

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-565

SUMMARY REVIEW

Summary basis for Regulatory Action

Date	May 27, 2010
From	Joel Schiffenbauer
Subject	Summary Review
NDA/BLA # Supp #	22-565
Proprietary / Established (USAN) Names	Advil Congestion Relief/ibuprofen and phenylephrine
Dosage Forms / Strength	Caplet; 200 mg ibuprofen and 10 mg phenylephrine
Proposed Indication(s)	temporary relief of symptoms associated with the common cold or flu
Action:	<i>Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Linda Hu/Robert Shibuya
Statistical Review	
Pharmacology Toxicology Review	W. Harrouck
CMC Review/OBP Review	G. Holbert
Microbiology Review	
Clinical Pharmacology Review	Ying Fan/P. Roy/A. Bhattaram
DDMAC	
DSI	Carol Rivera-Lopez
CDTL Review	
OSE/DMEPA	T. Turner
OSE/DDRE	
OSE/DSRCS	
Other (labeling)	A. Rowley/M. Chang

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

1. Introduction to Review

This memorandum will review issues regarding NDA 22-565, Advil Congestion Relief, which contains ibuprofen 200 mg, and phenylephrine 10 mg (substituted for pseudoephedrine).

Advil Cold & Sinus caplets (NDA 19-771) contains ibuprofen 200 mg and pseudoephedrine HCl 30 mg and is available OTC. However, as a pseudoephedrine-containing drug product it has been moved behind the counter, pursuant to The Combat Methamphetamine Epidemic Act of 2005. The same ingredients and dosages as the product under review (ibuprofen 200 mg and phenylephrine 10 mg) are available OTC as single ingredient products.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

A combination of the OTC analgesic ibuprofen (IBU) with the nasal decongestant pseudoephedrine hydrochloride (PSE) was approved as a solid, oral dosage form on September 19, 1989 (Advil Cold & Sinus, NDA 19-771), as a suspension on April 18, 2002 (NDA 21-373), and as a liquid-filled capsule on May 30, 2002 (NDA 21-374). The solid, oral dosage form product is being reformulated with the substitution of phenylephrine hydrochloride (PE) for PSE.

This application is a 505 (b)(2) NDA application for a new combination of ibuprofen (IBU) (200 mg) and phenylephrine (PE or PHE) (10 mg) to provide an alternative to the ibuprofen (200 mg)/pseudoephedrine HCl (30 mg) product currently marketed under the trade name Advil Cold & Sinus (NDA 19-771). PE is a sympathomimetic amine with GRASE status as a decongestant in the monograph entitled Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (21 CFR 341.20). PE has been available for use as an OTC nasal decongestant since the early 1960s.

The original submission received a non-approval in 2008, and the applicant received the following comments:

The submitted PK data for phenylephrine are unreliable due to major flaws in the analytical assay methodology. Further, any differences noted between the original and repeat results between samples within a subject, was highly variable and did not demonstrate a similar level of underestimation within a batch. Therefore, we do not believe that extrapolating the results of reanalysis of a subset of subject samples from Study AD-06-06 to Study AQ-05-03, that were analyzed using the flawed original method, is justified.

A cross-study comparison of ibuprofen PK data from Study AQ-05-03 to the historical ibuprofen PK data suggests that the mean T_{max} values of ibuprofen increased approximately 0.6 hr in the presence of phenylephrine. In addition, a lower ibuprofen C_{max} value was observed under fed conditions compared to fasting conditions. Further analysis is needed to

assess the impact of delayed T_{max} in the presence of phenylephrine, and lower C_{max} under fed conditions on clinical efficacy.

Therefore, you should submit pharmacokinetic data for phenylephrine using an adequately validated analytical assay method. With advances in analytical method for free phenylephrine, we recommend that you develop a sensitive assay for quantifying unmetabolized phenylephrine in the plasma samples. You should analyze newly acquired phenylephrine PK samples. We recommend that you also include ibuprofen (single ingredient) in any new PK study that you perform.

Alternatively you may select to reanalyze the stored PK samples from your previous PK study AQ-05-03 for phenylephrine, provided stability of these samples can be assured. However, you will still need to address the T_{max} and C_{max} changes for ibuprofen.

You should submit any new protocols for our review.

3. CMC/Microbiology/Device

I concur with the conclusions reached by Dr. Holbert regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

5.1. Notable issues

During the previous review cycle, no clinical efficacy and safety trial was conducted. Rather, a single human pharmacokinetic study was submitted in support of the NDA. Study AQ-05-03 was a four-way crossover, food effect/formulation effect/drug interaction bioavailability study with the earlier formulation of ibuprofen/phenylephrine that did not contain the antioxidant, propyl gallate. The reader is referred to Dr. Zhang's original review for details of the results of the clinical pharmacology studies and discussion of the analytical assay for phenylephrine.

However, during the first review cycle, a site inspection was conducted by the Division of Scientific Investigations (DSI) for the clinical and analytical portions of the pivotal PK study, AQ-05-03 which identified major flaws for the analytical assay that quantified the total PE. As

noted, the applicant was required to either re-do the studies or re-analyze the samples from the original study (if available).

In regards to ibuprofen, compared to historical ibuprofen data, phenylephrine appeared to delay the T_{max} of ibuprofen by 0.6 hours, although AUC and C_{max} were comparable. The data suggest that under fed conditions, a clinical effect may be delayed (compared to ibuprofen alone). The applicant was also asked to address the delay in T_{max} in regards to clinical effect. Please see the clinical section below for a summary of the clinical review.

For the complete response, the applicant conducted 3 new PK studies (AQ-08-12, AQ-08-13, and AQ-06-08) to address the deficiencies communicated in the NA letter (see the clinical pharmacology review for details of each study). Study AQ-05-03 was previously reviewed in the original NDA review cycle (see Dr. Lei Zhang's Clinical Pharmacology review for NDA 22-112, April 28, 2008).

A site inspection was conducted by the Division of Scientific Investigations (DSI) for the clinical and analytical portions of the pivotal PK studies, Study AQ-08-12 and Study AQ-08-13 (see below for results; the studies were considered acceptable).

The data from Study AQ-08-12 suggested no formulation effect (see Tables 1 and 2, in appendix). Ninety percent (90%) confidence intervals (CIs) around the point estimates for AUC and C_{max} of IBU met the BE 80-125% criteria. The addition of phenylephrine appeared to delay T_{max} of ibuprofen by 0.5 hr (Table 1, Treatment A vs. Treatment C).

Study AQ-08-13 evaluated food effect and drug-drug interaction. Under fasted conditions, the test product met the BE 80-125% criteria for geometric mean ratios when compared to Motrin IB and Sudafed PE in terms of AUC and C_{max} (Table 3). Under fed conditions, the test product met the BE criteria (90% CI between 80-125) for IBU compared to Motrin IB for both AUC and C_{max}, and only for AUC and not for C_{max} for free PE when compared to Sudafed PE (Tables 3 and 4). The lower bound of the 90% confidence interval for free PE C_{max} was outside the lower limit for BE, 76.4% (Table 4). For IBU, the 90% CI for C_{max} (fed/fasted) was 79.8- 96.1% (Table 3). See also the clinical pharmacology review for more details.

For phenylephrine, the 90% CIs for AUCL and AUCI for the comparison of IBU+PE caplet under fed condition vs. fasted condition (B/A ratio) was within 80-125%; however, the geometric mean ratio and 90% CI for C_{max} (fed/fasted) was 77.8 (66.3- 91.3%) (Table 4).

Dr. Atul Bhattaram (pharmacometrics reviewer) conducted simulations (ibuprofen PK/PD model for analgesic model) to examine the potential impact of delayed T_{max} of IBU in combination with PE on clinical efficacy. Based on his analysis, the differences in T_{max} do not appear to result in clinically important differences in pain relief scores (see the clinical pharmacology review for details). Also the observed T_{max} of ibuprofen from the proposed IBU/PE formulation is in similar range to other approved IBU formulations (see also the clinical review by Dr. Shibuya).

The recommendation from the Clinical pharmacology reviewer was that the data was acceptable.

It should be noted that there does appear to be a food effect mainly regarding the C_{max} for PE (see tables 3 and 4 in the appendix). This is unlikely to have a clinically important effect for the following reasons: 1) the AUC remains bioequivalent even with food, and therefore the clinical benefit over the first day is not likely to be affected; 2) even PE alone shows a food effect and this single ingredient has not previously been labeled as such; there have not been any significant issues with efficacy related to a food effect for the single ingredient; 3) the food effect is determined using a somewhat artificially high fat meal, which is unlikely to be used with this product in many instances; 4) the PK parameters for the ibuprofen component are not impaired by food, and at least some of the effect on symptoms (albeit not necessarily on congestion) are likely to be contributed by the ibuprofen component of the product; the consumer will start to get relief, at least for some symptoms that are unaffected by food. Therefore, based on these reasons, I do not feel that labeling need address the potential effect of food on the C_{max} and therefore on efficacy.

6. Clinical Microbiology

Not relevant for this product.

7. Clinical/Statistical

7.1. General Discussion

No efficacy studies were submitted with this application as PE is being substituted for PSE. Both ingredients are GRASE and can be found in 21 CFR 341.

7.2. Efficacy

No efficacy studies were submitted. The only study was a PK study.

As part of the original review, the applicant was asked to address the issue of the delayed T_{max}, and whether this would have an impact on clinical efficacy. DNCE noted that the delay in T_{max} of 0.6 hours could be problematic because either time to pain relief would be delayed or consumers may take a second dose.

Dr. Shibuya in DAARP reviewed the information provided by the applicant. Wyeth submitted data comparing this product to several other marketed ibuprofen containing products. Dr. Shibuya notes "...in the context of the approved indication, headache and myalgia due to the common cold, we felt that it was unlikely that the observed small difference in T_{max} would be meaningful." He also commented that " We do not believe that the difference in T_{max} for the ibuprofen component is clinical meaningful."

7.3. Safety

7.3.1. Safety findings from submitted trials

No new safety information was submitted with this CR.

7.3.2. Post-marketing safety

Safety Update

Based on the spontaneous AE cases received both by FDA and by the Sponsor involving ingestion of both IBU and PHE, Dr. Hu concludes that no new safety-related issues were identified for Advil Congestion Relief and I agree with her assessment.

8. Advisory Committee Meeting

No Advisory Committee meeting was held for this submission. There was no new indication, no safety issues, and the ingredients are either previously well studied (ibuprofen) or appear in a monograph as GRASE (phenylephrine).

9. Other Regulatory Issues

9.1. Pediatrics

The applicant is requesting a waiver of pediatric studies for children less than 12 years of age, and labeling down to the age of 12 based on the monograph dosing for phenylephrine. This product is likely to be used in a substantial number of children ages 2-11. At this time, studies may be waived for children less than 2 years of age based on safety concerns (discussed extensively at the Advisory committee meeting on cough and cold products and use in children, held October 2007).

For children 2 to less than 12 years of age, the applicant makes the case that the combination does not represent a significant improvement in the treatment of colds etc., that it is not likely to be used in a substantial number of patients because a number of already approved and labeled over the counter products already exist, and that the dosing is not rational due to the different dosing intervals for ibuprofen and phenylephrine. Of these argument, the most compelling is that the dosing intervals are different. For example, for children under 12 years of age the dosing for ibuprofen is every 6 hours, while for phenylephrine it is every 4 hours. Therefore developing an age appropriate formulation would require developing a new dosing interval for one or both of the ingredients, and would require new PK and most likely, efficacy studies. It may also require developing a liquid formulation for younger children in this age range.

For children 12-17 years of age, the need for pediatric studies has been discussed extensively including within FDA. Based on the fact that the cough and cold monograph allows dosing down to 12, it would appear appropriate to label this product down to 12. This is based on the monograph for phenylephrine supporting dosing down to 12, the clinical data for ibuprofen supporting efficacy for children down to 12, and the PK data showing that there is no interaction between ibuprofen and phenylephrine that would affect the efficacy of each ingredient.

However, the applicant does propose to perform 2 studies in children 2-11 years of age, the first to be a single dose PK study and the second to be a single dose PK/PD study in children with the common cold, in which peak inspiratory nasal airflow as well as rating of severity of cold symptoms, will be measured. The applicant presented a timeline whereby all studies will be completed and submitted by November 2013.

A meeting with the PeRC was held on May 19, 2010 to consider the applicant's proposed studies. The PeRC recommended the following: for children less than 2 years of age, a waiver may be granted because of safety concerns when used in children of this age; for children 2 to 11 years of age, studies to include a dose ranging PK study for phenylephrine (with or without ibuprofen; these studies would identify the appropriate dosing interval for phenylephrine), as well as a clinical efficacy and safety study (short term for efficacy and collect safety data for proposed length of use) with appropriate clinical (symptom score) endpoints (to include children 6-12 first, followed by younger children as needed, although it may not be possible to study efficacy in younger children and extrapolation using PK data may be adequate). Any studies should not include normal children but should include children at risk or who are symptomatic. A waiver for 2-4 years old may be considered after additional data is obtained. For ages 12-17 the PeRC recommended a PK study to allow for extrapolation of efficacy from adults to adolescents. I do not agree with the recommendation for studies in 12-17 year old children for reasons discussed above related to the monograph for adults. There was also some discussion regarding the appropriate dosing interval for ibuprofen, although there did not appear to be a consensus on the need for PK studies to determine if the dosing interval for ibuprofen could be changed to every 4 hours in the under 12 age group.

Therefore, it seems appropriate to waive the studies for the ages 12-17, and to require, but defer (since the drug is ready for approval in adults) the studies proposed by the applicant for ages 2-11. Studies for less than 2 may also be waived because of safety concerns in this age group. PK and clinical studies should focus on identifying whether the phenylephrine dosing interval can match ibuprofen for children 2-<12 and allow the two ingredients to be combined in a drug product intended for this age range. See also Comments to be Conveyed to the Applicant (below).

Please also see the previous consult performed by Dr. Hari Sachs, that addresses some of these issues in detail.

10. Financial Disclosure

No new information provided in this CR.

11. Labeling

The amount of phenylephrine (10 mg) in each tablet exceeds monograph dosing for children < 12 years of age. The applicant requested that the label for this product state that the product should not be used by children under the age of 12. I agree with this

recommendation. However, PREA is triggered and the applicant will likely need to develop an age appropriate formulation (see section 9) if this product is eventually approved.

Appropriate language will be included in the label to address why dosing is not labeled for less than 12 at this time. The proposed language will express the following: Do not use under 12. There is too much medication for your child in this product. This was discussed with the division director and conveyed to the applicant. I agree with the DNRD labeling reviewer's comments.

(b) (4)
Additional DMEPA labeling comments provided to us on May 26, 2010, are addressed in the DNRD label review, and would not preclude approval.

12. DSI Audits

The reader is referred to the review by Dr. O'Shaughnessy for details of the DSI evaluation for the initial review cycle.

DSI conducted an audit of the clinical and analytical portions of the pivotal BE study (AQ-05-03) (b) (4) conducted the analytical portions of the study. DSI concludes that the bioanalytical method for total phenylephrine is flawed and the reported subject sample concentrations are not accurate. This conclusion was based on the findings of (b) (4) of incomplete hydrolysis of the PE-conjugates and instability of unconjugated PE under the conditions of hydrolysis. The inspection also found that the quality control samples used for the run acceptance were different from the subject samples, in that the quality controls were spiked with unconjugated PE only.

A Clinical Pharmacology Office level briefing for NDA 22-112 was held subsequently and the conclusions were that NDA 22-112 is not acceptable because the PK data for PE are not reliable. The recommendation by Dr. Zhang was that either a re-analysis of the stored PK samples be performed, or that a new PK study be performed using the TBM-formulation and the updated analytical methodology.

For the complete response, the applicant performed 3 additional PK studies AQ-08-12 and AQ-08-13, and AQ-06-08. Two of these study sites were inspected (-12 and -13). The DSI reviewer concludes that both studies are acceptable for Agency review.

13. Conclusions and Recommendations

13.1. Regulatory action

It is recommended that this product be approved.

13.1.1. Important issues (*resolved or outstanding*)

There are no outstanding issues except for PREA related issues (see below).

13.1.2. Required studies (*PREA; Subpart E/H/I approvals*)

PREA is triggered by this application. The applicant will need to develop an age appropriate formulation to cover the ages 2-12 years. However, I believe it is appropriate to approve the product down to the age of 12 (based on clinical data for ibuprofen and monograph dosing for phenylephrine).

13.2. Comments to be conveyed to the applicant

The following comments should be conveyed to the applicant:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application for ages 0 to 2 years for the temporary relief of common cold and flu symptoms because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric age group. FDA strongly recommends that over-the-counter (OTC) cough and cold products should not be used for infants and children under 2 years of age because serious and potentially life-threatening side effects could occur; they include death, convulsions, rapid heart rates, and decreased levels of consciousness.

We are deferring submission of your pediatric studies ages 2 years to less than 12 years for this application, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

Study 1.

You must conduct a PK trial in children 6 to <12 who may benefit from the drug rather than in otherwise healthy pediatric volunteers. You should conduct a single and multiple dose, dose ranging, PK trial that would evaluate the appropriate dosing interval based on pharmacokinetics, safety, and tolerability of phenylephrine in children. (b) (4)

[REDACTED]

Final Protocol Submission: April 2011
Final Study Report Submission: May 2012

Study 2.

You must conduct a randomized, double blind, placebo controlled clinical trial(s) in children 6 to <12 years of age to evaluate PD response and clinical symptoms response of phenylephrine for temporary relief of nasal decongestion associated with the common cold. This trial should evaluate clinical efficacy as well as safety of phenylephrine in this population, obtain data to support the appropriate dosing interval, and allow dosing to cover the expected period of clinical use (for example, up to 7 days). This study must include adequate representation of these age groups and be conducted in the target population, i.e. children with cough and cold symptoms.

Final Protocol Submission: September 2012
Final Study Report Submission: May 2014

Study 3

You must conduct a PK trial in children 2 to <6 who may benefit from the drug rather than in otherwise healthy pediatric volunteers. You should conduct a single and multiple dose, dose ranging, PK trial that would evaluate the appropriate dosing interval based on pharmacokinetics, safety, and tolerability of phenylephrine in children (b) (4)

Final Protocol Submission: April 2014
Final Study Report Submission: May 2015

Study 4

You must conduct a clinical trial(s) in children 2 to <6 years of age to evaluate PD response and clinical symptoms response of phenylephrine for temporary relief of nasal decongestion associated with the common cold. This trial should evaluate clinical efficacy as well as safety of phenylephrine in this population, define the appropriate dosing interval, and allow dosing to cover the expected period of clinical use. This study must include adequate representation of these age groups and be conducted in the target population, i.e. children with cough and cold symptoms.

Final Protocol Submission: September 2015
Final Study Report Submission: May 2017

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated “Required Pediatric Assessment(s)”.

This product is appropriately labeled for use in children ages 12 to less than 17 years for these indications. Therefore, no additional pediatric studies are needed in this age group.

Appendix

Table 1. Mean (SD) IBU Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-12).

	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C _{max} (mcg/mL)	T _{max} ** (hr)
Mean (SD)				
A (n=41)	72.7 (21.2)	74.0 (21.7)	19.6 (4.1)	2.0 (0.3-6.0)
B (n=41)	72.5 (19.6)	73.7 (19.9)	21.3 (5.8)	2.0 (0.5-4.0)
C (n=41)	75.7 (21.9)	77.0 (22.3)	22.2 (5.3)	1.5 (0.5-6.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/B*	99.7 (96.4-103.0)	99.6 (96.4-103.0)	93.8 (87.5-100.5)	—
A/C*	95.9 (92.8-99.2)	96.0 (92.8-99.2)	89.5 (83.5-95.9)	—

*: Reference product ^: Based on fitted log-transformed parameters.

** : Median (range)

A: IBU + PHE Caplet – Fasted

B: Motrin IB Tablet + Sudafed PE Tablet - Fasted

C: Advil-Fasted

Table 2: Mean (SD) Free PE Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-12)

	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C _{max} (pg/mL)	T _{max} ** (hr)
Mean (SD)				
A (n=41)	1018.8 (295.8)	1058.4 (303.5)	1139.7 (640.6)	0.5 (0.2-2.0)
B (n=41)	980.1 (249.9)	1016.1 (254.7)	1139.2 (580.1)	0.3 (0.2-2.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/B*	103.5 (97.2-110.3)	103.7 (97.5-110.4)	100.0 (87.3-114.6)	—

*: Reference product ^: Based on fitted log-transformed parameters.

** : Median (range)

A: IBU + PHE Caplet – Fasted

B: Motrin IB Tablet + Sudafed PE Tablet - Fasted

Table 3. Mean (SD) IBU Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-13)

	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max}** (hr)
Mean (SD)				
A (n=42)	76.1 (15.7)	77.2 (15.7)	21.2 (5.6)	2.0 (0.5-6.0)
B (n=42)	63.3 (11.2)	65.9 (11.5)	19.5 (7.3)	1.4 (0.5-4.0)
C (n=42)	75.7 (14.5)	76.7 (14.5)	23.3 (5.6)	1.6 (0.5-4.0)
D (n=42)	62.3 (10.4)	63.7 (10.5)	20.3 (8.1)	1.1 (0.3-4.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/C*	100.4 (97.8-103.2)	100.6 (98.0-103.2)	91.2 (83.1-103.2)	—
B/D*	101.3 (98.7-104.1)	103.2 (100.5-105.9)	96.0 (87.5-105.2)	—
B/A*	83.5 (81.3-85.8)	85.8 (83.6-88.0)	87.6 (79.8-96.1)	—

*: Reference product ^: Based on fitted log-transformed parameters.

** : Median (range)

A: IBU + PHE Caplet – Fasted

B: IBU + PHE Caplet – Fed

C: Motrin IB Tablet – Fasted

D: Motrin IB Tablet – Fed

Table 4. Mean (SD) Free PE Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-13)

	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max}** (hr)
Mean (SD)				
A (n=42)	754.2 (188.0)	790.1 (193.7)	822.0 (336.8)	0.5 (0.2-0.8)
B (n=42)	824.8 (211.9)	854.6 (218.5)	695.1 (352.3)	0.8 (0.3-3.0)
E (n=42)	716.0 (196.3)	753.3 (200.1)	867.7 (560.8)	0.3 (0.2-1.0)
F (n=42)	828.9 (216.6)	864.8 (235.3)	819.4 (522.9)	0.7 (0.3-4.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/E*	106.7 (102.4-111.2)	106.2 (101.9-110.8)	100.9 (86.0-118.4)	—
B/F*	99.6 (95.5-103.8)	99.1 (95.1-103.3)	89.7 (76.4-105.3)	—
B/A*	108.2 (103.9-112.8)	107.0 (102.6-111.5)	77.8 (66.3-91.3)	—

*: Reference product ^: Based on fitted log-transformed parameters.

** : Median (range)

A: IBU + PHE Caplet – Fasted

B: IBU + PHE Caplet – Fed

E: Sudafed PE Tablet – Fasted

F: Sudafed PE Tablet – Fed

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22565

ORIG-1

WYETH
CONSUMER
HEALTHCARE

ADVIL COLD & SINUS
PE(IBUPROFEN 200MG/PH

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

/s/

JOEL SCHIFFENBAUER
05/27/2010