in that >95% of Ibuprofen was dissolved in 5 minutes. It appears that a tighter specification of would be preferable, based on the above data, even though the proposed specifications are the same as the current USP

specifications for Ibuprofen suspension. Also the review chemist (Dr. Rao Puttangunta informed me that the applicant stated that the dissolution specification for Ibuprofen in the combination product for the stability studies was [redacted] Based on this it appears that the applicant intends to maintain two different specifications, one for stability use and the USP specification for release purposes.

VIII. Overall Conclusions

1. The multiple dose study cross comparison in children aged 4-11 years old suggested that there was a lack of systemic interaction between Ibuprofen and Pseudoephedrine in terms of the rate and extent of absorption when administered as a combination.
2. The cross comparison indicated that the rate and extent of absorption of Ibuprofen in febrile children aged 0.25-12 years old were comparable to that of healthy children aged 4-11 years old.
3. The cross comparison also indicated that the rate and extent of absorption of Pseudoephedrine in children with seasonal allergic rhinitis aged 6-12 years old were comparable to that of healthy children aged 4-11.7 years old.
4. The bioequivalence study in healthy adults further demonstrated that there was no systemic interaction between Ibuprofen and Pseudoephedrine in terms of the rate and extent of absorption when administered as a combination to adults.
5. Although there was a statistically significant difference between means for Pseudoephedrine AUC, Cmax and Tmax in the bioequivalence study in adults, this difference was not significant from the regulatory perspective since the CI were still within the FDA acceptable range.
6. There were no statistically significant gender effects on Cl/F, $T_{1/2}$ and Vd/F for Pseuodephedrine.
7. There were no statistically significant gender effects on Cl/F and Vd/F for Ibuprofen. There was a significant gender difference and group by gender difference for $T_{1/2}$ that indicated that the gender difference in children is almost negligible ~ 2.3% and may not be clinically relevant in this case.
8. The pharmacokinetic data submitted was comparable for children down to 2 years old for Ibuprofen, however, for Pseudoephedrine there was no pharmacokinetic data submitted for children aged 2-4 years old.
9. Since Pseudoephedrine is a monograph drug currently recommended down to 2 years old as a single ingredient, the decision as to whether this combination should be given to children down to 2 years old resides with the medical team. The pharmacokinetic data as submitted is not supportive of dosing the combination down to 2 years old.
10. The dissolution data submitted supports a specification of [redacted] since > 95% of Ibuprofen was dissolved in 5 minutes from both flavors of the Ibuprofen-Pseudoephedrine suspension.

IX. Comment:

The Agency prefers the adoption of a single dissolution method/specification for both stability and release. The proposed stability specification of [redacted] is the preferred dissolution specification as it more accurately reflects in vivo performance -

/S/

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

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

CC:
NDA 21-128 (ORIGINAL)
HFD-550 (Div.File)
HFD-550 (CSO/COOK)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Adebowale)
HFD-340 (Viswanathan)
CDR: ATTN: Barbara Murphy

Appendix

Page 1

6.5 Study Abstract Sheets for Reviewers

NDA 21-128 SUBMISSION DATE: September 1999

Multiple-Dose Pharmacokinetic Study of an Ibuprofen-Pseudoephedrine HCl Suspension in Children (Protocol 97-024)

DESIGN:

☐ Single Dose ☒ Multiple Dose ☐ Crossover ☐ Parallel ☐ Washout

DEMOGRAPHICS (completed): Total n = 24 Males = 16 Females = 8

☒ Normal Subjects ☐ Patients ☒ Young ☐ Elderly
☐ Impaired Subjects ☐ Renal ☐ Hepatic ☐ Other

MALES	Range	Mean	FEMALES	Range	Mean
Age (y)	4.8 to 11.9	8.6	Age (y)	4.0 to 11.7	7.9
Weight (lb)	39 to 104	66	Weight (lb)	37 to 102	63
Height (in)	43 to 60	51	Height (in)	42 to 61	50

DRUG ADMINISTRATION:

Treatment	Dosage Form	Strength	Batch Number	Size
IBU 7.5 mg/kg PSE 1.125 mg/kg q 6 h X 5	Ibuprofen-Pseudoephedrine Suspension, Grape	100 mg -15 mg per 5 mL	C-846-3C	

☐ Fasted
☒ Non-Fasted ☐ Food Study ☐ High Fat Breakfast

SAMPLES: ☒ Plasma ☐ Serum Before (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, and 6 hours after fifth dose
☒ Urine pH only

ASSAY METHODS:

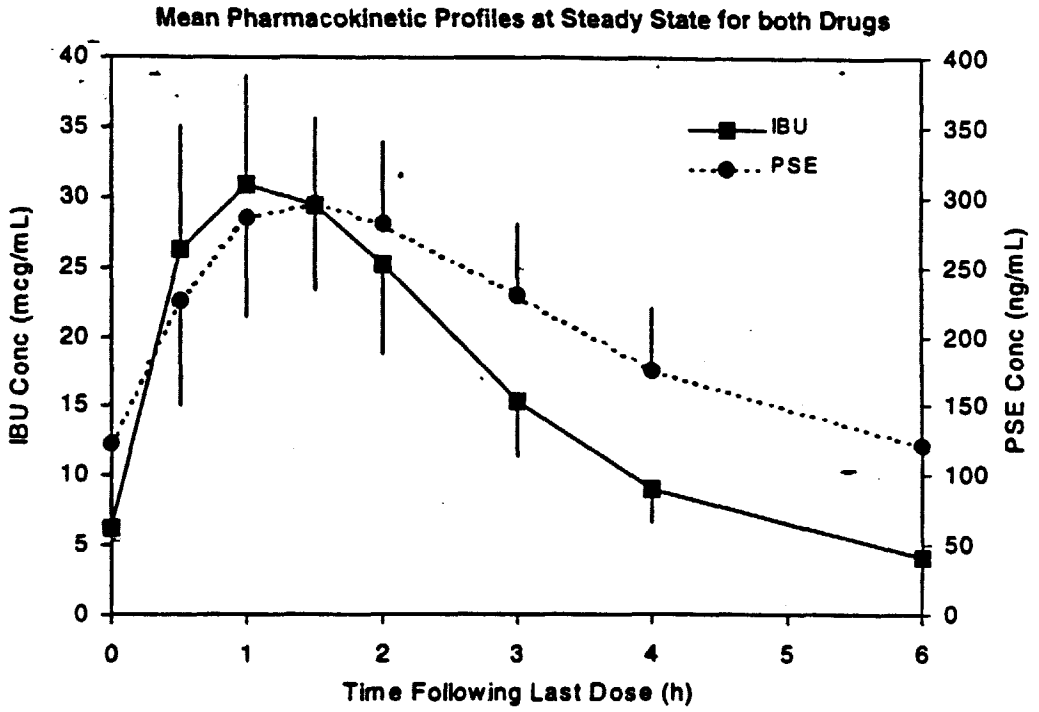
ASSAY SENSITIVITY:

ASSAY ACCURACY:

McNeil Pharmacokinetic Study 97-024

Pharmacokinetic Parameter	Ibuprofen One-Compartment PK Modeling	Ibuprofen Noncompartment Methods	Pseudoephedrine[a] One-Compartment PK Modeling	Pseudoephedrine[a] Noncompartment Methods
AUC_τ	99.3 µg·h/mL (21.1, 21%)	96.4 µg·h/mL (20.4, 21%)	1276 ng·h/mL (280, 22%)	1258 ng·h/mL (274, 22%)
$C_{AVG,SS}$	16.5 µg/mL (3.5, 21%)	16.1 µg/mL (3.4, 21%)	213 ng/mL (47, 22%)	210 ng/mL (46, 22%)
$C_{MAX,SS}$	32.0 µg/mL (6.7, 21%)	33.3 µg/mL (6.6, 20%)	295 ng/mL (60, 20%)	318 ng/mL (62, 19%)
$C_{MIN,SS}$	3.97 µg/mL (1.55, 39%)	5.20 µg/mL (1.84, 35%)	115 ng/mL (37, 32%)	122 ng/mL (37, 30%)
$T_{MAX,SS}$	0.97 h (0.31, 32%)	1.0 h (0.4, 34%)	1.39 h (0.38, 28%)	1.5 h (0.5, 31%)
Cl/F	77.5 mL/h/kg (16.4, 21%)	79.7 mL/h/kg (16.5, 21%)	12.3 mL/min/kg (2.2, 18%)	12.5 mL/min/kg (2.2, 18%)
Vd/F	0.147 L/kg (0.037, 25%)	0.189 L/kg (0.065, 35%)	2.52 L/kg (0.47, 19%)	3.54 L/kg (0.66, 19%)
k_A	1.887[b] 1/h (1.192, 63%)	not determined	1.417 1/h (1.100, 78%)	not determined
k_{EL}	0.546 1/h (0.131, 24%)	0.437 1/h (0.068, 15%)	0.303 1/h (0.082, 27%)	0.215 1/h (0.039, 18%)
$t_{½}$	1.3 h (0.3, 25%)	1.6 h (0.3, 18%)	2.5 h (0.7, 27%)	3.4 h (0.7, 20%)
FI	1.71 (0.28, 17%)	1.77 (0.23, 13%)	0.86 (0.19, 22%)	0.95 (0.18, 19%)

a: Means of 23 subjects due to an interference peak that precluded the determination of pseudoephedrine plasma concentrations in Subject 7.
b: The k_A for Subject 12 was more than four standard deviations above the mean and was not included.



CONCLUSIONS FROM MCNEIL PHARMACOKINETICS STUDY 97-024

Study Report:

- Results from both the nonlinear regression modeling and noncompartmental methods used to determine the multiple-dose pharmacokinetics of ibuprofen and pseudoephedrine at steady state were similar, which indicate that the analyses were equally reliable.
- The pharmacokinetic profiles confirmed that neither drug accumulated considerably in children with multiple-dosing. No substantial accumulation was expected, because ibuprofen and pseudoephedrine have relatively short elimination half-lives and a sufficiently long dosing interval.
- Pseudoephedrine did not affect Cl/F, t½, or Vd/F for ibuprofen when both drugs were administered concurrently as the combination product. Results were comparable with those from previous single-ingredient studies.
- When the effect of urine pH was considered, which is necessary for evaluating pseudoephedrine Cl/F and t½ from different studies, the results of the multiple-dose study of the combination product indicate that ibuprofen did not alter the elimination of pseudoephedrine. Also, Vd/F was relatively constant across studies.

- Overall, ibuprofen-pseudoephedrine suspension was well tolerated. Adverse events categorized by the principal investigator as probably or likely related to study drug were few and mild, and no clinically relevant changes in vital signs or clinical laboratory tests were observed.

Report Supplement 1:

- Linear regression analyses between age and Cl/F, t½, and Vd/F indicate that, overall, children ages two through 11 years exhibited age-independent ibuprofen and pseudoephedrine pharmacokinetics. Therefore, the pharmacokinetic data for the combination suspension determined in children ages four through 11 years can be extrapolated to two- and three-year old children.

Report Supplement 2:

- Results of the analyses across McNeil Pharmacokinetic Study 97-024 and Bioequivalence Study 98-057 indicate that children were more efficient in the elimination of both ibuprofen and pseudoephedrine than adults. Differences in Cl/F, t½, and Vd/F means by age group for the combination suspension are in agreement with known age group differences in the pharmacokinetics for each drug individually and with many other drugs in general.

- Based on simulated pharmacokinetic profiles for both ibuprofen and pseudoephedrine in children and adults, the proposed weight-based, pediatric, OTC dosing schedule for the combination suspension is appropriate. The pediatric OTC doses (mg/kg) are somewhat higher than the current adult OTC doses (mg/kg), which reflect children having higher elimination rates for both drugs than adults. Therefore, no further dosing adjustments for the combination suspension are needed in children.

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9.4 Comparison with Pharmacokinetics from Single-Ingredient Studies

9.4.1 Comparison with Ibuprofen Pharmacokinetics

Pharmacokinetic data for ibuprofen administered as liquids or tablets were available from four published [1-4] and two McNeil-sponsored (Studies 86-642 and 91-113), single-dose studies [5,6] in children. The design and overall results from these studies are summarized in Table 12-1, located in Section 12, Supportive Tables and Figures. Pharmacokinetic parameters used in the cross-study comparison with results from McNeil Pharmacokinetics Study 97-024 are listed by dosage form in Table 9-2. Some studies included more than one dose of ibuprofen, so data are listed in order of increasing dose (mg/kg).

Table 9-2. Ibuprofen Pharmacokinetics From Published and McNeil-Sponsored Studies

Reference	Age Range (years)	N	Dose (mg/kg)	AUC_{INF} (µg•h/mL)	Cl/F (mL/h/kg)	t½ (h)	Vd/F (L/kg)
Suspension							
Brown et al [1]	2.5 to 12	17	5	88.3 (43.6)	67 (28)	1.7[a] (1.3)	0.13 (0.05)
McNeil 91-113 [6]	2 to 11	19	5	88.9 (25.0)	64 (18)	2.2 (1.3)	0.19 (0.08)
Nahata et al [2]	3 to 10	9	5	NR	72 (24)	1.6 (0.6)	NR
McNeil 86-642 [5]	1 to 11.3	18	6	90.6 (25.9)	71 (21)	1.9 (1.0)	0.20 (0.15)
McNeil 97-024	4 to 11	24	7.5	99.3[c] (21.1)	78 (16)	1.3 (0.3)	0.15 (0.04)
Kauffman et al [3]	0.25 to 10.4 (Median 2.5yr)	38	8	102.6 (35.2)	NR	1.6 (0.7)	NR
Brown et al [1]	2.5 to 12	26	10	126.0 (35.1)	86 (25)	1.5[a] (0.7)	0.19 (0.16)
McNeil 91-113 [6]	2 to 11	22	10	154.1 (35.0)	68 (13)	2.1 (1.3)	0.20 (0.10)
Nahata et al [2]	3 to 10	8	10	NR	84 (30)	1.6 (0.5)	NR
Chewable Tablet							
McNeil 91-113 [6]	2 to 11	20	5	86.1 (28.0)	69 (18)	2.2 (1.6)	0.12 (0.11)
McNeil 91-113 [6]	2 to 11	21	10	171.6[b] (40.6)	61[b] (14)	2.0 (0.6)	0.17[b] (0.06)
Tablet							
Konstan et al [4]	8 to 11	4	14	188.9 (56.7)	78 (12)	1.4 (0.3)	0.16 (0.04)

a: Means of 38 children for the 5 mg/kg dose and 46 children for the 10 mg/kg dose, which include those children in the study below 2.5 years of age.
b: Mean of 17 children due to incomplete data that precluded determination of all parameters.
c: AUC_T value. NR = not reported

9.4.2 Comparison with Pseudoephedrine Pharmacokinetics

Pharmacokinetic data for pseudoephedrine in children were available from three published [7-9] studies. In Simons' study [7], 14 children, ages six through 11 years, were dosed with either 5- or 10-mL Sudafed® liquid, which are equivalent to 30 or 60 mg (~ 1 or 2 mg/kg), respectively. In Auritt's study [8], five children, ages six through 11 years, were dosed with Sudafed® syrup at 60 mg or 2 mg/kg. Table 9-3 lists the available pharmacokinetic data from these studies, which show that pseudoephedrine exhibits linear pharmacokinetics, and the parameters from McNeil Pharmacokinetics Study 97-024 that were amenable to the cross-study comparison. The design and overall results from these studies are summarized in Table 12-2 located in Section 12, Supportive Tables and Figures.

In Brater's study [9] that included both children and adults, only the elimination half-life and urine pH were reported for three children whose ages were not specified. Two children were healthy and one child had type I renal tubular acidosis, which tends to shift urine pH to higher values. A single, 5 mg/kg dose was administered to each subject as 30-mg Sudafed® tablets. The elimination t½ for children KS, DS, and MS were about 6.3, 5.4, and 21 hours with urine pH values of 6.6, 7.0, and 7.8, respectively.

Table 9-3. Mean Pharmacokinetic Parameters for Pseudoephedrine in Children (sd, cv%)

Pharmacokinetic Parameter	McNeil (n = 24) 5 X 33 mg Doses	Simons (n = 7) 1 X 30 mg Dose	Simons (n = 7) 1 X 60 mg Dose	Auritt (n = 5) 1 X 60 mg Dose
AUC_τ (ng·h/mL)	1276 (280, 22%)	NA	NA	NA
AUC_{INF} (ng·h/mL)	NA	1260 (309, 25%)	2414 (823, 34%)	NR
$C_{MAX,SS}$ (ng/mL)	295 (60, 20%)	NA	NA	NA
$C_{MAX,1}$ (ng/mL)	218 (38, 18%)	244 (51, 21%)	492 (176, 36%)	338
$T_{MAX,SS}$ (h)	1.39 (0.38, 28%)	NA	NA	NA
$T_{MAX,1}$ (h)	1.68 (0.55, 33%)	2.1 (0.7, 33%)	2.4 (0.5, 21%)	1.86
Cl/F (mL/min/kg)	12.3 (2.2, 18%)	10.3 (2.9, 28%)	9.2 (1.7, 18%)	8.5
Vd/F (L/kg)	2.52 (0.47, 19%)	2.6 (0.7, 27%)	2.4 (1.0, 42%)	3.33
t½ (h)	2.5 (0.7, 27%)	3.1 (1.2, 39%)	3.1 (1.0, 32%)	4.6
Urine pH	5.3 (0.3, 6%)	6.5[a] (0.7, 11%)	6.5[a] (0.7, 11%)	NR

a: Mean of all 14 children reported; NA = not applicable; NR = not reported

NDA 21-128 SUBMISSION DATE: September 1999

Bioequivalence of the Ibuprofen-Pseudoephedrine Suspension With Children's Motrin® Ibuprofen Suspension and Children's Sudafed® Nasal Decongestant Liquid (Protocol 98-057)

DESIGN:

☒ Single Dose ☐ Multiple Dose ☒ Crossover ☐ Parallel Washout = 7 days

DEMOGRAPHICS (completed): Total n = 24 Males = 10 Females = 14

☒ Normal Subjects ☐ Patients ☐ Young ☐ Elderly

☐ Impaired Subjects ☐ Renal ☐ Hepatic ☐ Other

MALES	Range	Mean	FEMALES	Range	Mean
Age (y)	23 to 47	31.2	Age (y)	20 to 45	27.9
Weight (lb)	139 to 199	174	Weight (lb)	112 to 154	133
Height (in)	68 to 74	72	Height (in)	61 to 70	66

DRUG ADMINISTRATION:

Treatment	Dose	Dosage Form	Strength	Formula/Lot Number	Batch Size
A	Ibuprofen 7.5 mg/kg - Pseudoephedrine 1.125 mg/kg	Ibuprofen-Pseudoephedrine Suspension, Grape	100 mg -15 mg/ 5 mL		
B	Ibuprofen- 7.5 mg/kg	Motrin® Ibuprofen Suspension	100 mg/5 mL		
C	Pseudoephedrine 1.125 mg/kg	Sudafed® Nasal Decongestant Liquid	15 mg/5 mL		

☒ Fasted

☐ Non-Fasted ☐ Food Study ☐ High Fat Breakfast

SAMPLES: ☒ Plasma ☐ Serum Before (0 hour) and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 14 hours after dosing

☒ Urine pH only

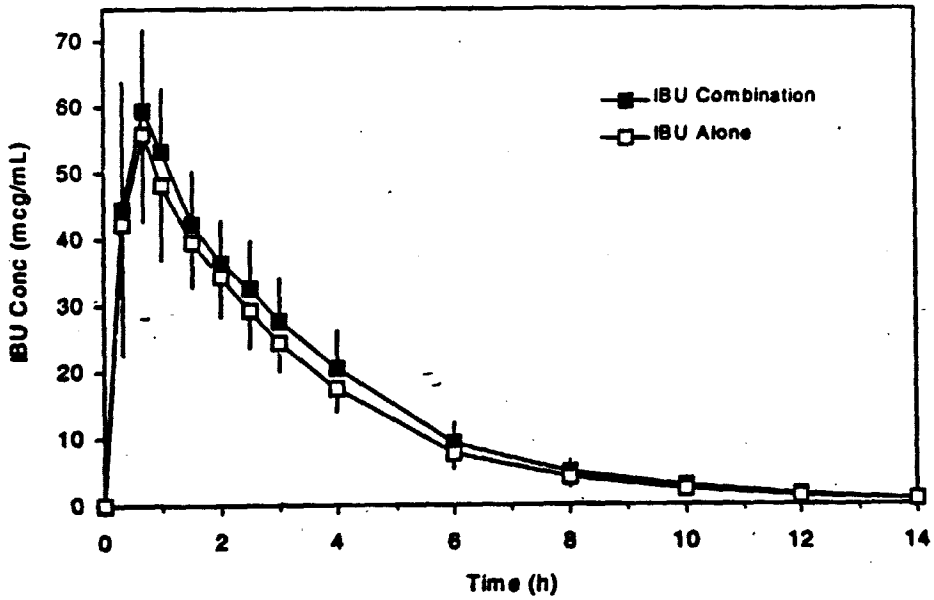
ASSAY METHODS:

ASSAY SENSITIVITY:

ASSAY ACCURACY:

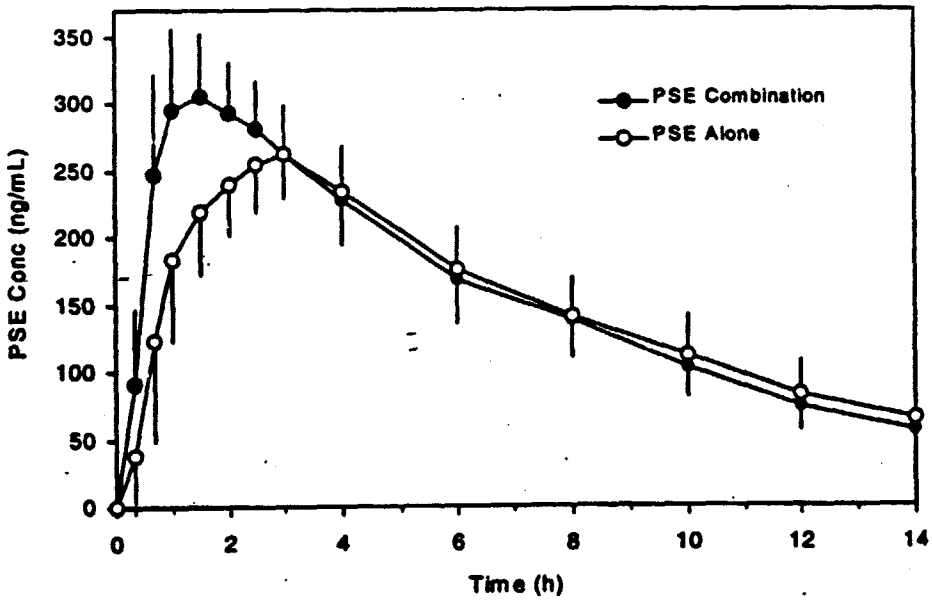
Bioequivalence Study 98-057		
	Mean (sd) Ibuprofen Plasma Concentration (μg/mL)	
Time (h)	Ibuprofen-Pseudoephedrine Suspension	Children's Motrin® Ibuprofen Suspension
0	0.0 (0.0)	0.0 (0.0)
0.33	44.7 (19.4)	42.8 (19.2)
0.67	59.5 (12.6)	56.7 (11.0)
1	53.3 (9.7)	49.1 (9.8)
1.5	42.1 (7.8)	39.6 (6.6)
2	36.6 (6.2)	34.4 (6.3)
2.5	32.7 (7.1)	29.4 (5.7)
3	27.7 (6.4)	24.4 (4.5)
4	20.5 (5.8)	17.4 (3.6)
6	9.3 (3.2)	7.7 (2.3)
8	4.9 (1.8)	4.1 (1.6)
10	2.9 (1.3)	2.3 (1.0)
12	1.5 (0.8)	1.2 (0.6)
14	0.9 (0.5)	0.7 (0.4)
AUC_{INF} (μg-h/mL)	205.1 (39.6)	183.4 (32.5)
C_{MAX} (μg/mL)	61.9 (12.3)	60.3 (12.6)
T_{MAX} (h)	0.70 (0.25)	0.74 (0.34)

Mean Pharmacokinetic Profiles for Ibuprofen-Pseudoephedrine Suspension and Motrin® Suspension



Bioequivalence Study 98-057		
	Mean (sd) Pseudoephedrine Plasma Concentration (ng/mL)	
Time (h)	Ibuprofen-Pseudoephedrine Suspension	Children's Sudafed® Nasal Decongestant
0	0 (0)	0 (0)
0.33	91 (56)	38 (26)
0.67	247 (75)	123 (48)
1	296 (61)	184 (52)
1.5	305 (47)	219 (47)
2	292 (39)	240 (41)
2.5	282 (35)	255 (32)
3	262 (33)	262 (28)
4	228 (32)	234 (37)
6	169 (33)	177 (34)
8	135 (29)	144 (35)
10	101 (25)	112 (28)
12	73 (22)	81 (27)
14	56 (18)	64 (25)
AUC_{INF} (ng-h/mL)	2614 (485)	2633 (611)
C_{MAX} (ng/mL)	322 (36.5)	273 (26.3)
T_{MAX} (h)	1.48 (0.74)	2.60 (0.69)

Mean Pharmacokinetic Profiles for Ibuprofen-Pseudoephedrine Suspension and Sudafed® Liquid



CONCLUSIONS FROM McNEIL BIOEQUIVALENCE STUDY 98-057:

- The 90% confidence intervals for the geometric means of ibuprofen AUC, AUCINF, and CMAX were within 80 to 125%, indicating that the combination product and Motrin® suspension were bioequivalent.

- The 90% confidence intervals for the geometric means of pseudoephedrine AUC, AUCINF, and CMAX were within 80 to 125%, indicating that the combination product and Sudafed® liquid were bioequivalent.

- Pseudoephedrine's absorption rate from the combination product was faster than that from the Sudafed® liquid. Faster absorption resulted in a higher CMAX mean and a TMAX mean that was earlier by about one hour, and these differences were statistically significant. Although CMAX was higher, it was within the range acceptable for equivalence to that for Sudafed® liquid. Additionally, both the CMAX and TMAX means were consistent with those reported in published literature and McNeil-sponsored studies for immediate-release pseudoephedrine products.

- The ibuprofen-pseudoephedrine suspension was well tolerated by the study subjects. No subjects withdrew because of an adverse event and no serious events were reported.

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Table 14.3-13 Statistical Analysis of Ibuprofen Pharmacokinetic Parameters

	AUC (µg·h/mL)	AUC_{INF} (µg·h/mL)	C_{MAX} (µg/mL)	*ln* AUC (µg·h/mL)	*ln* AUC_{INF} (µg·h/mL)	*ln* C_{MAX} (µg/mL)	T_{MAX} (h)	Half-Life (h)
Combination Suspension (A)								
Mean	202	205	61.9	199	201	60.7	0.70	2.2
%CV	19	19	20				36	12
n	24	24	24	24	24	24	24	24
Motrin® Suspension (B)								
Mean	181	183	60.3	179	181	59.0	0.74	2.2
%CV	17	18	21				46	13
n	24	24	24	24	24	24	24	24
Least-Squares Mean								
Combination Suspension (A)	202	205	61.9				0.70	2.2
Motrin® Suspension (B)	181	183	60.3				0.74	2.2
Ratio of Least-Squares Squares Means								
(A/B)%	111.6	111.8	102.7	111.2	111.4	102.8	94.3	100.4
90% Confidence Intervals								
(A/B)%								
lower limit	105.2%	105.3%	94.6%	105.0%	105.1%	94.6%	NA	NA
upper limit	117.9%	118.3%	110.7%	117.7%	118.0%	111.6%	NA	NA
p-Value (ANOVA)								
A vs B	0.0047	0.0048	0.5743	0.0040	0.0041	0.5771	0.6254	0.8608
Statistically Significant Difference								
A vs B	A>B	A>B	NS	A>B	A>B	NS	NS	NS
Power								
A vs B (REF=B)	99.9%	99.8%	98.1%	>99.9%	>99.9%	99.1%	37.1%	100.0%
Mean of Individual Ratios								
(A/B)%	112.7%	112.9%	105.5%	111.2%	111.4%	102.8%	108.2%	101.0%
Intrasubject %CV	12	12	16	12	12	17	41	7

For *ln*-transformed parameters, the antilog of the mean (i.e., the geometric mean) is reported.

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Table 14.3-28 Statistical Analysis of Pseudoephedrine Pharmacokinetic Parameters

	AUC (ng·h/mL)	AUC_{INF} (ng·h/mL)	C_{MAX} (ng/mL)	*ln* AUC (ng·h/mL)	*ln* AUC_{INF} (ng·h/mL)	*ln* C_{MAX} (ng/mL)	T_{MAX} (h)	Half-Life (h)
Combination Suspension (A)								
Mean	2223	2614	322	2199	2568	320	1.48	4.65
%CV	15	19	11				50	20
n	24	24	24	24	24	24	24	24
Sudafed® Liquid (C)								
Mean	2125	2633	273	2097	2566	272	2.60	5.10
%CV	16	23	10				27	25
n	24	24	24	24	24	24	24	24
Least-Squares Mean								
Combination Suspension (A)	2223	2614	322				1.48	4.65
Sudafed® Liquid (C)	2125	2633	273				2.60	5.10
Ratio of Least-Squares Squares Means								
(A/C)%	104.6	99.3	118.2	104.8	100.1	118.0	56.9	91.3
90% Confidence Intervals								
(A/C)%								
lower limit	101.1%	94.2%	113.9%	101.2%	95.3%	113.3%	NA	NA
upper limit	108.1%	104.4%	122.5%	108.6%	105.1%	122.8%	NA	NA
p-Value (ANOVA)								
A vs C	0.0343	0.8114	0.0001	0.0326	0.9788	0.0001	0.0001	0.0529
Statistically Significant Difference								
A vs C	A>B	NS	A>B	A>B	NS	A>B	A<B	NS
Power								
A vs C (REF=C)	100.0%	>99.9%	100.0%	100.0%	100.0%	100.0%	91.0%	99.2%
Mean of Individual Ratios								
(A/C)%	105.3%	101.0%	118.7%	104.8%	100.1%	118.0%	58.0%	93.3%
Intrasubject %CV	7	10	8	7	10	8	26	16

For *ln*-transformed parameters, the antilog of the mean (i.e., the geometric mean) is reported.

Figure 9-5. Mean (sd) Pharmacokinetic Profiles for Ibuprofen in Men

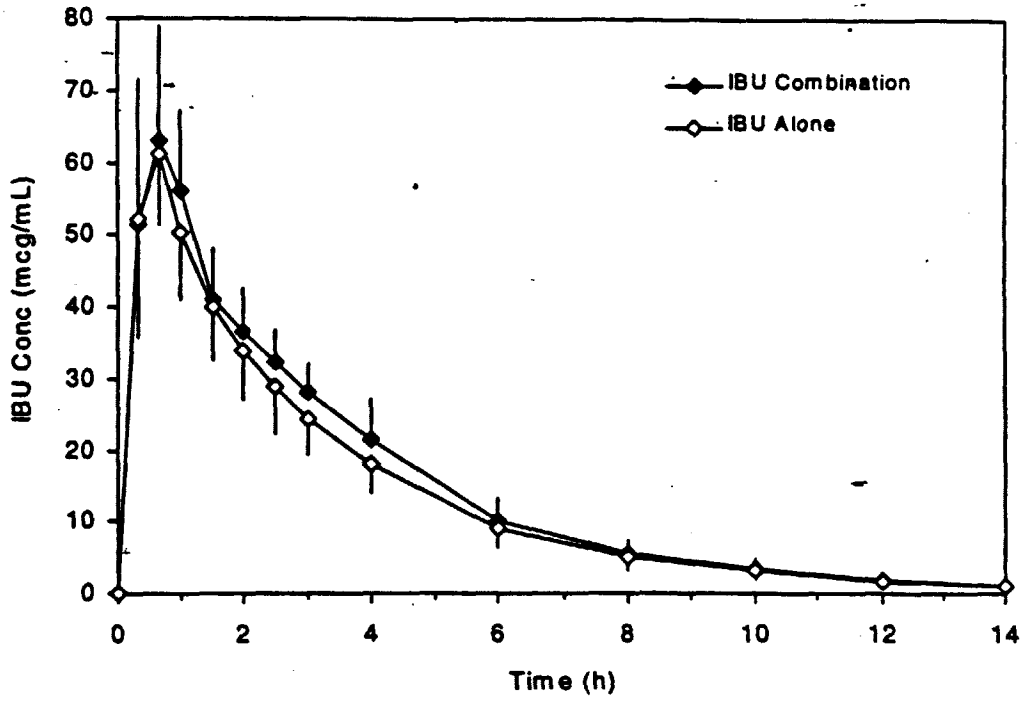


Figure 9-6. Mean (sd) Pharmacokinetic Profiles for Ibuprofen in Women

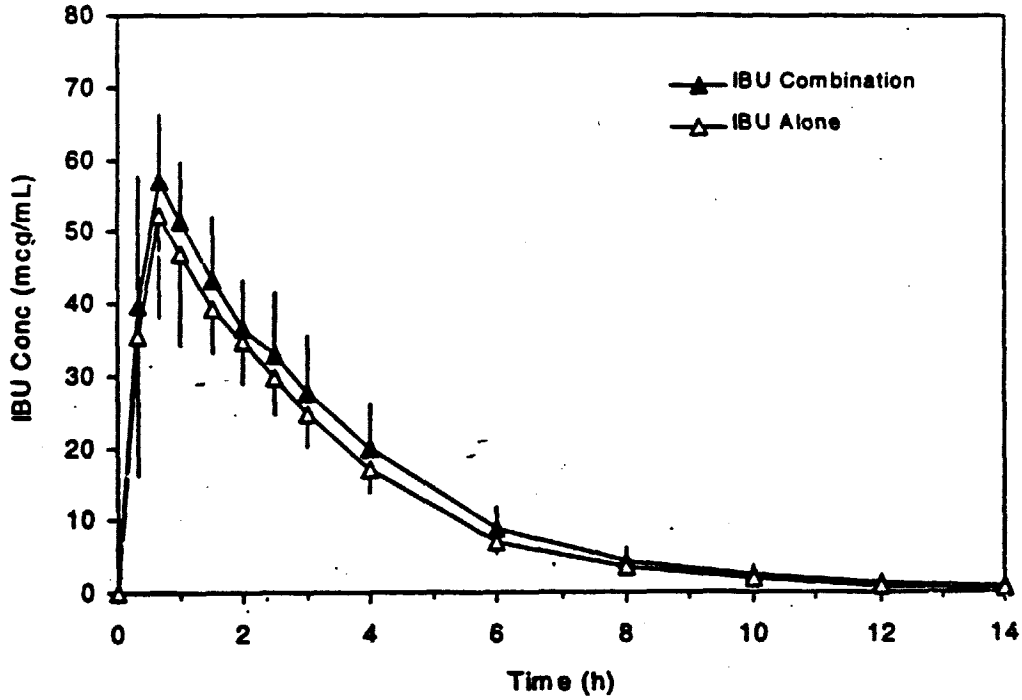


Table 9-5. Summary of Ibuprofen Parameters by Gender (Mean, sd, cv%)

	AUC (μg·h/mL)	AUCINF (μg h/mL)	CMAX (μg /mL)	TMAX (h)	Half-Life (h)	Cl/F (mL/h/kg)	Vd/F (L/kg)
Men (n = 10)							
Combination	213	217	66.0	0.67	2.4	35.2	0.12
Suspension	(31)	(33)	(14.6)	(0.16)	(0.2)	(5.7)	(0.01)
	15%	15%	22%	24%	10%	16%	11%
Motrin®	194	198	63.6	0.64	2.4	39.3	0.13
Suspension	(39)	(40)	(12.2)	(0.19)	(0.2)	(8.4)	(0.02)
	20%	20%	19%	30%	10%	21%	14%
Women (n = 14)							
Combination	194	197	58.9	0.71	2.1	40.0	0.12
Suspension	(42)	(43)	(9.8)	(0.30)	(0.2)	(8.8)	(0.02)
	21%	22%	17%	42%	10%	22%	15%
Motrin®	172	173	57.8	0.81	2.1	44.0	0.13
Suspension	(21)	(22)	(12.7)	(0.41)	(0.2)	(5.8)	(0.02)
	12%	12%	22%	50%	12%	13%	18%

Figure 9-7. Mean (sd) Pharmacokinetic Profiles for Pseudoephedrine in Men

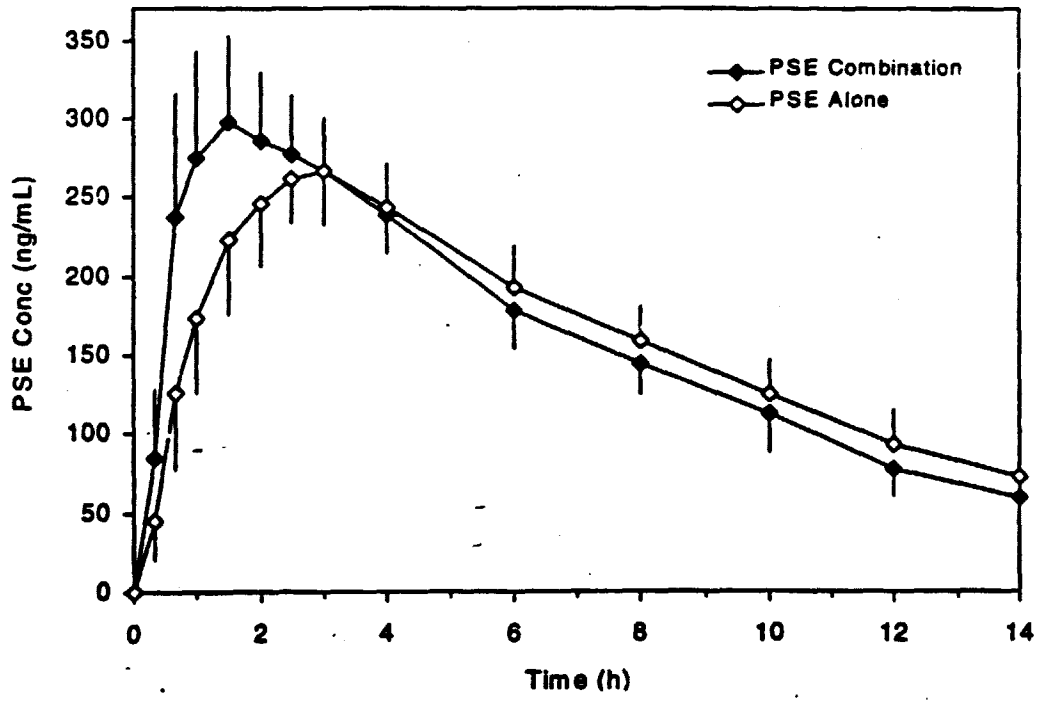


Figure 9-8. Mean (sd) Pharmacokinetic Profiles for Pseudoephedrine in Women

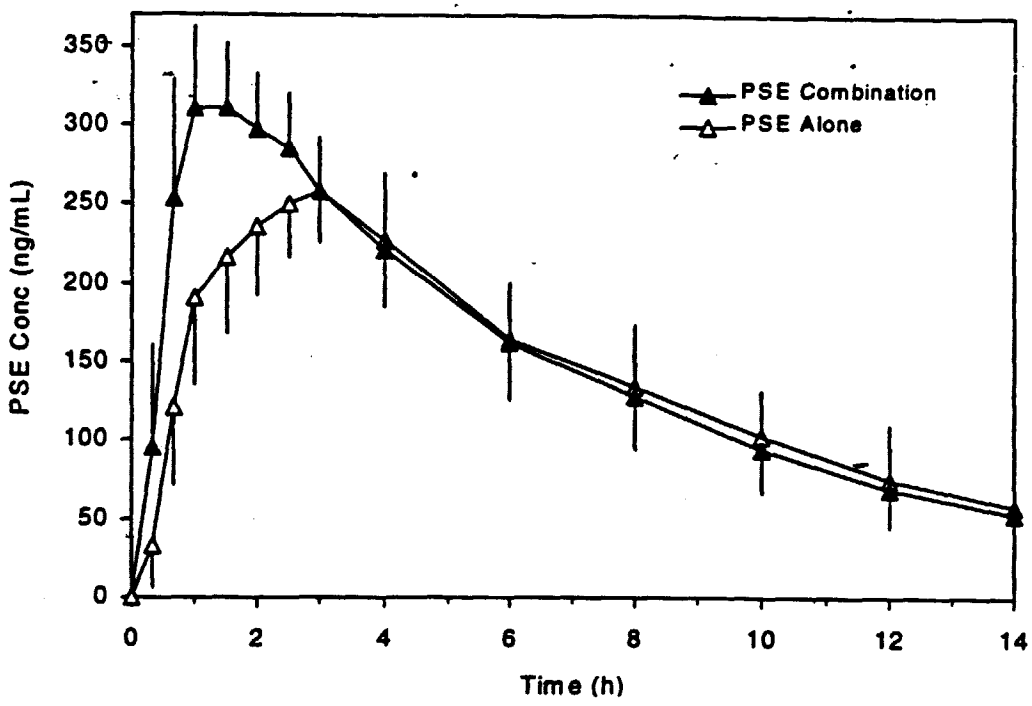


Table 9-6. Summary of Pseudoephedrine Parameters by Gender (Mean, sd, cv%)

	AUC (ng·h/mL)	AUCINF (ng·h/mL)	CMAX (ng/mL)	TMAX (h)	Half-Life (h)	Cl/F (mL/min/kg)	Vd/F (L/kg)
Men (n = 10)							
Combination	2285	2695	312	1.67	4.7	5.8	2.3
Suspension	(265)	(390)	(39)	(0.95)	(0.9)	(0.9)	(0.3)
	12%	14%	12%	57%	18%	16%	12%
Sudafed®	2269	2835	273	2.65	5.2	5.5	2.4
Liquid	(277)	(442)	(23)	(0.71)	(1.0)	(0.9)	(0.3)
	12%	16%	10%	27%	18%	17%	14%
Women (n = 14)							
Combination	2178	2555	330	1.35	4.6	6.3	2.4
Suspension	(368)	(550)	(34)	(0.53)	(1.0)	(1.5)	(0.4)
	17%	22%	10%	40%	22%	23%	15%
Sudafed®	2023	2488	273	2.57	5.0	6.6	2.7
Liquid	(368)	(686)	(29)	(0.70)	(1.5)	(1.6)	(0.4)
	18%	28%	11%	27%	30%	24%	16%

Figure 4-1. Oral Clearance of Ibuprofen in Children and Adults

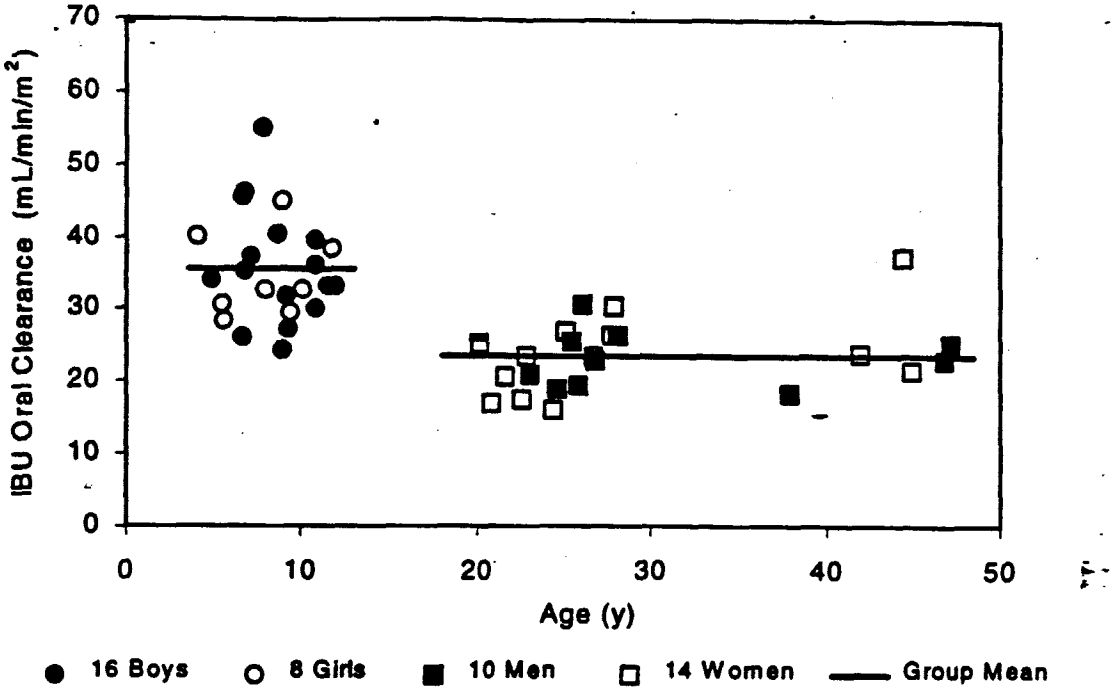


Figure 4-2. Elimination Half-Life of Ibuprofen in Children and Adults

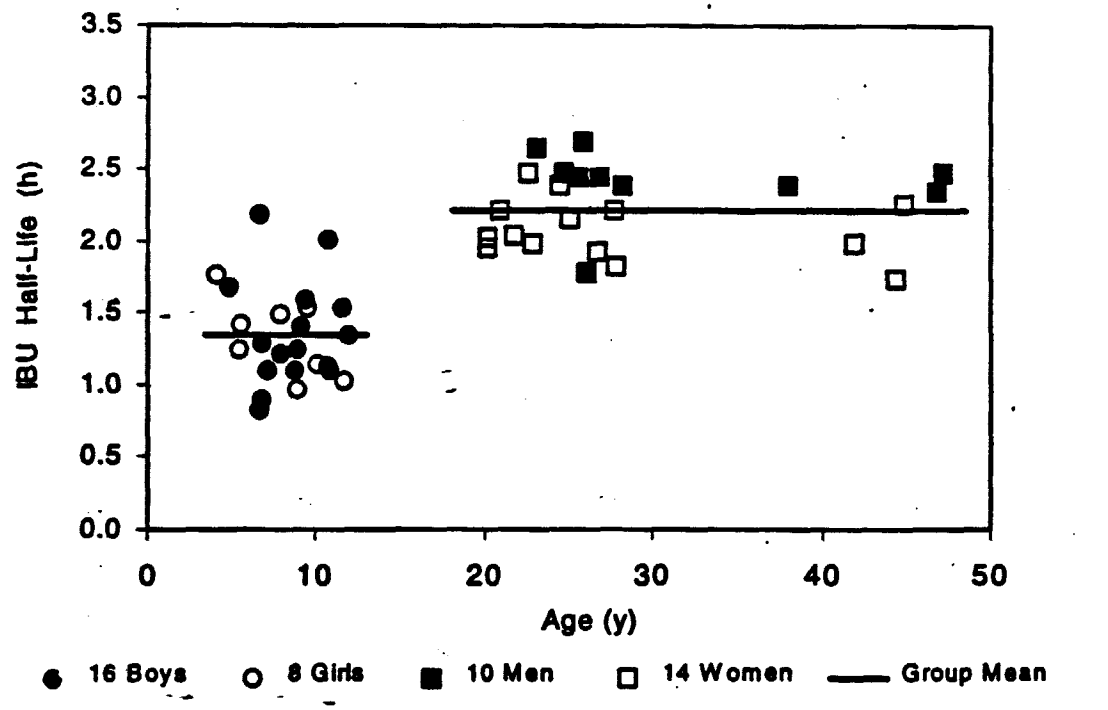


Figure 4-3. Distribution Volume of Ibuprofen in Children and Adults

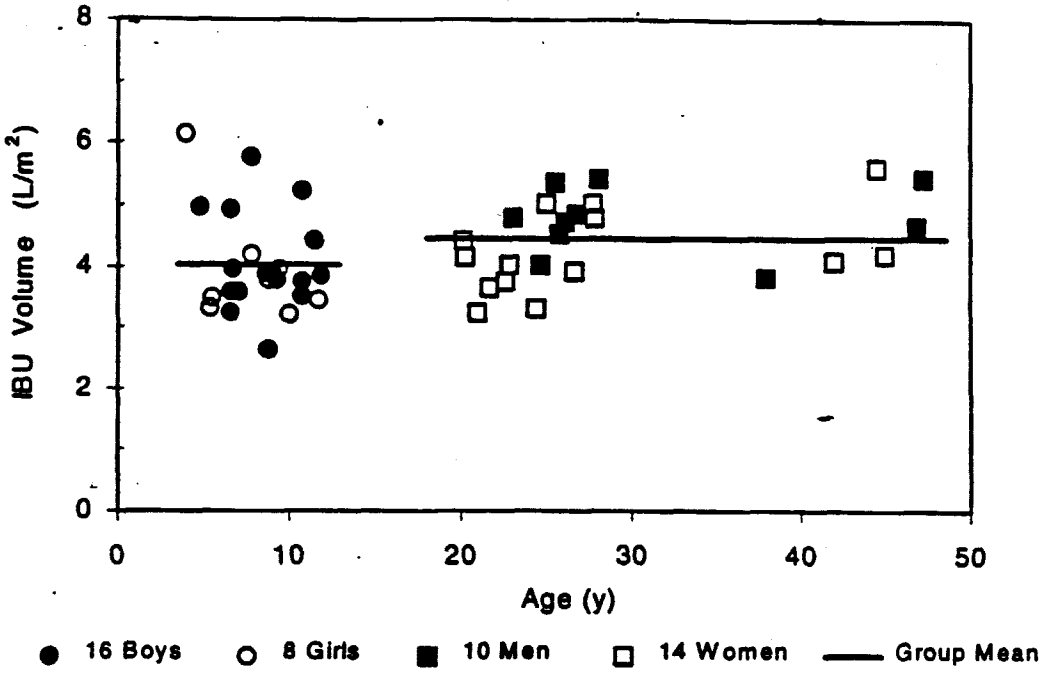


Table 4-3. Primary Analysis for Ibuprofen Pharmacokinetics (One-Way ANOVA)

Parameter	LSM[a] from One-Way ANOVA		Age Group	p-Value
	Children	Adults	% Difference[b]	Children vs Adults
Cl/F (mL/min/m²)	35.6	23. 6	50.0	0.0001
t½ (h)	1.34	2.22	-39.6	0.0001
Vd/F (L/m²)	4.02	4.45	-9.66	0.0564

a: LSM = least squares mean
b: Percent difference = 100 (LSM for Children - LSM for Adults) / LSM for Adults

Mean values of Cl/F, t½, and Vd/F for ibuprofen were also analyzed in a two-way ANOVA [age group (children, adult) and gender] with a two-way interaction term (age group-by-gender) included. Results of this analysis are summarized in Table 4-4.

The two-way ANOVA also indicates significant differences between children and adults on all three pharmacokinetic parameters. In addition, there was both a significant gender difference and group-by-gender interaction for t½. The nature of the interaction indicates that there was essentially no difference in t½ means between gender for children and a 16% longer t½ for male adults compared with female adults. This finding is consistent with the higher likelihood for adults to have gender differences in drug pharmacokinetics and

metabolism than children, because of hormonal influences and/or differences in lean body mass. Drugs that undergo extensive hepatic metabolism, such as ibuprofen, may be more sensitive to gender differences.

Table 4-4. Secondary Analysis for Ibuprofen Pharmacokinetics (Two-Way ANOVA)

	LSM[a] from Two-Way ANOVA				Gender % Difference[b]		p-Value		
	Children		Adults						
Parameter	M	F	M	F	Children	Adults	Ch. vs Adult	Gender	Interaction[c]
Cl/F (mL/min/m^2)	36.0	34.8	23.1	23.9	3.4	-3.3	0.0001	0.8973	0.5984
t½ (h)	1.35	1.32	2.41	2.08	2.3	15.9	0.0001	0.0501	0.0975
Vd/F (L/m^2)	4.06	3.94	4.76	4.23	3.0	12.5	0.0338	0.1573	0.3654

a: LSM = least squares mean
b: Percent difference = 100 (LSM for Males - LSM for Females) / LSM for Females
c: Age Group-by-Gender

4.3 Pseudoephedrine Pharmacokinetics

Scatter plots of Cl/F, t½, and Vd/F for pseudoephedrine from McNeil Studies 97-024 and 98-057 are shown in Figures 4-4 through 4-6, respectively. Two solid lines on each plot indicate the location of mean values for children and adults. Results from the one-way ANOVA are summarized in Table 4-5, and they indicate that children were more efficient in the elimination of pseudoephedrine than adults. Mean Cl/F was 50% higher, mean t½ was 47% shorter, and mean Vd/F was 22% lower in children, and these differences were highly significant ($p < 0.0001$). These findings are in agreement with known differences in single-ingredient pseudoephedrine pharmacokinetics between children and adults.

Figure 4-4. Oral Clearance of Pseudoephedrine in Children and Adults

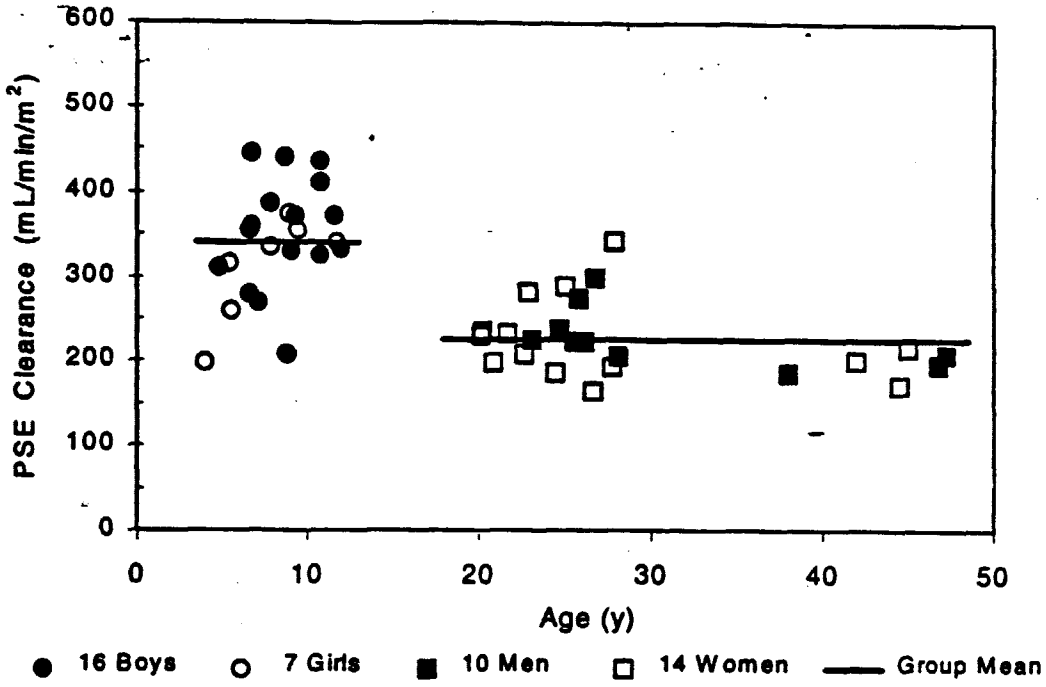


Figure 4-5. Elimination Half-Life of Pseudoephedrine in Children and Adults

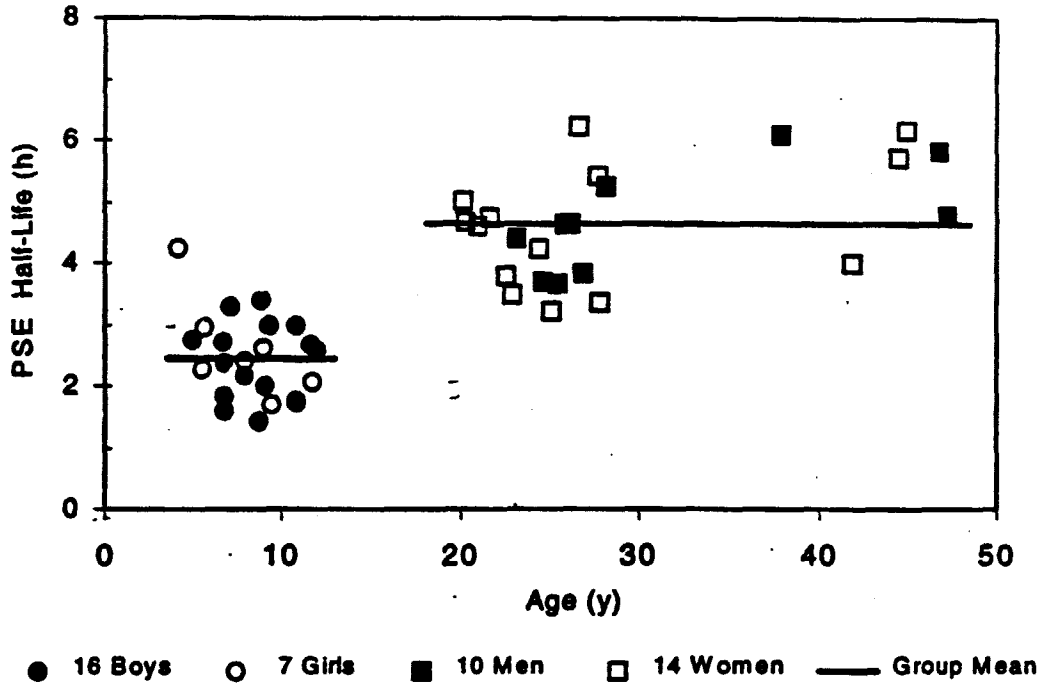


Figure 4-6. Distribution Volume of Pseudoephedrine in Children and Adults

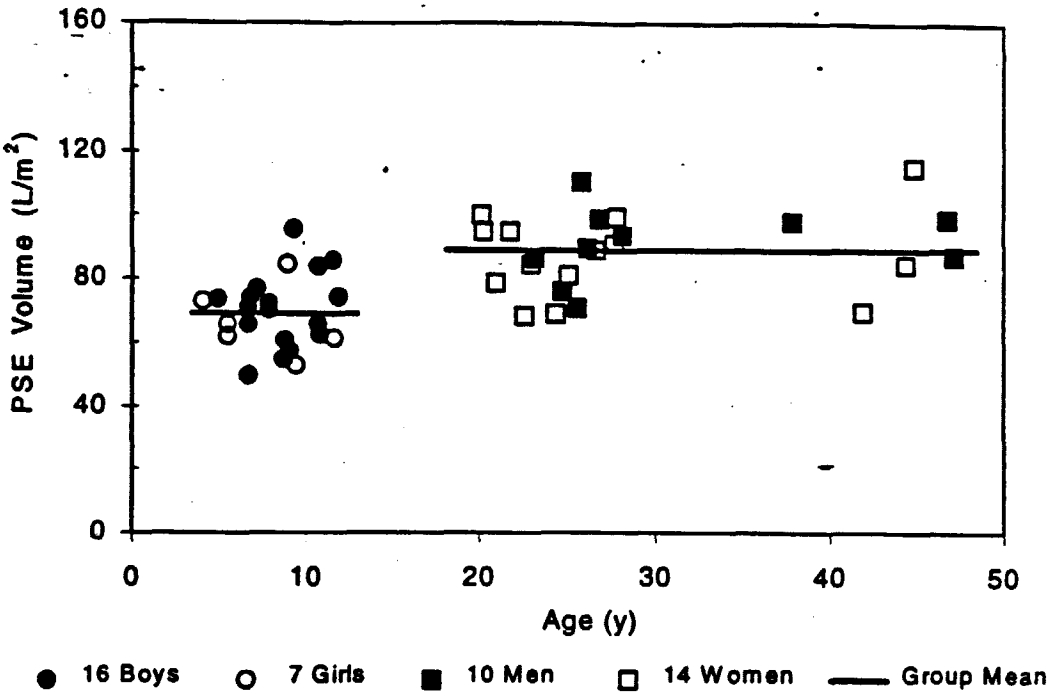


Table 4-5. Primary Analysis for Pseudoephedrine Pharmacokinetics (One-Way ANOVA)

Parameter	LSM[a] from One-Way ANOVA		Age Group	p-Value
	Children	Adults	% Difference[b]	Children vs Adults
Cl/F (mL/min/m²)	339.7	226.1	50.2	0.0001
t½ (h)	2.45	4.65	-47.3	0.0001
Vd/F (L/m²)	69.0	88.8	-22.1	0.0001

a: LSM = least squares mean
b: Percent difference = 100 (LSM for Children - LSM for Adults) / LSM for Adults

Mean values of Cl/F, t½, and Vd/F for ibuprofen were also analyzed in a two-way ANOVA [age group (children, adult) and gender] with a two-way (age group-by-gender) interaction term included. Results of this analysis are summarized in Table 4-6.

The two-way ANOVA also indicates significant differences between children and adults on all three pharmacokinetic parameters, but no significant effects of gender nor significant age group-by-gender interactions were found for any parameter.

Table 4-6. Secondary Analysis for Pseudoephedrine Pharmacokinetics (Two-Way ANOVA)

	LSM[a] from Two-Way ANOVA				Gender % Difference[b]		p-Value		
	Children		Adults						
Parameter	M	F	M	F	Children	Adults	Ch. vs Adult	Gender	Interaction[c]
CL/F (mL/min/m^2)	352.3	311.1	227.9	224.9	13.3	1.3	0.0001	0.1997	0.2677
t½ (h)	2.39	2.61	4.69	4.62	-8.6	1.5	0.0001	0.7630	0.5645
Vd/F (L/m^2)	70.1	67.0	91.0	87.2	4.7	4.4	0.0001	0.3601	0.9262

a: LSM = least squares mean
b: Percent difference = 100 (LSM for Males - LSM for Females) / LSM for Females
c: Age Group-by-Gender

4.4 Assessment of Any Dosing Adjustments in Children

4.4.1 Proposed OTC Pediatric Dosing for the Combination Suspension

The proposed OTC pediatric dosing schedule for the ibuprofen-pseudoephedrine suspension is shown in Table 4-7. The proposed schedule is based on a target average dose of 7.5 mg/kg for ibuprofen and 1.125 mg/kg for pseudoephedrine HCl, and it provides for acceptable doses of both drugs that may be repeated every six to eight hours, but not more than four times a day.

Table 4-7. Proposed OTC Pediatric Dosing Schedule for the Ibuprofen-Pseudoephedrine HCl Suspension, 100 mg-5 mg/5 mL

Weight Range (lb)	Age (y)	Dose[a] (teaspoon)	Ibuprofen Dose[a] (mg)	Pseudoephedrine HCl Dose[a] (mg)
Under 24	Under 2	Consult Doctor	Consult Doctor	Consult Doctor
24 - 35	2 - 3	1	100	15
36 - 47	4 - 5	1 ½	150	22.5
48 - 59	6 - 8	2	200	30
60 - 71	9 - 10	2 ½	250	37.5
72 - 95	11	3	300	45

a: Dosage may be repeated every six to eight hours, but not more than four times a day.

Because there are differences in the age groupings currently used in the ibuprofen and pseudoephedrine OTC pediatric dosing schedules, it was necessary to modify the dosing of ibuprofen and/or pseudoephedrine for the combination suspension. The proposed OTC pediatric dosing schedule for the combination suspension keeps the weight- and age-

Figure 4-7. Multiple-Dose Simulations of Ibuprofen Pharmacokinetics in Children and Adults

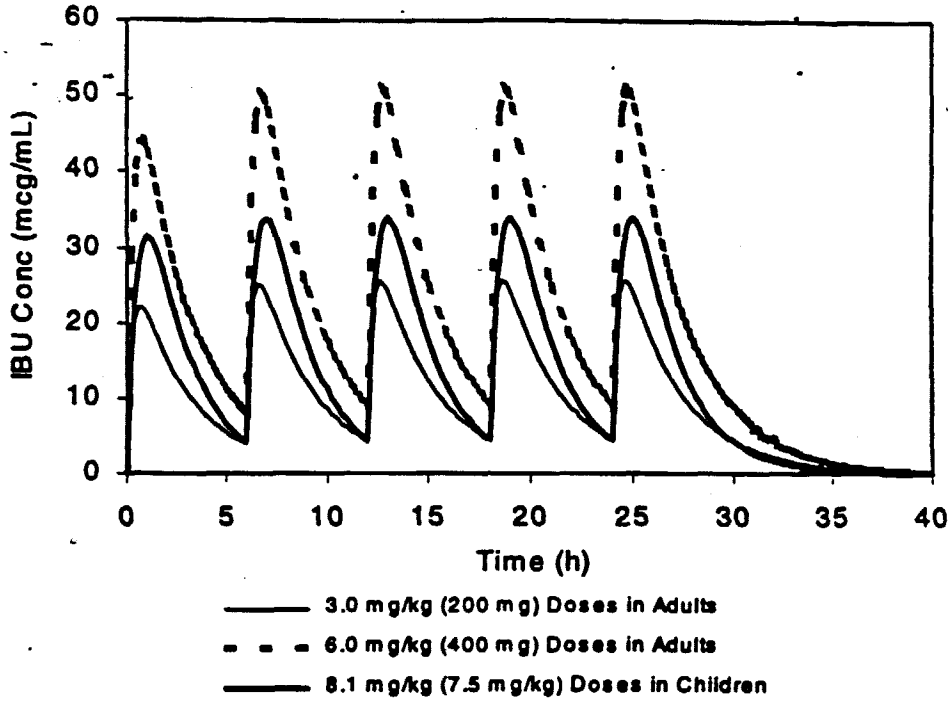
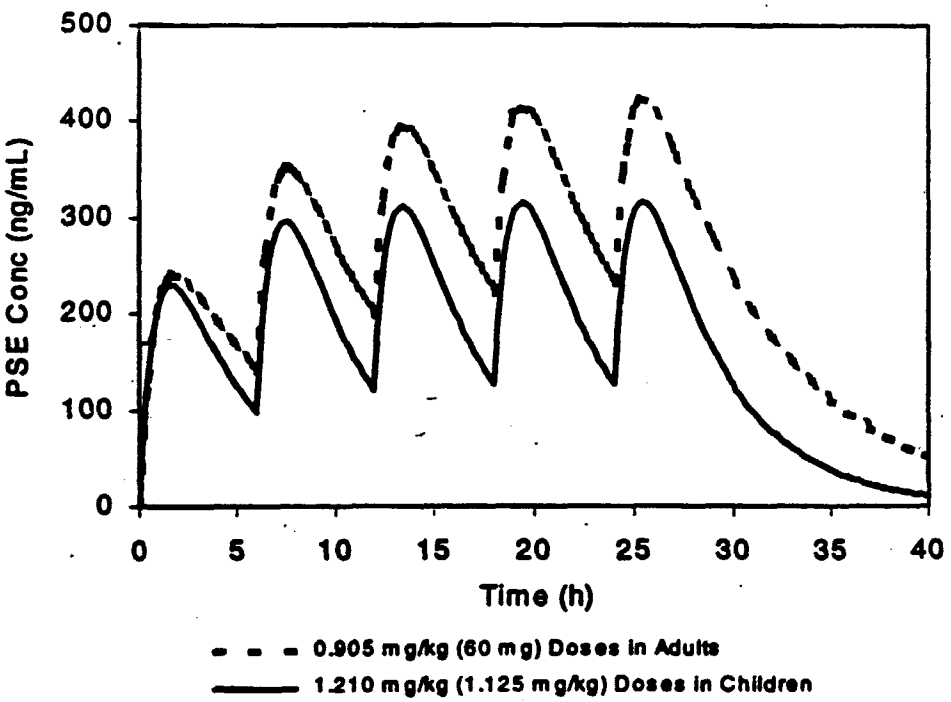


Figure 4-8. Multiple-Dose Simulations of Pseudoephedrine Pharmacokinetics in Children and Adults



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4.2 Ibuprofen Pharmacokinetics and Age

Individual values of Cl/F, t½, and Vd/F for all subjects in McNeil Pharmacokinetics Study 97-024 [1] and two McNeil-sponsored, single-dose ibuprofen studies [3,4] in children were pooled, providing a data set of 82 children. Figures 4-2 through 4-4 show scatter plots of these data and, although a few outliers are present in each figure, the scatter as a whole indicated consistency across age.

Results of the linear regression analyses between each pharmacokinetic parameter and age are provided in Table 4-3. All correlations with age (slope) were not significant, indicating that these pharmacokinetic parameters were independent of age. Mean Cl/F, t½, and Vd/F values for the five age subgroups are listed in Table 4-4. These parameters were similar across age groups, which further indicate that ibuprofen pharmacokinetic data determined in children ages four through 11 years could be extrapolated to two- and three-year old children.

Figure 4-2. Oral Clearance of Ibuprofen in Children From Three McNeil Studies

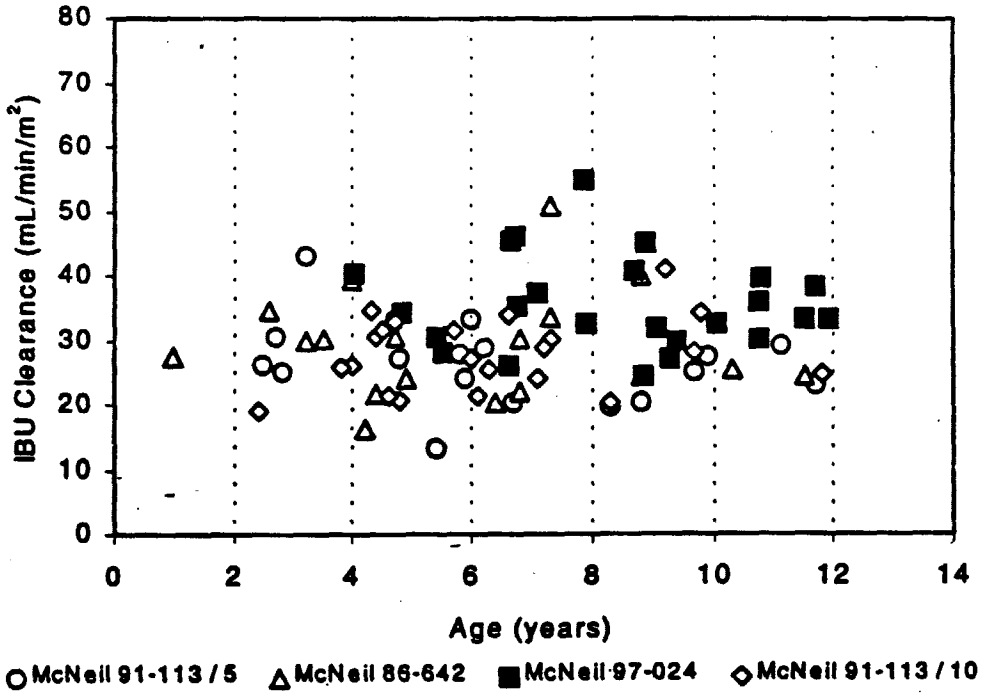

Figure 4-3. Elimination Half-Life of Ibuprofen in Children From Three McNeil Studies

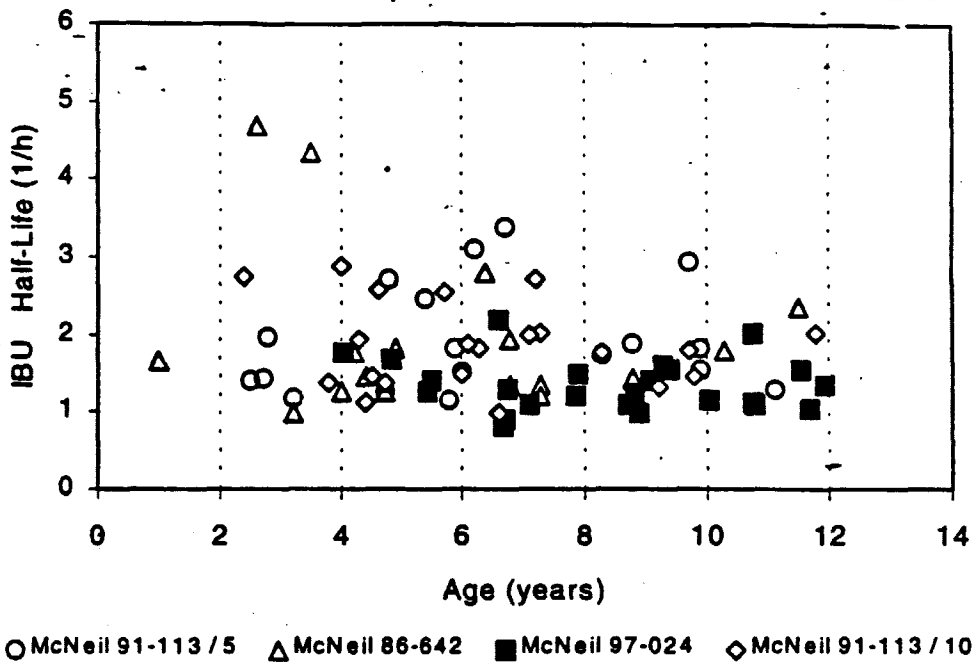

Figure 4-4. Distribution Volume of Ibuprofen in Children From Three McNeil Studies

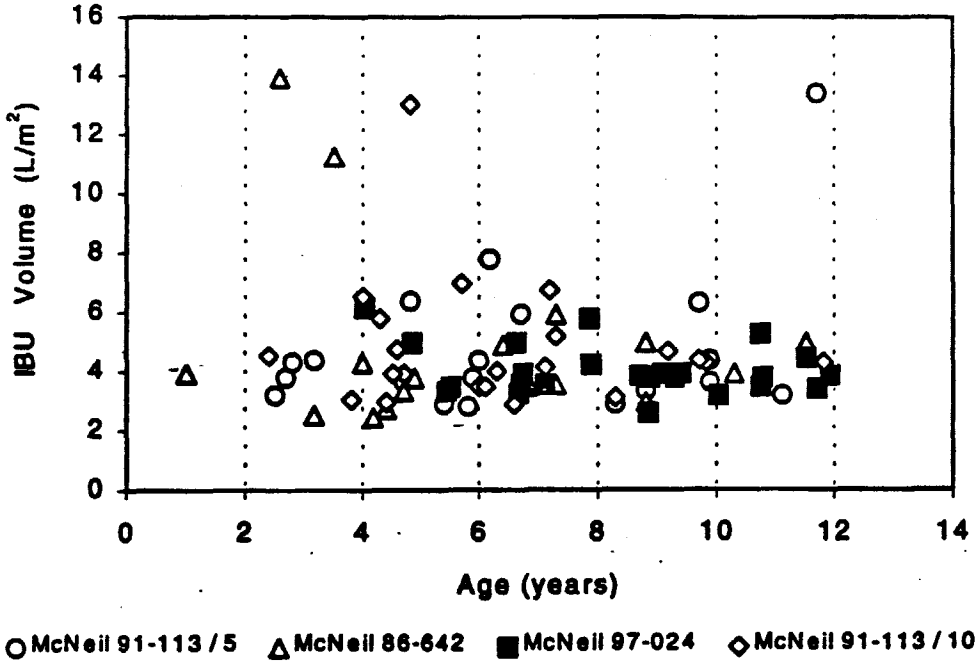

Table 4-3. Linear Regression Analyses[a] of Ibuprofen Pharmacokinetics and Age

Pharmacokinetic Parameter	Intercept	Intercept p-Value	Slope (Age)	Slope p-Value	r
Cl/F (mL/min/m^2)	27.8 (2.3)	0.0001	0.32 (0.32)	0.3074	0.114
t½ (h)	2.1 (0.3)	0.0001	-0.04 (0.04)	0.3944	0.095
Vd/F (L/m^2)	5.1 (0.7)	0.0001	-0.07 (0.09)	0.4414	0.085

a: Results for the intercept and slope are listed as estimates with standard errors in parentheses.

Table 4-4. Mean (%cv) Ibuprofen Data Pooled From McNeil Studies[a] By Age Subgroup

Pharmacokinetic Parameter	Age Subgroup (y)				
	2.0 to 3.9	4.0 to 5.9	6.0 to 7.9	8.0 to 9.9	10.0 to 11.9
Cl/F (mL/min/m^2)	29.3 23%	28.2 24%	32.1 31%	30.0 26%	30.8 18%
t½ (h)	2.2 63%	2.0 65%	1.8 41%	1.6 27%	2.0 80%
Vd/F (L/m^2)	5.7 72%	4.6 50%	4.5 28%	3.9 22%	4.8 59%
Number of Subjects	9	22	21	18	12

a: McNeil Pharmacokinetics Study 97-024 [1], McNeil Clinical Study 86-642 [3], and McNeil Clinical Study 91-113 [4]

4.3 Pseudoephedrine Pharmacokinetics and Age

No individual age and pseudoephedrine pharmacokinetic data in children were available to pool with data for the 23 children in McNeil Pharmacokinetics Study 97-024 [1]. Figures 4-5 through 4-7 show scatter plots of Cl/F, t½, and Vd/F as a function of age. Although a few outliers are present in each figure, the overall scatter indicated consistency across age.

Results of the linear regression analyses between each pharmacokinetic parameter and age are provided in Table 4-5. The correlations of both t½ and Vd/F with age (slope) were not significant, indicating that these pharmacokinetic parameters were independent of age. The correlation of Cl/F with age for this group of children was significant ($p < 0.0382$); however, the slope of the relationship was relatively shallow. Mean Cl/F, t½, and Vd/F values for the five age subgroups are listed in Table 4-6. They were similar among the subgroups, except that Cl/F was lower in the 4.0-to-5.9-year subgroup, which was comprised of four children.

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Overall, these results indicate that the pharmacokinetics of pseudoephedrine in children were independent of age. Although the available data for pseudoephedrine were limited, they are supportive of there being no clinically relevant, age-related effects on the pharmacokinetics. Moreover, renal tubular function is mature by six months of age [9] and pseudoephedrine is mainly excreted unchanged in the urine by renal tubular filtration and secretion. Based on this, one would not expect an effect of age on its pharmacokinetics within the children's age category.

Figure 4-5. Oral Clearance of Pseudoephedrine in Children From McNeil Study 97-024

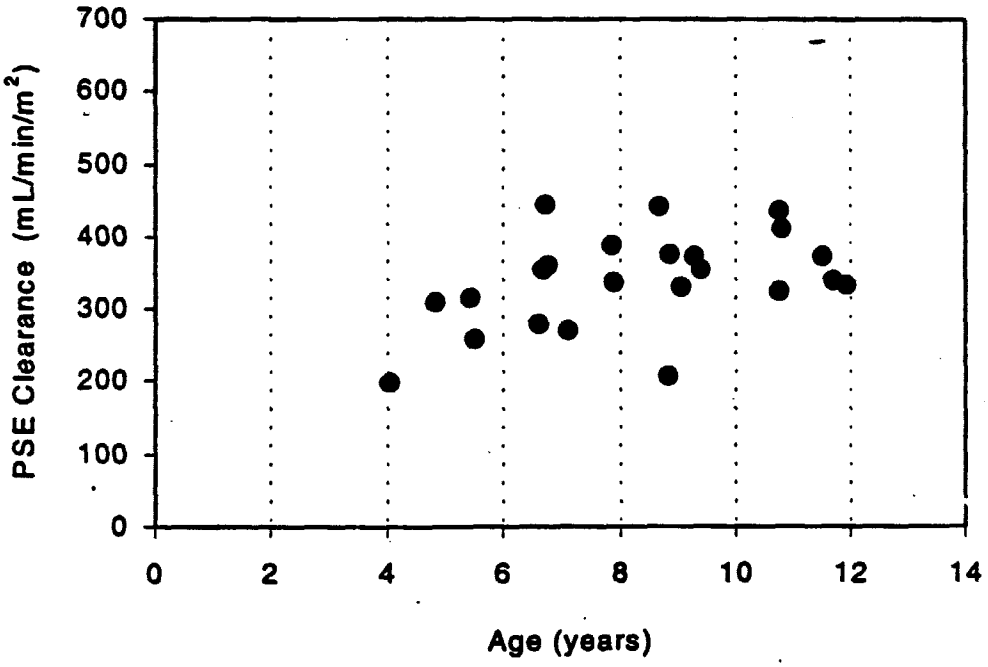

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Figure 4-6. Elimination Half-Life of Pseudoephedrine in Children From McNeil Study 97-024

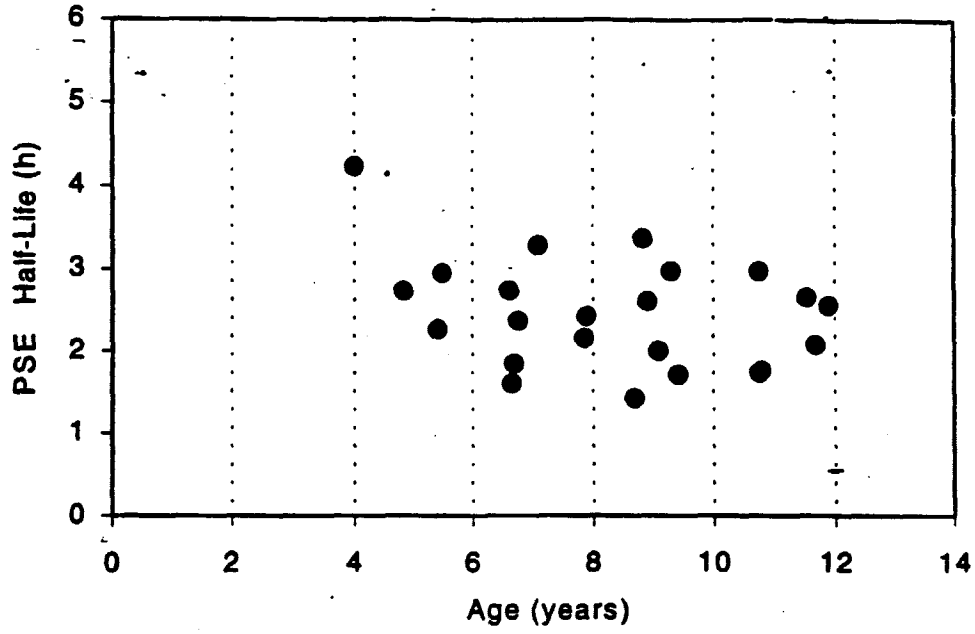

Figure 4-7. Distribution Volume of Pseudoephedrine in Children From McNeil Study 97-024

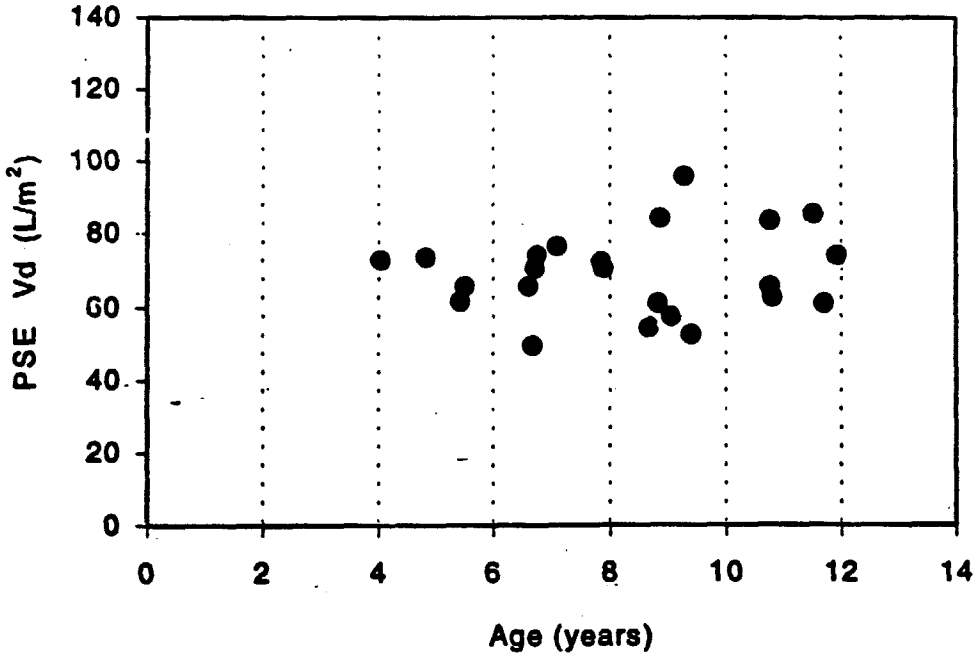

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Table 4-5. Linear Regression Analyses[a] of Pseudoephedrine Pharmacokinetics and Age

Pharmacokinetic Parameter	Intercept	Intercept p-Value	Slope (Age)	Slope p-Value	r
Cl/F (mL/min/m^2)	235 (49)	0.0001	12.6 (5.7)	0.0382	0.435
t½ (h)	3.3 (0.5)	0.0001	-0.10 (0.06)	0.1212	0.332
Vd/F (L/m^2)	64 (9)	0.0001	0.6 (1.1)	0.5856	0.120

a: Results for the intercept and slope are listed as estimates with standard errors in parentheses.

Table 4-6. Mean (%cv) Pseudoephedrine Data From McNeil Study 97-024 By Age Subgroup

Pharmacokinetic Parameter	Age Subgroup (y)			
	4.0 to 5.9	6.0 to 7.9	8.0 to 9.9	10.0 to 11.9
Cl/F (mL/min/m^2)	271 20%	348 17%	347 22%	369 12%
t½ (h)	3.0 28%	2.3 24%	2.4 32%	2.3 22%
Vd/F (L/m^2)	68 8%	69 13%	68 27%	72 15%
Number of Subjects	4	7	6	6

6.7.3 Expanded Dissolution Profiles

Ibuprofen dissolution profiles over 60 minutes were determined for the grape- and berry-flavored, ibuprofen-pseudoephedrine suspensions. In addition, they were determined for Formula C-163-7 of Children's Motrin® Ibuprofen Suspension, which was used as the marketed reference product in McNeil Bioequivalence Study 98-057.

[redacted] Results for the grape-flavored, combination suspension (Batch C-846-3C), Children's Motrin® Ibuprofen Suspension (Formula C-163-7, Lot BEM045), and the berry-flavored, combination suspension (Batch C-822-4A) are listed in Tables 6.7-4, 6.7-5, and 6.7-6, respectively. Dissolution profiles for individual aliquots are plotted in sets of six vessels for the three products in Figures 6.7-1 through 6.7-6.

Table 6.7-4. Dissolution Data for Ibuprofen-Pseudoephedrine Suspension, Grape (C-846-3C)

Test Date	Vessel Number	Time in Minutes 5	10	15	30	45	60
Set 1 10/15/98	1	[redacted]					
	2						
	3						
	4						
	5						
	6						
Set 2 10/15/98	7						
	8						
	9						
	10						
	11						
	12						
Mean		99	99	99	100	100	100
sd		1	1	1	1	1	1
%cv		1	1	1	1	1	1
Min		98	99	98	99	99	99
Max		100	101	101	101	102	102
n		12	12	12	12	12	12

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Figure 6.7-1. Set 1 Vessels for Ibuprofen-Pseudoephedrine Suspension, Grape (C-846-3C)

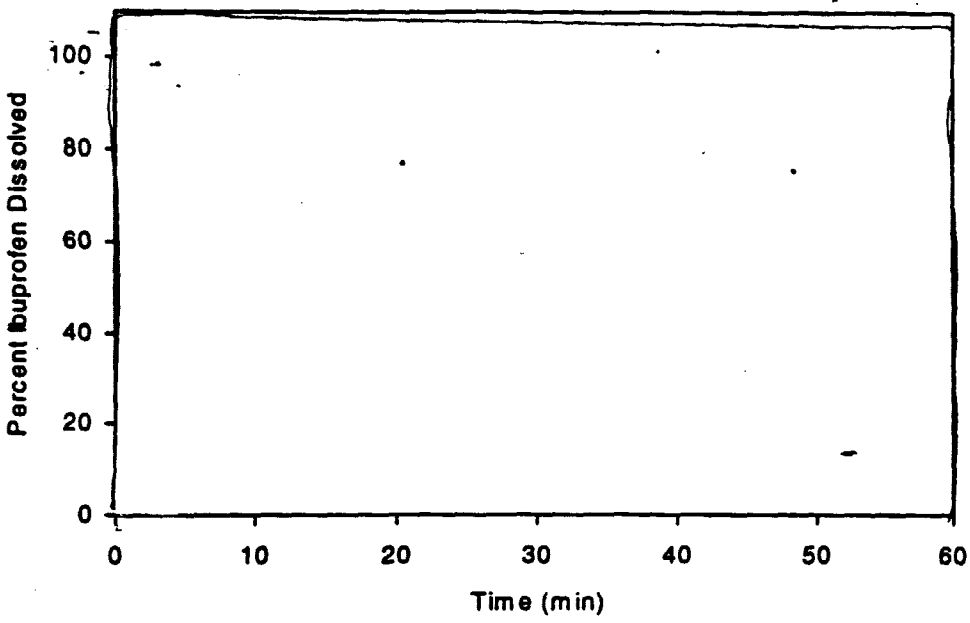

Figure 6.7-2. Set 2 Vessels for Ibuprofen-Pseudoephedrine Suspension, Grape (C-846-3C)