CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-565

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
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Clinical Team Leader Memo

To:	NDA 22-565 Advil Cold & Sinus PE caplets
From:	Robert B. Shibuya, M.D., Clinical Team Leader Division of Anesthesia, Analgesia, and Rheumatology Products
Through:	Sharon Hertz, M.D., Deputy Director Division of Anesthesia, Analgesia, and Rheumatology Products
Submission date:	28 July 2009
Date:	13 January 2010

Background

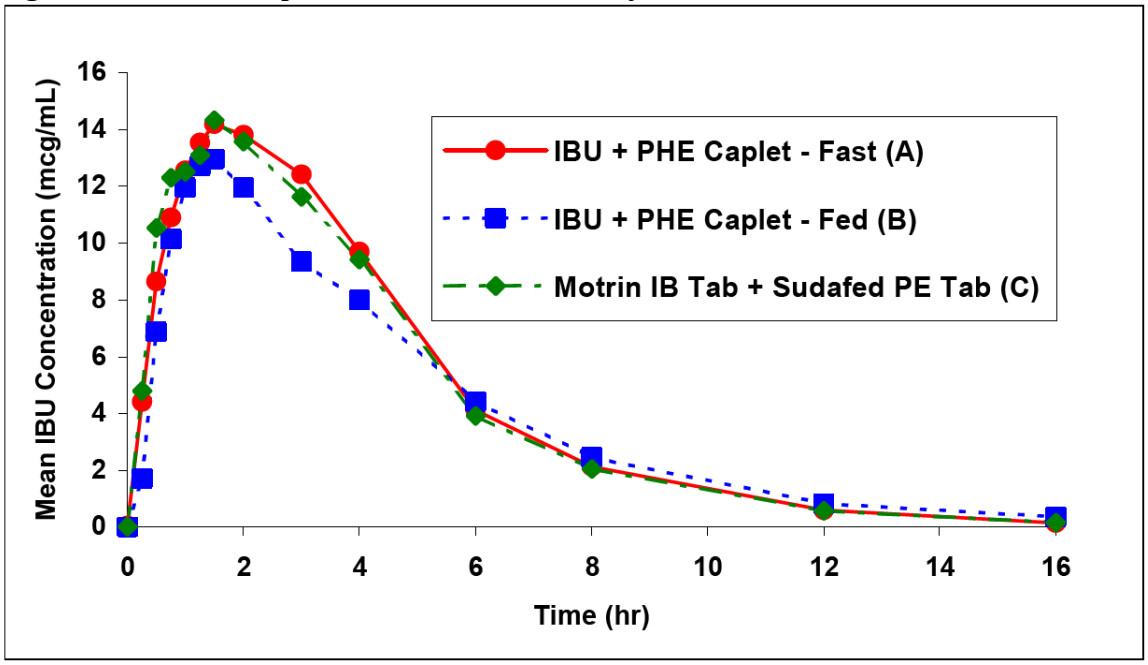
Advil Cold & Sinus PE (ACSPE) is a combination drug consisting of ibuprofen 200 mg/ phenylephrine 10 mg. There are similar approved products [Advil Cold & Sinus, NDAs 19-771, 21-373, 21-374 (solid oral dosage form, suspension, liquid-filled capsule)] that contain 30 mg of pseudoephedrine (PSE) instead of the 10 mg of phenylephrine (PE). The indications for the product include temporary relief of symptoms associated with the common cold, or flu including headache, fever, sinus pressure, minor aches and pains, and nasal congestion in adults and children ages 12 years and older.

ACSPE was developed in response to the Combat Methamphetamine Epidemic Act of 2005. The Agency has been accepting a bioequivalence approach to support approval of new formulations that substitute pseudoephedrine with phenylephrine.

Regulatory History:

In July 2007, the Sponsor submitted NDA 22-112 that included a single pharmacokinetic study (Study AQ-05-03) to support the approval of the reformulated drug. Figure 1 and Table 1 show the key data for the ibuprofen component.

Figure 1: Mean IBU plasma concentration, Study AQ-05-03



Source: NDA 21-112, CSR for Study AQ-05-03, p 30/132 of pdf

Table 1: Summary PK data, Study AQ-05-03

	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max} (h)
Mean (SD)				
Treatment A (n=38)	72.16 (18.45)	73.33 (18.73)	19.96 (4.70)	1.92 (1.00)
Treatment B (n=36)	65.78 (17.42)	68.25 (18.59)	16.77 (4.75)	1.73 (1.12)
Treatment C (n=39)	70.77 (20.36)	71.92 (20.60)	19.97 (4.99)	1.80 (1.11)
Ratio (90% Confidence Intervals)^				
B/A* %	91.16 (87.81-94.64)	92.98 (89.51-96.58)	81.18 (73.97-89.10)	—
A/C* %	103.44 (99.76-107.27)	103.37 (99.63-107.25)	102.22 (93.40-111.87)	—

*: Reference product ^: Based on fitted log-transformed parameters.
A: IBU + PHE Caplet – Fasted
B: IBU + PHE Caplet – Fed
C: Motrin IB Tablet + Sudafed PE Tablet

Source: NDA 21-112, CSR for Study AQ-05-03, p 34/132 of pdf

While, in Study AQ-05-03, the Tmax appeared to be similar for the reformulated product and the reference ibuprofen-containing product (Motrin IB), the Division of Nonprescription Clinical Evaluation (DNCE) observed that the Tmax was prolonged compared to historical data from ibuprofen-containing products.

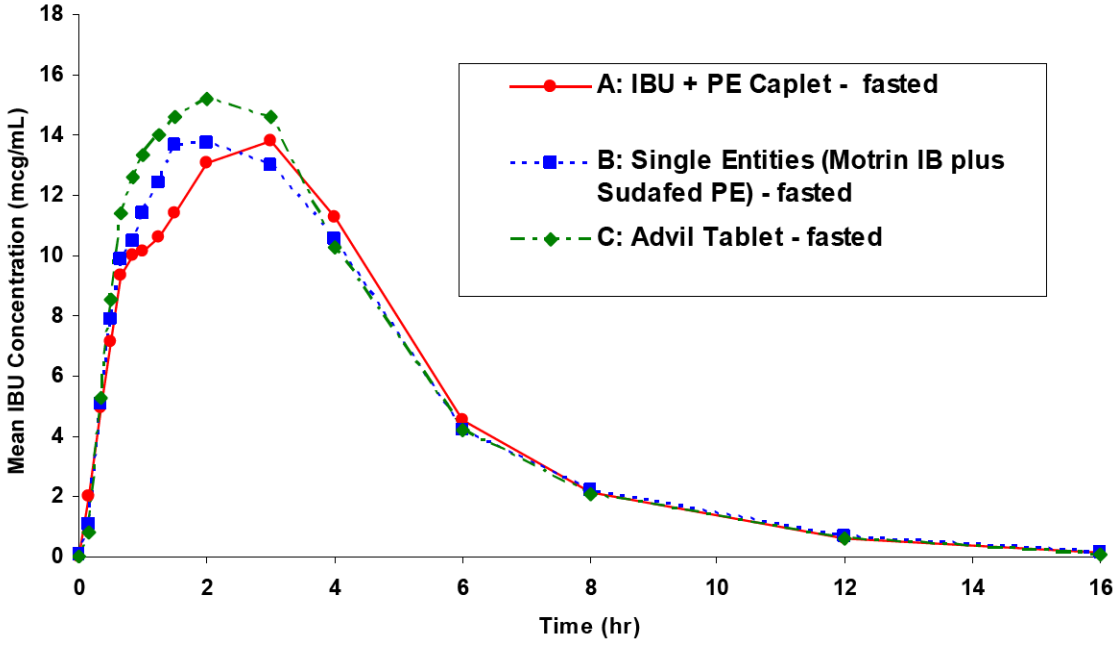
On 7 May 2008, DNCE issued a Non-Approvable letter for NDA 21-112. The deficiencies noted in the letter included:

1. The PK data for the phenylephrine component were unreliable due to flawed analytical methodology.
2. Comparing the PK data for the ibuprofen component of the study drug to historical ibuprofen PK data show an increase in mean Tmax values of ~0.6 hour.

Wyeth addressed the analytical issue and conducted two other bioequivalance studies, AQ-08-12 and AQ-08-13, which were submitted to the IND (63,798) and NDA 22-565.

Key data for the ibuprofen component are summarized in Figures 2 and 3 and Tables 2 and 3. ACSPE meets the bioequivalence standards for both ibuprofen and phenylephrine components.

Figure 2: Ibuprofen plasma concentrations vs. time, Study AQ-08-12



Source: NDA 22-565, Synopsis for Study AQ-08-12, p 7/8 of pdf

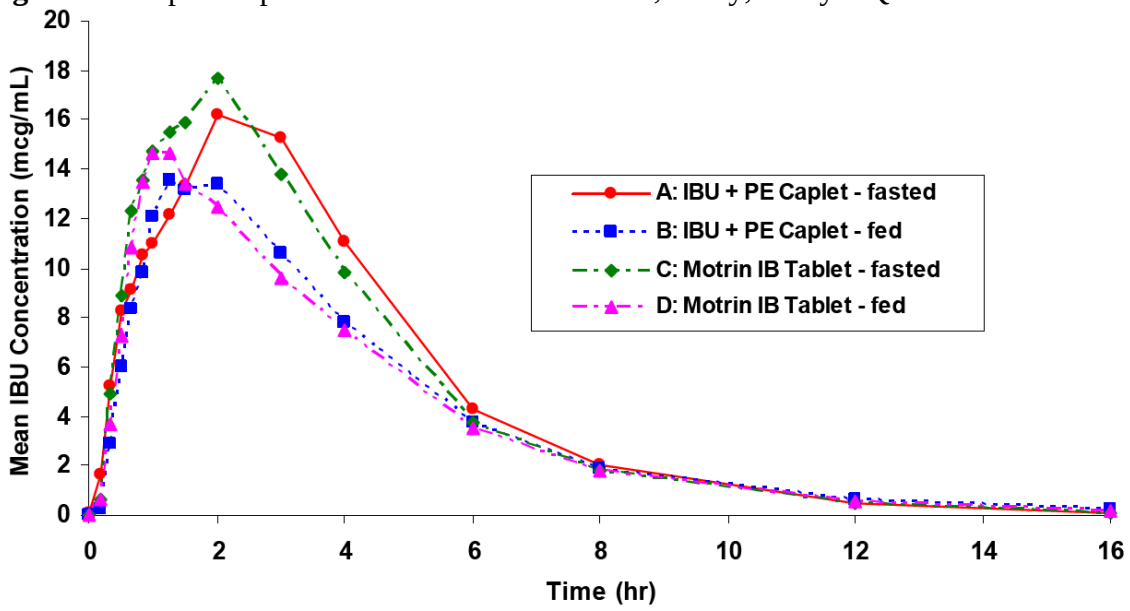
Table 2: Summary ibuprofen data, Study AQ-08-12

Treatment	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
A	72.7 (21.2)	74.0 (21.7)	19.6 (4.1)	145.5 (74.1)	2.0 (0.4)
B	72.5 (19.6)	73.7 (19.9)	21.3 (5.8)	127.0 (67.4)	2.1 (0.5)
C	75.7 (21.9)	77.0 (22.3)	22.2 (5.3)	116.0 (67.9)	2.0 (0.3)
Ratio (90% CI) ^					
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.
A: IBU+PE Caplet – fasted; B: Single Entities (Motrin IB Tablet plus Sudafed PE Tablet administered concomitantly) – fasted; C: Advil Tablet

Source: NDA 22-565, Synopsis for Study AQ-08-12, p 5/8 of pdf

Figure 3: Ibuprofen plasma concentrations vs. time, Study, Study AQ-08-13



Source: NDA 22-565, Synopsis for Study AQ-08-13, p 9/10 of pdf

Table 3: Summary ibuprofen data, Study AQ-08-13

Treatment	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
IBU/PE caplet – fasted (A)#	76.1 (15.7)	77.2 (15.7)	21.2 (5.6)	131.4 (62.6)	2.0 (0.3)
IBU/PE caplet – fed (B)	63.3 (11.2)	65.9 (11.5)	19.5 (7.3)	97.5 (56.2)	2.8 (2.3)
Motrin IB tablet – fasted (C)	75.7 (14.5)	76.7 (14.5)	23.3 (5.6)	99.8 (48.8)	2.0 (0.3)
Motrin IB tablet – fed (D)	62.3 (10.4)	63.7 (10.5)	20.3 (8.1)	92.5 (62.6)	2.2 (0.6)
Ratio (90% CI) ^					
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)	—	—

Source: NDA 22-565, Synopsis for Study AQ-08-13, p 5/10 of pdf

The data from Studies AQ-08-12 and AQ-08-13 show that the Tmax for ibuprofen is delayed by approximately 0.6 hours compared to the reference product (Motrin IB).

DNCE felt that the delay in Tmax could be problematic because patients may become impatient waiting for the onset of analgesia and asked Wyeth either to conduct a clinical study to address the onset of action or to provide a scientific rationale to support the notion that the observed delay in Tmax would not be clinically significant.

In March of 2009, Wyeth submitted a rationale, comparing ACSPE to several other marketed ibuprofen-containing products, as well as a protocol to address this issue for Special Protocol Assessment. The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) was consulted. After qualitatively assessing the concentration-time curves for ibuprofen in Studies AQ-08-12 and AQ-08-13, we noted that, 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 Tmax would be meaningful.

On 23 April 2009, DNCE issued a SPA No Agreement Letter, releasing Wyeth from conducting a clinical trial to address this issue. DNCE wrote, "…based on the additional pharmacokinetic information submitted along with your protocol, we have determined that a clinical trial is not necessary to address the Division's concerns regarding the clinical implications of the delay in Tmax of the ibuprofen component of your product."

Labeling recommendations:

DAARP has no labeling recommendations.

Recommendation:

We do not believe that the difference in Tmax for the ibuprofen component is clinically meaningful. Therefore, pending confirmation that Wyeth has met the bioequivalence criteria from the Clinical Pharmacology team from DNCE, we recommend Approval.

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/

ROBERT B SHIBUYA
01/25/2010

SHARON H HERTZ
01/25/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-565
Priority or Standard	S
Submit Date(s)	July 28, 2009
Received Date(s)	July 30, 2009
PDUFA Goal Date	January 28, 2009
Division / Office	DNCE/ONP
Reviewer Name(s)	Linda Hu, MD
Review Completion Date	December 17, 2009
Established Name	Ibuprofen 200mg /phenylephrine 10mg
(Proposed) Trade Name	Advil Cold & Sinus PE Caplets
Therapeutic Class	Analgesic/decongestant
Applicant	Wyeth Consumer Healthcare
Formulation(s)	Caplet
Dosing Regimen	one caplet every 4 hours, up to six per day
Indication(s)	Temporary relief of cold or flu symptoms
Intended Population(s)	Adults and children 12 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval for OTC marketing is recommended for Advil Cold & Sinus PE. The proposed indication, for adults and children aged 12 and above, is:

- temporarily relieves these symptoms associated with the common cold or flu:
  - headache • fever • sinus pressure
  - nasal congestion • minor aches and pains.
- reduces swelling of the nasal passages
- temporarily restores freer breathing through the nose

A new label warning is needed, not to take the combination product with food, because of reduced serum drug levels under fed versus fasted conditions.

1.2 Risk Benefit Assessment

Analgesic/decongestant combination products are allowed under the cough/cold combination monograph, but not with ibuprofen as the analgesic, as ibuprofen is not a monograph ingredient. The proposed combination of ibuprofen 200 mg/ phenylephrine 10 mg has an acceptable safety profile for OTC marketing. While this combination has not previously been marketed, the individual ingredients have been marketed OTC for a significant time and extent as either an NDA single ingredient product (ibuprofen) or a monograph single ingredient product (phenylephrine). Consumers can purchase these products separately and take them together. Both ingredients are also marketed in combination with other ingredients such as antihistamines, and phenylephrine is marketed with other analgesics.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

Wyeth Consumer Healthcare (WCH) is submitting this new NDA for a drug combination product, containing phenylephrine HCl 10 mg as the nasal decongestant and ibuprofen 200 mg, under the trade name Advil Cold & Sinus PE. WCH currently markets ibuprofen 200 mg/pseudoephedrine HCl 30 mg as a combination pain reliever/fever reducer and nasal decongestant under the trade name Advil Cold & Sinus caplets (NDA 19-771). Although the

latter product was approved for over-the-counter (OTC) use, it (as well as all pseudoephedrine-containing drug products) was moved behind the counter, in compliance with The Combat Methamphetamine Epidemic Act of 2005. WCH was advised by the Agency that phenylephrine could be substituted for pseudoephedrine in this combination product as long as pharmacokinetic studies demonstrate noninterference. In 2005, the FDA's policy was not to request any additional safety or efficacy data as long as pharmacokinetics of the new formulation was comparable to that of the single ingredients. This product is submitted in order to reestablish an OTC option for the consumer.

2.1 Product Information

Ibuprofen (IBU), a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID). In drug products combined with a nasal decongestant, its indications include temporary relief of symptoms associated with the common cold or flu, such as headache, fever, sinus pressure and minor body aches and pains. Like all NSAIDs, ibuprofen has analgesic, antipyretic, and anti-inflammatory properties. Ibuprofen was first approved for prescription use in 1969, and for OTC use in the UK and US in 1983 and 1984, respectively. Since then, it has become widely used for the temporary relief of acute pain and fever. Ibuprofen is an OTC ingredient that is labeled down to the age of 6 months for pain and fever. The chemical structure is shown in Figure 1, and the molecular formula is $C_{13}H_{18}O_2$

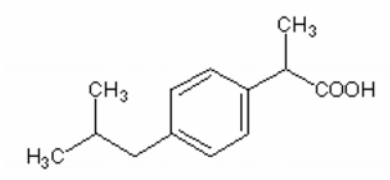

Figure 1. Ibuprofen

Phenylephrine (PE) is a sympathomimetic amine that acts predominantly by a direct effect on α-adrenergic receptors. In therapeutic doses, the drug has no substantial stimulant effect on the β-adrenergic receptors of the heart (β1) and does not stimulate β-adrenergic receptors of the bronchi or peripheral blood vessels (β2). It is believed that α-adrenergic effects result from the inhibition of the production of cyclic adenosine-3′,5′-monophosphate by inhibition of the enzyme adenyl cyclase. Phenylephrine is an oral nasal decongestant in the Final Monograph of Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (21 CFR 341.20). Phenylephrine hydrochloride has been available for use as an OTC nasal decongestant since the early 1960s. Phenylephrine is labeled in the monograph down to the age of 2. The chemical structure is shown in Figure 2, and the molecular formula is $C_9H_{13}NO_2 \cdot HCl$.

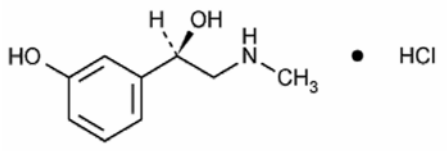

Figure 2. Phenylephrine

The reformulated Advil Cold & Sinus PE product contains 200 mg ibuprofen and 10 mg phenylephrine HCl per caplet. The amount of IBU and PE in a single caplet was selected to

provide the recommended amount of each active ingredient when administered at a 4-hour dosing interval with a 6-tablet daily maximum. For IBU, OTC labeling permits 200 mg every four hours with a 1200 mg daily maximum. For PE, the OTC monograph dose is 10 mg every four hours with a daily maximum of 60 mg.

2.2 Tables of Currently Available Treatments for Proposed Indications

The Advil Cold & Sinus product (NDA 19-771) contains ibuprofen 200 mg and pseudoephedrine HCl 30 mg and is available OTC, although as a pseudoephedrine-containing drug product; it has been moved behind the counter pursuant to The Combat Methamphetamine Epidemic Act of 2005. The proposed product has similar indications as the currently marketed product Advil Cold & Sinus, albeit with a different decongestant ingredient. The same ingredients and dosages as the present product (ibuprofen 200 mg and phenylephrine 10 mg) are available OTC as single ingredient products and can be taken together. OTC analgesic and decongestant combination products are allowed by the monograph and are available, but other combination products with the same ingredients as Advil Cold & Sinus PE are not available at the time of this review.

2.3 Availability of Proposed Active Ingredient in the United States

The Sponsor does not market a combination product containing ibuprofen and phenylephrine HCl anywhere in the world. Additionally the Sponsor states that the proposed combination is not marketed commercially anywhere by any sponsor. Ibuprofen single ingredient products are available OTC, as are single ingredient phenylephrine products.

2.4 Important Safety Issues With Consideration to Related Drugs

See Section 7 for review of safety issues. Use of ibuprofen at higher than recommended OTC doses, or for longer than recommended, leads to increased risk of GI bleeds. In addition, cardiovascular risks of NSAIDs have also become a concern. In February, 2005, the European Medicines Agency imposed strengthened warnings on coxibs, stating that they should not be used in patients with coronary heart disease or who have had a stroke, and that they should be used with caution in patients at risk for heart disease. The FDA announced changes in NSAID marketing on April 7, 2005, whereby a black box warning was thereafter required for celecoxib, and strengthened warnings were required for all NSAIDs (including nonselective NSAIDs) to highlight increased risks for cardiovascular events as well as gastrointestinal bleeding. The agency believes the overall benefit versus risk profile for the non-prescription NSAIDs remains favorable when they are used according to the labeled directions. (Jenkins and Seligman, April 6, 2005 FDA memo). To further encourage the safe use of the non-prescription NSAIDs, the agency requested revisions to product labeling to include more specific information about the potential CV and GI risks ("this product … may cause severe stomach bleeding [and] the chance is higher if you take more or for longer than directed"; "the risk of heart attack or stroke may increase if you use more than directed or for longer than directed").

Phenylephrine is a sympathomimetic and is listed as a decongestant in the Final Monograph of cold, cough, allergy, bronchodilator, and antiasthmatic drug products. All drug products

containing a related sympathomimetic drug, pseudoephedrine, were moved behind the counter in compliance with The Combat Methamphetamine Epidemic Act of 2005 because of diversion to illicit drug manufacturing.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The 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 reformulation results from government and retailer actions to comply with The Combat Methamphetamine Epidemic Act of 2005.

The Sponsor stated, in a meeting held on 3/19/07, that the formulation of Advil Cold & Sinus PE would be ibuprofen 200mg/phenylephrine 10mg.

NDA 22-112 for the ibuprofen 200 mg/ PE 10 mg formulation was submitted on July 9, 2007, and a Not Approvable Letter was issued by the FDA on May 7, 2008. The pivotal pharmacokinetic (PK) trial AQ-05-03, whose results were used to demonstrate bioequivalence to single ingredient PE, was found to have employed a flawed methodology. The Agency recommended that the Sponsor submit PK data using an adequately validated assay for quantifying unmetabolized (free) PE in plasma. Additionally, the Agency requested that Sponsor address the potential impact on clinical efficacy of delayed IBU Tmax in the presence of PE and lower IBU Cmax under fed conditions. The Sponsor submitted the present NDA 22-565 in response to the Not Approvable Letter. As recommended and agreed due to administrative issues, Wyeth is submitting this response to the NAL under a new NDA number identified as NDA 22-565.

In response, WCH conducted two PK studies, AQ-08-12 and AQ-08-13, using the final formulation. These two studies investigated drug interactions, formulation effects and food effects. A new assay that measures free PE was employed in these two studies. In addition, samples were also assayed for total PE using a revised total PE assay. This revised assay was different from the one used in studies AQ-05-03 and AQ-06-08.

2.6 Other Relevant Background Information

Citizen's Petition: Pediatric Use of Cold/Cough Drugs
An Advisory Committee meeting was held on October 18 and 19, 2007 to discuss the use of cough and cold drugs (including phenylephrine) in pediatric age groups (0 to 6 years) in response to a Citizen Petition. The Committee recommended that cough and cold products should not be used below 2 years of age either as single ingredients or in combination. The Committee recommended assessing the clinical safety and efficacy of ingredients used in cough and cold products, including pharmacokinetic studies in the 2 to 6 year age group. The Committee did not address use of cough and cold products in the 6 to 12 year age group. Since then, most of the manufacturers have voluntarily relabeled their OTC pediatric drug products to recommend not to use below 4 years of age, even though the Final Monograph allowing dosing down to 2 years has not been changed.

Citizen's Petition: Efficacy of Phenylephrine
A Citizen's Petition was submitted, questioning the efficacy of 10 mg phenylephrine as a decongestant and recommending higher doses. This issue was discussed in the Nonprescription Drug Advisory Committee (NDAC) meeting in December, 2007. The NDAC recommended that the 10 mg phenylephrine dose should remain on the market, given evidence of efficacy for the 10 mg dose, but also recommended efficacy in subpopulations be examined and that higher doses be studied.

WCH initially conducted study AQ-05-03 to support this product (NDA 22-112). Subsequent to completing study AQ-05-03, WCH discovered through routine formula optimization activities that the addition of an antioxidant (b) (4) 0.25% propyl gallate (PG), (b) (4) an (b) (4) degradant (b) (4) below that of the ICH threshold (0.5%). Accordingly, WCH then conducted PK study, AQ-06-08, designed as a bridge between the IBU/PE formula studied in AQ-05-03 and the formula intended for commercialization. The difference between the two formulas involved the addition of PG. In study AQ-06-08, the two products were bioequivalent for IBU with a T_{max} of 1.60 and 1.66 hours, for the non-PG and PG formulations, respectively. The PE results were considered flawed because of a methodological issue with the assay. The flawed assay measured total PE (conjugated plus unconjugated PE) and was used in studies AQ-05-03 and AQ-06-08.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A DSI inspection was ordered for this NDA.

3.2 Compliance with Good Clinical Practices

The clinical studies were conducted under the sponsorship of the applicant and its affiliates and were reviewed and approved by Independent Ethics Committees and Institutional Review Boards. The studies were conducted in accordance with the principles of Good Clinical Practices.

3.3 Financial Disclosures

The sponsor submitted Form 3454 certifying that the investigators lacked any significant financial interest in this product or significant equity in the Sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry review is pending.

4.2 Clinical Microbiology

NA

4.3 Preclinical Pharmacology/Toxicology

See Dr. Harrouk's review under NDA 22-112 during the initial review cycle of this product.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

See 2.1

4.4.2 Pharmacodynamics

The clinical pharmacology review is pending.

4.4.3 Pharmacokinetics

The present submission includes two PK trials AQ-08-12 and AQ-08-13, which studied drug interactions, formulation effects and food effects. Summaries of the results of these studies as presented by the sponsor follow. The clinical pharmacology review is pending at this time. Refer to the clinical pharmacology review for a detailed analysis.

I. Study AQ-08-12 A Three-Way Crossover, Formulation Effect and Drug Interaction, Bioavailability Study Of A Caplet Formulation Of Ibuprofen 200 MG And Phenylephrine Hydrochloride 10 MG

Study Design:
This was a 16-hour, single-center, randomized, open-label, single-dose, 3-way crossover study of normal volunteers. Each treatment was separated by 48 hours. The treatment groups in this study were selected to investigate whether the IBU/PE 200/10 mg combination caplet is subject to any formulation effects or drug interaction effects. Subjects received a single dose of one of the following treatments during each of the three treatment periods:
• **Treatment A:** one Advil Cold & Sinus caplet containing IBU 200 mg and PE 10 mg administered under fasted conditions.
• **Treatment B:** one Motrin IB tablet (IBU 200 mg/tablet) plus one Sudafed PE tablet (PE 10 mg/tablet) administered concomitantly under fasted conditions
• **Treatment C:** one Advil tablet (IBU 200 mg/tablet) administered under fasted conditions.

OBJECTIVES:
• To characterize the rate and extent of absorption of ibuprofen (IBU) and phenylephrine (PE) from a caplet containing IBU 200 mg and PE 10 mg compared to currently marketed IBU (Motrin IB) 200 mg and currently marketed PE (Sudafed PE) 10 mg single entity products administered concomitantly.
• To characterize the rate and extent of absorption of IBU from a caplet containing IBU 200 mg and PE 10 mg compared to a currently marketed IBU (Advil) 200 mg single entity product administered alone.

Inclusion Criteria
Subjects were eligible for inclusion in the study provided they met all of the following criteria:
a. Healthy male and female volunteer subjects between 18-45 years of age with a body mass index (BMI) of 18 – 29;
b. Females of child-bearing potential and those who were post-menopausal for less than 2 years must have been using a reliable method of contraception;
c. Subjects agreed to refrain from ingesting any medication, central nervous system stimulants, nutritional supplements, weight loss and energy drinks, herbal teas, and herbal supplements for 14 days prior to and during the study period; any caffeine/xanthine-containing product for 24 hours prior to and during the study period; and alcohol for 3 days prior to and during the study period. (Note: Contraceptives, vitamins, and mineral supplements were allowed.);

Exclusion Criteria

Subjects were excluded from participating in the study if any of the following were noted:

a. Presence of any condition or a history of any significant hepatic, renal, endocrine, cardiovascular, neurological, psychiatric, gastrointestinal, pulmonary, hematologic, or metabolic disorder felt by the Principal Investigator to place the subject at increased risk;
b. Presence or history of hypertension; diabetes mellitus, heart disease, peripheral vascular disease, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy;
c. History of alcohol abuse (*i.e.,* consuming ≥3 alcoholic drinks/day on a regular basis) or substance abuse. (Note: One "drink" of alcohol is 1 oz. liquor, 6 oz. wine, or 12 oz. beer.);
d. Hypersensitivity to PE, PSE, IBU, aspirin, sympathomimetic drugs, central nervous system stimulants or any other nonsteroidal anti-inflammatory drug;
e. Concomitant use of monoamine oxidase inhibitors;
f. Any laboratory result outside of the normal range that is judged by the Principal Investigator to be clinically significant;
g. Subjects with any condition or history felt by the Principal Investigator to place the subject at increased risk;
h. Current smokers or subjects who had smoked or chewed a tobacco-containing substance or have used smoking cessation products within 6 months prior to the first treatment period. (Note: Smoking is defined as ≥3 episodes of smoking per week.);
i. Inability or unwillingness to comply with the requirements of the protocol as judged by the Principal Investigator;
j. Use of an investigational drug or participation in an investigational trial within 30 days prior to the first treatment period;
k. Participation in a PK trial or donation of blood or plasma:
l. Previous participation in the trial;
m. Members of the study site staff directly involved with the study, an employee of the Sponsor, or a relative of study site personnel directly involved with the study or Sponsor.

SUBJECT POPULATION:

Forty-two subjects (21 males and 21 females) were randomized. Subject No. 208 withdrew voluntarily before period two. As the subject did not provide data from at least two treatment periods, this subject was, per protocol, excluded from all PK analyses. The majority of subjects were white (95.2%) followed by Asian (2.4%) and Other (2.4%). The average age was 26.3 years.

PHARMACOKINETICS AND STATISTICAL METHODS:

The **primary** analysis was based on unconjugated (free) PE and IBU pharmacokinetic data of all eligible subjects. A secondary analysis was also performed on total PE. Subjects providing evaluable data for at least 2 treatment periods of the study were included in the respective PK and statistical analyses. Summary statistics based on those contributing to the statistical analysis were presented for plasma concentrations at each sampling time, and for all PK parameters.
The following comparisons were evaluated in this study:

- IBU + PE caplet – fasted (Treatment A) vs. Motrin IB tablet – fasted (Treatment B*)
- IBU + PE caplet – fasted (Treatment A) vs. Sudafed PE tablet – fasted (Treatment B*)
- IBU + PE caplet – fasted (Treatment A) vs. Advil tablet – fasted (Treatment C*)

* Reference treatment/formulation

SAFETY ASSESSMENT METHODS:

Adverse events (AE) were recorded as they occurred during the treatment phases of the study and if voluntarily reported by the subject within 15 days following the conclusion of the subject's participation in the study. Serious AEs (SAEs) were to be reported any time they occurred after the subject signed the informed consent.

PHARMACOKINETICS RESULTS:

The Sponsor's PK results on mean plasma ibuprofen are presented in Figure 3 and Table 1. The IBU/ PE combination caplet (A) was bioequivalent in terms of ibuprofen AUC and Cmax to Motrin IB and Sudafed PE given concomitantly (B) and to Advil alone (C) under fasted conditions.

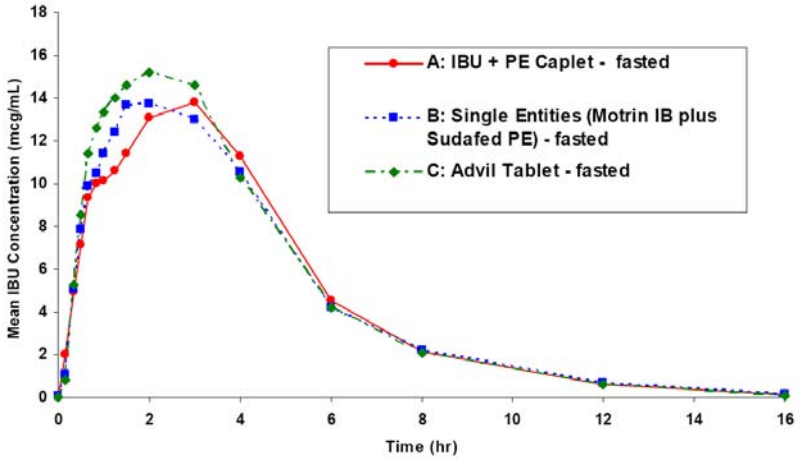

Figure 3. AQ-08-12 Mean IBU Plasma Concentration

Table 1. AQ-08-12 IBU Pharmacokinetic Results (N=41; Mean, SD, and 90% CIs)

Treatment	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
A	72.7 (21.2)	74.0 (21.7)	19.6 (4.1)	145.5 (74.1)	2.0 (0.4)
B	72.5 (19.6)	73.7 (19.9)	21.3 (5.8)	127.0 (67.4)	2.1 (0.5)
C	75.7 (21.9)	77.0 (22.3)	22.2 (5.3)	116.0 (67.9)	2.0 (0.3)
Ratio (90% CI) ^					
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.
A: IBU+PE Caplet – fasted; B: Single Entities (Motrin IB Tablet plus Sudafed PE Tablet administered concomitantly) – fasted; C: Advil Tablet

The Sponsor's PK results on free PE are presented in Figure 4 and Table 2. A secondary analysis was also performed on the results of the total PE assay. The PK results on total PE concentration are summarized in Table 3. The combination IBU/PE caplet was bioequivalent in terms of AUC and Cmax for free and total PE when compared to the concomitant administration of Motrin IB and Sudafed PE.

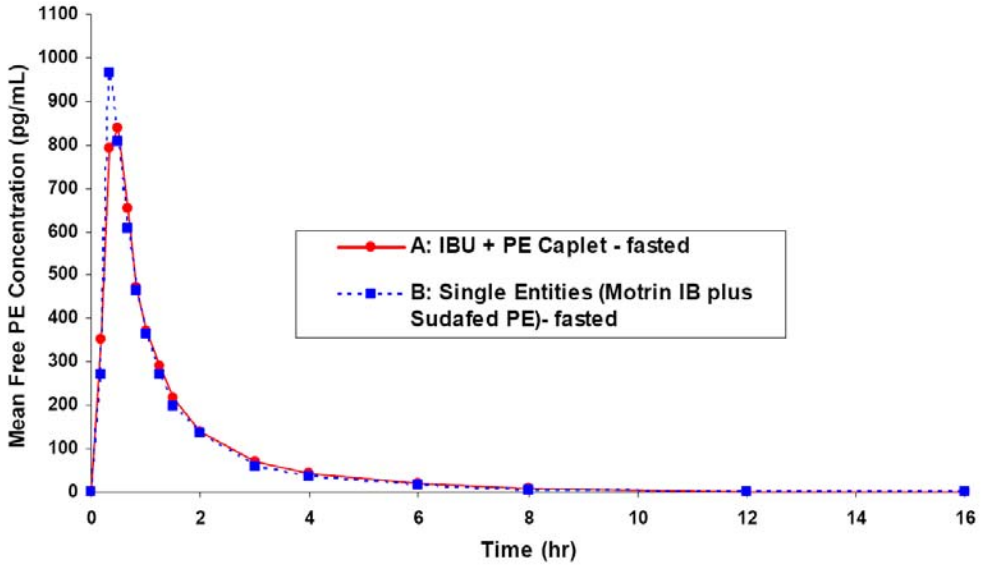

Figure 4. AQ-08-12 Mean Free PE Plasma Concentration

Table 2. AQ-08-12 Free PE Pharmacokinetic Results

(N=41; Mean, SD, and 90% CIs)

Treatment	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
A	1018.8 (295.8)	1058.4 (303.5)	1139.7 (640.6)	30.7 (18.4)	1.9 (1.0)
B	980.1 (249.9)	1016.1 (254.7)	1139.2 (580.1)	28.7 (17.6)	1.8 (0.7)
Ratio (90% CI) ^					
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
A: IBU+PE Caplet –fasted; B: Single Entities (Motrin IB Tablet plus Sudafed PE Tablet administered concomitantly) – fasted

Table 3. AQ-08-12 Summary of Results – Total PE Pharmacokinetic Results

(N=41; Mean, SD, and 90% CIs)s

Treatment	AUCL (ng•h/mL)	AUCI (ng•h/mL)	C_{max} (ng/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
A	847.4 (139.5)	855.4 (141.2)	250.5 (53.6)	70.6 (36.9)	2.4 (0.3)
B	853.8 (131.9)	862.1 (133.9)	262.4 (58.9)	61.9 (29.3)	2.4 (0.3)
Ratio (90% CI) ^					
A/B* %	99.2 (96.3-102.3)	99.2 (96.3-102.3)	95.6 (89.6-102.1)	-	-

* Reference product
^ Based on fitted log-transformed parameters.
A: IBU+PE Caplet –fasted; B: Single Entities (Motrin IB Tablet plus Sudafed PE Tablet administered concomitantly) – fasted

The Sponsor noted (see Table 4) that the IBU Tmax of the combination caplet was 23 minutes later than for Motrin IB when concomitantly administered with Sudafed PE (treatment B) and 30 minutes later than for Advil administered alone (treatment C). The 30 min (A/C) difference was statistically significant. The T_{ec10} time was also significantly longer for the combination caplet than for single ingredient ibuprofen (22 min, A/C comparison).

Table 4. AQ-08-12 ibuprofen times to reach plasma concentrations (pairwise difference point estimates)

95% CIs and P-values@ (n=41)

Treatment	T_{max} (min)	T_{ec6} (min)	T_{ec10} (min)
	Mean	**Median$**	**Median$**
A	145.5	29.1	75.0
B	127.0	30.3	62.3
C	116.0	27.0	43.6
Pairwise Difference Point Estimates^ (95% CI) and P-values@			
A – B* (95% CI) p-value@	22.5 (-5.0, 45.0) 0.169	-2.4 (-18.4, 17.3) 0.676	1.7 (-18.1, 23.1) 0.814
A – C* (95% CI) p-value@	30.0 (5.0, 57.5) 0.024	4.4 (-7.6, 17.9) 0.464	22.4 (2.6, 42.3) 0.025

^ Hodges-Lehman estimates; @ p-values from a non-parametric analysis (Wilcoxon Rank-Sum Test)
* Reference product
A: IBU+PE Caplet –fasted; B: Single Entities (Motrin IB Tablet plus Sudafed PE Tablet administered concomitantly) – fasted; C: Advil Tablet
$ Some subjects never attained T_{ec10} (see Table S.3). They were assigned a value of 16 hrs. Since the means are heavily influenced by these values, the medians are shown instead.

MO Comments: *Three subjects never achieved ibuprofen plasma levels as high as 10 mcg/mL, one subject in each treatment group. The Sponsor assigned values of 16 hr for these subjects, and made comparisons of median values for Tec10 and Tec6 instead of means (because the mean Tec10 is strongly affected by the assigned 16 hr values).*

The Sponsor cited Lemmens et al. 1996 in support of the 6.4 mcg/mL ibuprofen concentration estimated to yield 50% pain relief (EC50), and a second reference which cited Lee et al. 1985, in support of 10 mcg/mL ibuprofen concentration as the effective concentration for antipyresis in children. Lemmens et al. is a published abstract only, and Lee et al. do not report any efficacy data (the article discusses stereo selective metabolism and elimination of ibuprofen). The estimate of 6 to 10 mcg/mL for efficacy is not well documented in the literature submitted by the Sponsor. See more discussion on this subject at the end of this section of the review.

Gender Effect
After the adjustment for body weight, the only gender effect (at the 0.10 level) was for Vd in the analysis of free PE. In general, females had higher AUCL and C_{max} values.

Within both gender groups, the combination caplet was bioequivalent to the single entities group with respect to AUCL, indicating that the combination caplet had an equivalent extent of PE absorption based on the free PE assay, compared to single entities. For C_{max}, however, the combination caplet was bioequivalent to single entities among females but not males. Among male subjects, the mean C_{max} for the combination caplet (1133.5 pg/mL) was higher compared to the single entities group (1120.3 pg/mL), and the upper limit of the C_{max} 90% CI (130.8%) fell outside of the acceptable bioequivalence limits.

SAFETY RESULTS:

The safety results for Study AQ-08-12 are presented in section 7.0.

SUMMARY:

Under fasted conditions, the IBU/PE combination caplet was bioequivalent to the concomitant administration of Motrin IB and Sudafed PE for IBU and PE AUC and C_{max}. The combination was also bioequivalent for AUC and C_{max} to Advil 200 mg tablets administered alone. IBU T_{max} of the combination caplet was achieved 23 minutes later than for Motrin IB when concomitantly administered with Sudafed PE and 30 minutes later than for Advil administered alone.

II. Study AQ-08-13 A Six-Way Crossover, Food Effect/Drug Interaction, Bioavailability Study of a Caplet Formulation of Ibuprofen 200 mg and Phenylephrine Hydrochloride 10 mg

Overall Study Design and Plan Description
This was a single dose, randomized, open-label, 6-way crossover, inpatient study. Each treatment was separated by 48 hours. Forty-two (42) healthy male and female subjects were enrolled to ensure that approximately 36 subjects (approximately equal numbers of males and females)

would complete the study. The treatment groups in this study were selected to investigate whether the IBU/PE combination caplet is subject to any drug interactions and/or food effects. An authorized IRB approved the protocol and consent form prior to study initiation.

Subjects received a single dose of one of the following treatments during each of the six treatment periods:

- **Treatment A:** one Advil Cold & Sinus caplet containing IBU 200 mg and PE 10 mg administered under fasted conditions;
- **Treatment B:** one Advil Cold & Sinus caplet containing IBU 200 mg and PE 10 mg administered under fed conditions;
- **Treatment C:** one Motrin IB tablet (IBU 200 mg/tablet) administered under fasted conditions;
- **Treatment D:** one Motrin IB tablet (IBU 200 mg/tablet) administered under fed conditions;
- **Treatment E:** one Sudafed PE tablet (PE 10 mg/tablet) administered under fasted conditions;
- **Treatment F:** one Sudafed PE tablet (PE 10 mg/tablet) administered under fed conditions

For Treatments B, D and F, a standard high fat breakfast was consumed prior to dosing. For each treatment period, blood samples were collected over 16-hours. All samples were analyzed for racemic IBU, total and free (unconjugated) PE using validated assay methodology. Subjects were housed in the clinic from the evening before dosing until approximately 24 hours after the final dose of study medication in Treatment period VI. All adverse events that occurred during the study as well as any that were voluntarily reported by subjects within 15 days of completing the study were recorded.

OBJECTIVES:
The objectives of this study were:

- To characterize, under fasted conditions, the rate and extent of absorption of ibuprofen (IBU) from a caplet containing IBU 200 mg and PE 10 mg compared to a currently marketed IBU 200 mg single entity product administered alone.
- To characterize, under fasted conditions, the rate and extent of absorption of phenylephrine (PE) from a caplet containing IBU 200 mg and PE 10 mg compared to a currently marketed PE 10 mg single entity product administered alone.
- To characterize the rate and extent of absorption of IBU and PE from a caplet containing IBU 200 mg and PE 10 mg when administered under fed conditions compared to the rate and extent of absorption of IBU and PE administered individually under fed conditions.

Inclusion Criteria
Subjects were eligible for inclusion in the study provided they met all of the following criteria:

a. Male and female volunteer subjects between 18-45 years of age with a body mass index (BMI) of 18 – 29;
b. Normal physical health as judged by physical and laboratory examinations and a negative urine-based drugs of abuse screen;

c. Females were not pregnant, as verified by a serum-based pregnancy test, or breast-feeding;
d. Females of child-bearing potential and those who were post-menopausal for less than 2 years must have been using a reliable method of contraception;
e. Subjects agreed to refrain from ingesting any medication, nutritional supplements, weight loss and energy drinks, herbal teas, and herbal supplements for 14 days prior to and during the study period; any caffeine/xanthine-containing product for 24 hours prior to and during the study period; and alcohol for 3 days prior to and during the study period. (Note: Contraceptives, vitamins, and mineral supplements were allowed.);
f. The subject was capable of reading, comprehending, and signing the informed consent form.

Exclusion Criteria

Subjects were excluded from participating in the study for the following criteria:

a. Presence of any condition or a history of any significant hepatic, renal, endocrine, cardiovascular, neurological, psychiatric, gastrointestinal, pulmonary, hematologic, or metabolic disorder felt by the Principal Investigator to place the subject at increased risk;
b. Presence or history of hypertension; diabetes mellitus, heart disease, peripheral vascular disease, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy;
c. History of alcohol abuse (*i.e.,* consuming ≥3 alcoholic drinks/day on a regular basis) or substance abuse. (Note: One "drink" of alcohol is 1 oz liquor, 6 oz. wine, or 12 oz. beer.);
d. Hypersensitivity to PE, PSE, IBU, aspirin, sympathomimetic drugs, or any other nonsteroidal anti-inflammatory drug;
e. Concomitant use of monoamine oxidase inhibitors;
f. Any laboratory result outside of the normal range that is judged by the Principal Investigator to be clinically significant;
g. Subjects with any condition or history felt by the Principal Investigator to place the subject at increased risk;
h. Current smokers or subjects who had smoked or chewed a tobacco-containing substance or have used smoking cessation products within 6 months prior to the first treatment period. (Note: Smoking is defined as ≥3 episodes of smoking per week.);
i. Inability or unwillingness to comply with the requirements of the protocol as judged by the Principal Investigator;
j. Use of an investigational drug or participation in an investigational trial within 30 days prior to the first treatment period;
k. Participation in a PK trial or donation of blood or plasma:
l. Previous participation in the trial;
m. Members of the study site staff directly involved with the study, an employee of the Sponsor, or a relative of study site personnel directly involved with the study or Sponsor.

NUMBER OF PATIENTS (PLANNED, ENROLLED, ANALYZED):

Forty-two (42) subjects were enrolled, and 41 subjects completed the study. Subject 212 withdrew voluntarily at the 12-hour blood draw during period 5 due to a family emergency. However, this subject had plasma level data for at least two treatment periods and was eligible for inclusion in the pharmacokinetic analysis. Subject No. 109's free PE concentrations were all below the limit of quantitation in the period when Sudafed PE in the fed state was administered. Thus the free PE concentration data from this period was excluded from all PK analyses. The

data from all 42 enrolled subjects were included in all other data analyses, including safety analyses.

PHARMACOKINETICS AND STATISTICAL METHODS:
The primary analysis was based on unconjugated (free) PE and IBU pharmacokinetic data of all eligible subjects. A secondary analysis was also performed on total PE. Subjects providing evaluable data for at least 2 treatment periods of the study were included in the respective PK and statistical analyses. Summary statistics based on those contributing to the statistical analysis were presented for plasma concentrations at each sampling time, and for all PK parameters.

SAFETY ASSESSMENT METHODS: Adverse events (AE) were recorded as they occurred during the treatment phases of the study and if voluntarily reported by the subject within 15 days following the conclusion of the subject's participation in the study. Serious AEs (SAEs) were reported any time they occurred after the subject signed the informed consent.

PHARMACOKINETICS RESULTS:
The Sponsor's PK results on mean plasma ibuprofen concentrations are presented in Figure 5 and Table 5. The IBU/PE combination caplet (A) was bioequivalent in terms of ibuprofen AUC and Cmax to Motrin IB alone (C) under fasted conditions. The IBU/PE combination caplet under fed conditions (B)was also bioequivalent in terms of ibuprofen AUC and Cmax to Motrin IB alone under fed conditions (D). The IBU/PE combination caplet, under fed versus fasted conditions (A/B comparison), was bioequivalent in terms of AUC but not Cmax.

MO Comment: *The Cmax for ibuprofen under fed conditions was lower, by an insignificant amount (19.5 vs. 21.2 mcg/mL).*

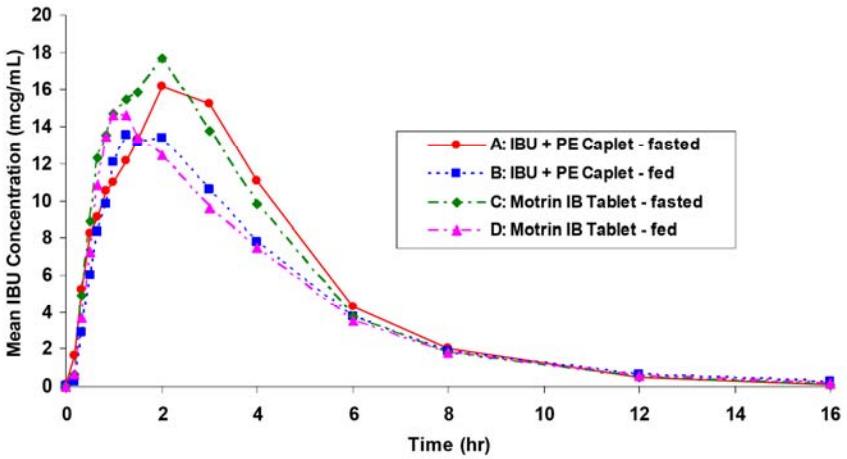

Figure 5. AQ-08-13 Mean IBU Plasma Concentration

Table 5. AQ-08-13 IBU Pharmacokinetic Results

(N=42; Mean, SD, and 90% CIs)

Treatment	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
IBU/PE caplet – fasted (A)#	76.1 (15.7)	77.2 (15.7)	21.2 (5.6)	131.4 (62.6)	2.0 (0.3)
IBU/PE caplet – fed (B)	63.3 (11.2)	65.9 (11.5)	19.5 (7.3)	97.5 (56.2)	2.8 (2.3)
Motrin IB tablet – fasted (C)	75.7 (14.5)	76.7 (14.5)	23.3 (5.6)	99.8 (48.8)	2.0 (0.3)
Motrin IB tablet – fed (D)	62.3 (10.4)	63.7 (10.5)	20.3 (8.1)	92.5 (62.6)	2.2 (0.6)
Ratio (90% CI) ^					
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.
# Subject No. 212 withdrew voluntarily before period 6. The treatment assigned for this period was A. Consequently, the summary statistics, ratio, and 90% CI for all PK parameters for treatment A were based on 41 subjects.

The Sponsor's PK results on free PE are presented in Figure 6 and Table 6. The PK results on total PE concentration are summarized in Figure 7 and Table 7. Under fasted conditions, the combination IBU/PE caplet (A) was bioequivalent in terms of AUC and Cmax for free and total PE when compared to the administration of Sudafed PE (E). The Sudafed PE row of Table 6 was corrected from the study synopsis (where it was incorrectly labeled (C)).

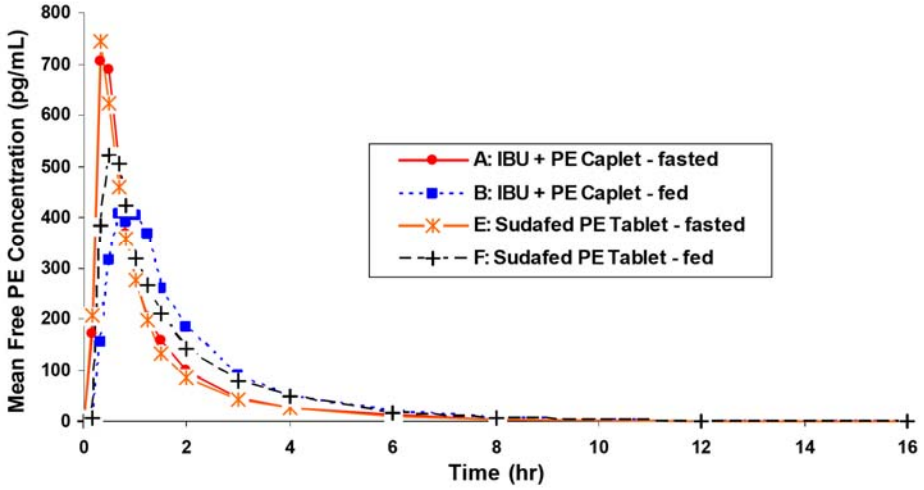

Figure 6. AQ-08-13 Mean free PE Plasma Concentration

Table 6. AQ-08-13 Free PE Pharmacokinetic Results

(N=42; Mean, SD, and 90% CIs)

Treatment	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
IBU/PE caplet – fasted (A)#	754.2 (188.0)	790.1 (193.7)	822.0 (336.8)	26.2 (7.3)	1.7 (1.1)
IBU/PE caplet –fed (B)	824.8 (211.9)	854.6 (218.5)	695.1 (352.3)	67.0 (43.0)	1.4 (0.9)
Sudafed PE tablet – fasted (E)	716.0 (196.3)	753.3 (200.1)	867.7 (560.8)	26.5 (11.9)	1.8 (1.2)
Sudafed PE tablet – fed (F)@	828.9 (216.6)	864.8 (235.3)	819.4 (522.9)	60.6 (49.3)	1.6 (1.1)
Ratio (90% CI) ^					
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.
Subject No. 212 withdrew voluntarily before period 6. The treatment assigned for this period was A. Consequently, the summary statistics, ratio, and 90% CI for all PK parameters for treatment A were based on 41 subjects.
@: Subject No. 109's concentrations for treatment F were all below the limit of quantitation and were deemed unevaluable. Consequently the summary statistics, ratios and 90% CI, for treatment F were based on 41 subjects.

Under fed conditions, the IBU/PE combination caplet (B) was bioequivalent in terms of free PE AUC to Sudafed PE given alone (F), although Cmax was too low for the combination (Table 6). The lower CI for Cmax (76.4%) was outside the boundary of the pre-specified limits. The IBU/PE combination caplet, under fed versus fasted conditions (B/A), was bioequivalent for free PE AUC, but not Cmax whose lower bound was 66.3%.

A secondary analysis was also performed on the results of the total PE assay. For total PE, the IBU/PE combination caplet was bioequivalent to Sudafed PE given alone for the comparisons A/E under fasted conditions and B/F under fed conditions (Figure 7 and Table 7). Unlike the results seen in free PE, the combination caplet administered under fed conditions was bioequivalent to the caplet administered under fasted conditions (B/A).

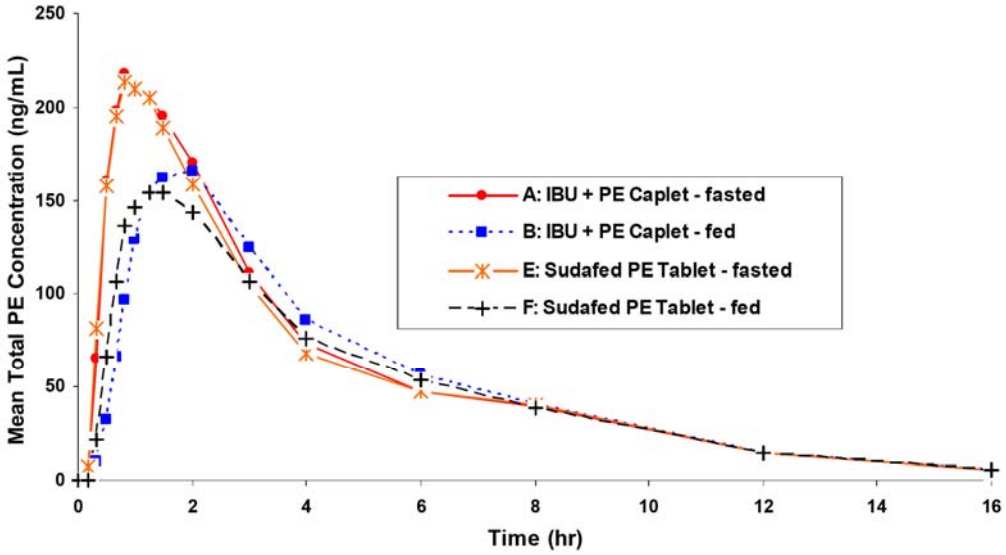

Figure 7. AQ-08-13 Mean Total PE Plasma Concentration

Table 7. AQ-08-13 Total PE Pharmacokinetic Results
(N=42; Mean, SD, and 90% CIs)

Treatment	AUCL (ng•h/mL)	AUCI (ng•h/mL)	C_{max} (n/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
IBU/PE caplet – fasted (A)#	907.8 (172.5)	929.1 (182.2)	233.8 (68.5)	66.8 (26.1)	2.7 (0.5)
IBU/PE caplet –fed (B)	835.5 (159.4)	856.0 (164.3)	205.0 (51.7)	109.4 (49.0)	2.7 (0.5)
Sudafed PE tablet – fasted (C)	882.7 (172.8)	902.9 (177.3)	237.0 (77.7)	58.0 (20.1)	2.7 (0.4)
Sudafed PE tablet – fed (F)@	805.8 (190.0)	828.4 (195.4)	200.1 (59.5)	103.5 (73.5)	2.8 (0.6)
Ratio (90% CI) ^					
A/E* %	103.4 (99.2-107.9)	103.4 (99.3-107.7)	99.4 (93.5-105.8)	—	—
B/F* %	104.9 (100.6-109.3)	104.5 (100.4-108.8)	103.6 (97.4-110.2)	—	—
B/A* %	91.7 (88.0-95.7)	92.0 (88.3-95.8)	88.3 (83.0-94.0)	—	—

* Reference product
^Based on fitted log-transformed parameters.
#: Subject No. 212 withdrew voluntarily before period 6. The treatment assigned for this period was A. Consequently, the summary statistics, ratio, and 90% CI for all PK parameters for treatment A were based on 41 subjects.

Table 8 shows that the IBU T_{max} for the combination caplet was longer (by 28 minutes) than the single entity Motrin IB under fasted conditions (A/C), but this difference was not statistically significant (p-value=0.061).

Table 8. AQ-08-13 IBU Means (or Medians), Pairwise Difference Point Estimates^ 95%CIs and P-values@ (n=42)

Treatment	T_{max} (min)	T_{ec6} (min)	T_{ec10} (min)
	Mean	Median$	Median$
IBU/PE caplet – fasted (A)#	131.4	36.0	68.0
IBU/PE caplet –fed (B)	97.5	49.3	61.4
Motrin IB tablet – fasted (C)	99.8	29.8	47.9
Motrin IB tablet – fed (D)	92.5	34.1	45.1
Pairwise Difference Point Estimates^ (95% CI) and P-values@			
A – C* (95% CI) p-value@	27.5 (0.0, 50.0) 0.061	13.5 (-1.5, 25.7) 0.100	12.8 (-3.0, 32.9) 0.136
B – D* (95% CI) p-value@	7.5 (-10.0, 27.5) 0.301	9.5 (-4.4, 22.0) 0.124	12.1 (-6.9, 27.1) 0.166

^ Hodges-Lehman estimates; @ p-values from a non-parametric analysis (Wilcoxon Rank-Sum Test)
* Reference product
# Subject No. 212 withdrew voluntarily before period 6. The treatment assigned for this period was A. Consequently, the summary statistics, point estimates, and 95% CI for treatment A were based on 41 subjects.
$ Some subjects never attained Tec6 and/or Tec10 (see Table-3). They were assigned a value of 16 hours. Since the means are heavily influenced by these values, the medians are shown instead.

MO Comments: *There were 6 subjects who did not achieve a plasma level of 10 mcg/mL and were therefore assigned T_{ec10} values of 16 hr. Three of these subjects were given the combination caplet under fed conditions (B), one was given the combination caplet fasted (A), and two were given single ingredient Motrin IB fed (D). The significance of T_{ec6} and T_{ec10} is not well documented (see MO Comment above).*

Safety Measurements
Adverse events (AEs) were recorded as they occurred during the treatment phases of the study and if voluntarily reported by the subject within 15 days following the conclusion of the subject's participation in the study. The reporting period for AEs started when the subject took the first dose of study medication. Serious AEs (SAE) were reported any time they occurred after the subject signed the informed consent.

Laboratory Determinations
The pre-study laboratory examination included a CBC, complete urinalysis, and serum chemistry profile. The serum chemistry profile consisted of glucose, creatinine, AST, ALT, total bilirubin, albumin, sodium, chloride, BUN, calcium, alkaline phosphatase, total protein, potassium, CO_2, direct (conjugated) bilirubin, and uric acid.

Vital Signs and Physical Examination
The pre-study physical examination included heart rate, blood pressure, weight, and height. The physical examination (excluding height) was repeated at the end of the study

Gender Effect
Significant gender and treatment-by-gender interaction effects were observed for IBU across all PK parameters (untransformed and log transformed). In general, females had higher AUCL and C_{max} values. Within both gender groups, the 90% CIs for AUCL in the comparison of the fasted caplet to the single fasted Motrin IB tablet fell within the pre-specified limits of bioequivalence. The corresponding 90% CIs for C_{max} fell within the limits of bioequivalence among females but just barely missed it for males. Among male subjects, the lower limit of the C_{max} 90% CI (78.9%) fell slightly outside of the acceptable bioequivalence limits. Bioequivalence criteria (with respect to AUCL and C_{max}) were satisfied within both gender groups in the comparison of the fed combination caplet and the fed Motrin IB tablet. Bioequivalence criteria were satisfied in the fed/fasted caplet ratio for AUCL and C_{max} among males but not females. The lower limits of the AUCL 90% CI (75.6%) and C_{max} 90% CI (66.7%) fell outside of the acceptable bioequivalence limits.

For free PE, there was a significant gender effect for Ln AUCL but not C_{max}.
For total PE, there were no significant gender or treatment-by-gender interaction effects for all parameters.
See Clinical Pharmacology review for discussion of the gender effect.

SAFETY RESULTS:

The safety results for Study AQ-08-13 are in section 7.0.

SUMMARY:
Under fasted conditions, the IBU/PE combination caplet was bioequivalent to Motrin IB and to Sudafed PE for AUC and C_{max}. The IBU T_{max} of the combination caplet was 28 minutes longer than for Motrin IB. Under fed conditions, the IBU/PE combination caplet was bioequivalent to Motrin IB for AUC and C_{max}, and to Sudafed PE for AUC. Under fed conditions, for free PE, the lower bound of the 90% CI for C_{max} was outside the limits for bioequivalence, 76%. There were no significant safety findings.

MO Comments: *The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) previously opined that they did not believe that the observed increase in Tmax is likely to be clinically meaningful. Their opinion was based upon a qualitative assessment of the concentration-time curves (Study AQ-08-13, Figure 5) showing that the shape of the curves is similar. In conjunction with the fact that the dosing interval is every 4 hours and the pain to be treated (headache and myalgia due to the common cold) is neither particularly intense nor requires rapid analgesia (as opposed to breakthrough pain), it seems unlikely that the observed small difference in Tmax would be clinically meaningful. This reviewer concurs with the DAARP assessment.*

Label directions should be revised to—"for best results, do not take with food", since under fed conditions, the lower bound of the CI for Cmax of free PE falls outside the limits for bioequivalence (low) for the combination caplet.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The present submission includes two PK trials AQ-08-12 and AQ-08-13, which studied drug interactions, formulation effects and food effects. A new assay that measures free PE was employed in these two studies. In addition, samples were also assayed for total PE using a revised total PE assay, which was different from that used in studies AQ-05-03 and AQ-06-08 for NDA 22-112.

Table 9. Clinical Trials for NDA 22-565

Study	Objectives	Design	Treatments	Subjects
AQ-08-12	Characterize rate and extent of IBU and PE absorption from IBU/PE 200/10 mg caplets compared to marketed Motrin IB (IBU 200 mg) and Sudafed PE (PE 10 mg) single ingredient products administered concomitantly and to Advil (IBU 200 mg) administered alone; fasted conditions only	Single dose, randomized, open-label, 3-way crossover, in-patient study. Each treatment was separated by 48 hours.	**A**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet **B**: Motrin IBU 200 mg and Sudafed PE 10 mg given concomitantly **C**: Advil IBU 200 mg (OTC single ingredient)	Forty-two (42) healthy male and female subjects were enrolled; 41 subjects completed all three treatment periods
AQ-08-13	Characterize, under fasted conditions, the rate and extent of IBU and PE absorption from IBU/PE 200/10 mg caplets compared to single ingredient Motrin IB (IBU 200 mg) and to Sudafed PE (PE 10 mg) administered alone; same comparisons under fed conditions	Single dose, randomized, open-label, 6-way crossover, in-patient study. Each treatment was separated by 48 hours.	**A**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fasted) **B**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fed) **C**: Motrin IBU 200 mg (fasted) **D**: Motrin IBU 200 mg (fed) **E**: Sudafed PE 10 mg (fasted) **F**: Sudafed PE 10 mg (fed)	Forty-two (42) healthy male and female subjects were enrolled; 41 subjects completed all six treatment periods

Also, safety results were cited from the PK trials AQ-05-03, which was submitted to NDA 22-112, and AQ-06-08. WCH initially conducted study AQ-05-03 to support this product (NDA 22-112). Subsequent to completing study AQ-05-03, WCH discovered through routine formula optimization activities that the addition of an antioxidant (b) (4), 0.25% propyl gallate (PG), (b) (4) an (b) (4) degradant (b) (4) below that of the ICH threshold (0.5%). Accordingly, WCH then conducted PK study, AQ-06-08, designed as a bridge between the IBU/PE formula studied in AQ-05-03 and the formula intended for commercialization. The difference between the two formulas involved the addition of PG. The PE results were considered flawed because of a methodological issue with the assay. The flawed assay measured total PE (conjugated plus unconjugated PE) and was used in studies AQ-05-03 and AQ-06-08.

Table 10. PK Trials for NDA 22-112 Cited in Present Submission

Study	Objectives	Design	Treatments	Subjects
AQ-05-03	Characterize drug interaction, formulation effect, and food effect	Single dose, open label, 4-way crossover	1. Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fasted); 2. Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fed); 3. Motrin IBU 200 mg and Sudafed PE 10 mg (fasted); 4. Sudafed PE 10 mg (fasted)	Forty-two (42) healthy male and female subjects were enrolled
AQ-06-08	Bridge formulations with and without the antioxidant propyl gallate	Single dose, open label, 2-way crossover	1. IBU/PE 200/10 without propyl gallate mg (fasted); 2. IBU/PE 200/10 mg with propyl gallate (fasted)	Forty-(40) healthy male and female subjects were enrolled

5.2 Review Strategy

PK Study AQ-08-12 and Study AQ-08-13 are summarized in Sections 4, and the safety results from Studies AQ-05-03, AQ-06-08, AQ-08-12, and AQ-08-13, are presented in Section 7. An updated review of the literature is provided in Section 9.1. Clinical Pharmacology will be providing a detailed review of the PK studies.

5.3 Discussion of Individual Studies/Clinical Trials

Study AQ-08-12 characterized the rate and extent of IBU and PE absorption from IBU/PE 200/10 mg caplets compared to marketed Motrin IB (IBU 200 mg) and Sudafed PE (PE 10 mg) single entity products administered concomitantly and to Advil (IBU 200 mg) administered alone. IBU/PE had an equivalent rate and extent of IBU and PE absorption relative to the single entity products, Motrin IB and Sudafed PE, when administered concomitantly. The IBU Tmax estimated difference in the comparison of IBU/PE versus Motrin IB + Sudafed PE was 23 minutes, but this difference was not statistically significant (p=0.169). IBU/PE was also bioequivalent (BE) to single entity Advil tablets, indicating that the combination had an equivalent rate and extent of IBU absorption. The IBU Tmax for the combination was longer by 30 minutes compared to Advil tablets (p=0.024).

Study AQ-08-13 characterized, under fasted conditions, the rate and extent of IBU and PE absorption from IBU/PE 200/10 mg caplets compared to single ingredient Motrin IB (IBU 200 mg) and to Sudafed PE (PE 10 mg) administered alone. It further characterized the rate and extent of IBU and PE absorption from IBU/PE administered under fed conditions to that of Motrin IB and Sudafed PE administered individually under fed conditions. The results showed that under fasted conditions, IBU/PE was BE to Motrin IB and Sudafed PE for AUC and Cmax. Tmax of the combination caplet was achieved 28 minutes later than for Motrin IB, but this difference was not statistically significant, p=0.061. Under fed conditions, IBU/PE was

bioequivalent (BE) to Motrin IB for AUC and Cmax and BE to Sudafed PE for AUC. The lower bound of the 90% confidence interval for Cmax in the free PE assay was outside the limits for BE, 76%.

6 Review of Efficacy

Efficacy Summary

No efficacy studies were performed for this NDA. WCH was advised by the Agency that phenylephrine could be substituted for pseudoephedrine in this combination product as long as pharmacokinetic studies demonstrate noninterference. In 2005, the FDA's policy was not to request any additional safety or efficacy data as long as pharmacokinetics of the new formulation was comparable to that of the single ingredients.

6.1 Indication

NA

6.1.1 Methods

NA

6.1.2 Demographics

NA

6.1.3 Subject Disposition

NA

6.1.4 Analysis of Primary Endpoint(s)

NA

6.1.5 Analysis of Secondary Endpoints(s)

NA

6.1.6 Other Endpoints

NA

6.1.7 Subpopulations

NA

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

NA

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

NA

6.1.10 Additional Efficacy Issues/Analyses

WCH met with the Agency on December 2, 2008 to discuss the results of studies AQ-08-12 and AQ-08-13. The Agency asked WCH to provide adequate clinical data to support that there is no delay in the onset of analgesic efficacy due to the delayed IBU Tmax of the IBU/PE formulation. The Agency also indicated that WCH could reference other ibuprofen products with a PK profile similar to that of Advil Cold &Sinus PE which have been demonstrated to provide adequate analgesia.

Described below are four examples of IBU containing products with PK profiles the Sponsor found to be similar to that of IBU/PE and that have been shown to provide adequate analgesia. The four examples consist of IBU products with Tmax ranging between 110-131 minutes (the mean Tmax of IBU/PE was 131 minutes). Additionally, the four products have been shown to be effective within one to two hours by different measures including pain intensity difference scores, fever reduction, sleep latency (which can be a surrogate of pain relief) and the proportion of subjects requiring rescue medication within 1-2 hours after dosing.

Table 11. IBU Products with Tmax of 110 min or more

Product	NDA	Ingredients	IBU Tmax	Efficacy Model
Advil Allergy Sinus	21-441	IBU, pseudoephedrine and chlorpheniramine	110 min	Pain Intensity Difference in allergy-associated pain
Advil Chew Tabs	20-944	IBU 100 mg chewable	112 min	Fever reduction in children 2-11 years old
Motrin Chew Tabs	20-135	IBU 50 mg chewable	117 min	Fever reduction in children 2-11 years old
Advil PM Caplets	21-394	IBU and diphenhydramine	131 min	Pain-associated sleep latency

7 Review of Safety

Safety Summary

The safety findings from studies AQ-05-03, AQ-06-08, AQ-08-12 and AQ-08-13 were unremarkable. Overall, 166 subjects participated in the 4 PK studies. Forty-two (42) of the 166 subjects participated in study AQ-05-03 which was reported in NDA 22-112. The remaining 124 subjects participated in studies AQ-06-08, AQ-08-12 and AQ-08-13. Taken together, 105 adverse events were reported by 49 subjects. Eighty-eight (88) of the AE's were rated as mild (84%), 16 were rated moderate (15%) and 1 was rated unknown. Most frequently reported AEs were headache (14 events), nausea (12 events), dizziness, (9 events), and abdominal pain (6 events). Thirty-two AEs (30%) were determined to be related to the study medication or study procedure. There were no deaths or other serious AEs. One subject in study AQ-05-03 was determined to be pregnant after completing two of the four treatment periods and was discontinued from the study.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study	Purpose	Design	Treatments	Subjects	Exposure
AQ-08-12	Formulation effects	Single dose, randomized, open-label, 3-way crossover, in-patient study. Each treatment was separated by 48 hours.	**A**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet **B**: Motrin IBU 200 mg and Sudafed PE 10 mg given concomitantly **C**: Advil IBU 200 mg (OTC single ingredient)	Forty-two (42) healthy male and female subjects were enrolled; 41 subjects completed all three treatment periods	Forty-two subjects to 600 mg ibuprofen and 20 mg PE
AQ-08-13	Drug interaction Food effects	Single dose, randomized, open-label, 6-way crossover, in-patient study. Each treatment was separated by 48 hours.	**A**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fasted) **B**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fed) **C**: Motrin IBU 200 mg (fasted) **D**: Motrin IBU 200 mg (fed) **E**: Sudafed PE 10 mg (fasted) **F**: Sudafed PE 10 mg (fed)	Forty-two (42) healthy male and female subjects were enrolled; 41 subjects completed all six treatment periods	Forty-one subjects to 800 mg ibuprofen and 40 mg PE (one subject dosed for 5 of 6 treatment periods)

Study	Purpose	Design	Treatments	Subjects	Exposure
AQ-05-03	Drug interaction Formulation effects Food effects	Single dose, open label, 4-way crossover	1. Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fasted); 2. Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fed); 3. Motrin IBU 200 mg and Sudafed PE 10 mg (fasted); 4. Sudafed PE 10 mg (fasted)	Forty-two (42) healthy male and female subjects enrolled	Forty-two subjects to 600 mg ibuprofen and 40 mg PE
AQ-06-08	Bridge formulations	Single dose, open label, 2-way crossover	1. IBU/PE 200/10 without propyl gallate mg (fasted); 2. IBU/PE 200/10 mg with propyl gallate (fasted)	Forty (40) healthy male and female subjects enrolled	Thirty-five subjects to 400 mg ibuprofen and 20 mg PE (five subjects dosed one treatment period)

7.1.2 Categorization of Adverse Events

Summary of the AEs by study is presented in Table 12 below.

Table 12. Summary of Adverse Events by Study

Study	Treatments	Subjects	Adverse Events
AQ-08-12	**A**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet **B**: Motrin IBU 200 mg and Sudafed PE 10 mg given concomitantly **C**: Advil IBU 200 mg (OTC single ingredient)	Forty-two (42) healthy male and female subjects were enrolled; 41 subjects completed all three treatment periods	6 subjects reported a total of 10 AEs; all reported AEs in only one period; most frequently reported events were dizziness (four instances across all treatments), followed by headache (three incidents; one incident per treatment); all mild
AQ-08-13	**A**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fasted) **B**: Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fed) **C**: Motrin IBU 200 mg (fasted) **D**: Motrin IBU 200 mg (fed) **E**: Sudafed PE 10 mg (fasted) **F**: Sudafed PE 10 mg (fed)	Forty-two (42) healthy male and female subjects were enrolled; 41 subjects completed all six treatment periods	23 subjects reported a total of 61 AEs; eight subjects reported AEs in two periods, one subject in three periods, and one in four periods; most frequently reported AEs among all Tx groups were nausea (9 instances across all Txs), followed by headache (8 incidences across four Tx; most of which were with the IBU/PE caplet fasted and Sudafed PE fasted Tx groups); all but 8 mild, 8 moderate.
AQ-05-03	1. Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fasted); 2. Advil Cold & Sinus IBU 200 mg and PE 10 mg caplet (fed); 3. Motrin IBU 200 mg and Sudafed PE 10 mg (fasted); 4. Sudafed PE 10 mg (fasted)	Forty-two (42) healthy male and female subjects were enrolled	8 subjects reported a total of 15 AEs, 3 reported AEs in more than one period; nausea and vomiting were the most frequently reported; 8 were mild, 6 moderate, 1 unknown
AQ-06-08	1. IBUPROFEN/PE 200/10 without propyl gallate mg (fasted); 2. IBU/PE 200/10 mg with propyl gallate (fasted)	Forty-(40) healthy male and female subjects were enrolled	12 subjects: total of 19 AEs, 4 reported AEs in more than one period; skin and subcutaneous tissue disorders were reported the most frequently (2 incidents in each treatment period); all but 2 were mild, 2 were moderate

GI Disorders and Nervous System Disorders were the system organ classes with the highest number of subjects reporting AEs. These occurrences tended to cluster by study as opposed to treatment. Twenty of the 25 subject reports of Gastrointestinal Disorders occurred in Study AQ-08-13. Within that study, the number of subjects reporting GI Disorders across the 6 treatments ranged from 2 to 5. No treatment in any of the other 3 studies had more than 2 subjects reporting GI Disorders. Twenty-two subjects reported AEs with Nervous System Disorders. Ten subjects across 5 of the 6 treatments reported nervous system AEs in Study AQ-08-13 (range 0-4) and 6 subjects reported AEs across 3 treatment groups (range 1-3) in Study AQ-08-12. The remainder of the nervous system AEs were from Studies AQ-05-03 and AQ-06-08.

MO Comment: *The number of AEs were notably higher in study AQ-08-13. This finding is of unclear significance. However, none of the events were serious.*

Study AQ-05-03 (originally submitted in NDA 22-112)
Throughout the study, 8 (19%) out of 42 subjects reported a total of 15 AEs, 3 of whom reported AEs in more than one period. Subject 223 was discontinued because she became pregnant after completing periods 1 and 2 (Motrin + Sudafed PE tablets taken concomitantly, and IBU/PE caplet under fed conditions). Her pregnancy was progressing normally, but she was lost to follow-up. The outcome of the pregnancy is unknown.The incidence of AEs across all treatments was low with nausea and vomiting being the most frequent (three incidents). Eight of the AEs were rated as mild in severity, six as moderate and one of unknown severity. All but two AEs were considered to be unrelated to the study medications. Within each of the treatments, one subject (2.4%) reported 3 AEs following treatment with IBU+PE caplet (fasted), four subject (9.5%) reported 6 AEs following treatment with IBU+PE caplet (fed), two subject (4.8%) reported 3 AEs following treatment with Motrin IB plus Sudafed PE administered concomitantly (fasted), and 3 subjects (7.3%) reported 3 AEs following treatment with Sudafed PE. No notable differences were seen in the individual AE rates between the treatments.

Study AQ-06-08
Throughout the study, 12 (30%) out of 40 subjects reported a total of 19 AEs, four of whom reported AEs in more than one period. The incidence of AEs for both treatments was relatively low, with skin and subcutaneous tissue disorders being the most frequent (two incidents in each treatment period). All but two AEs were rated as mild; the other two were rated as moderate. All but six AEs were considered to be unrelated to the study medications. Within each of the treatments, eight subjects (21.1%) reported 10 AEs following treatment with IBU+PE caplet without propyl gallate (PG), and eight subjects (21.6%) reported nine AEs following treatment with IBU+PE caplet with PG. No notable differences were seen in the individual AE rates between the treatments.

Study Results for AQ-08-12
The safety population consisted of all subjects who took at least one dose of study medication. Adverse events (AEs) were recorded as they occurred or were reported during the treatment phases of the study and if voluntarily reported by the subject within 15 days following the conclusion of the subject's participation in the study. The reporting period for AEs started when

the subject took the first dose of study medication. Serious AEs (SAE) were reported any time they occurred after the subject signed the informed consent. The incidence rates for adverse experiences were tabulated by the most recent treatment the subject received prior to experiencing the adverse experience. The adverse experiences were classified according to their severity and relationship to study medication.

Throughout the study, 6 (14%) subjects reported a total of 10 AEs. All six subjects reported AEs in only one period. The incidence was low for all AEs. The most common AEs among all treatments was dizziness (four incidences across all treatments), followed by headache (three incidences across all treatments; one incidence per treatment). All AEs were rated as mild. All but three AEs were considered to be related to the study medications.

Four AEs were reported by one subject (2.4%) following the IBU/PE caplet treatment, two AEs were reported by two subjects (4.8%) following the concomitant administration of the single entity products treatment, and four AEs were reported by three subjects (7.3%) following Advil tablet treatment. No notable differences among the treatments were seen in the individual AE rates. There were no deaths or other serious AEs noted during the study. None of the subjects discontinued due to an AE.

At least one laboratory test was abnormal in 38 (90.5%) subjects during the screening evaluation, but none were clinically significant. No post-study laboratory tests were performed. None of the vital sign(VS) readings at a given visit were abnormal by a clinically significant amount. Likewise, none of the VS changes from pre-study to final visit were clinically significant. There was one abnormal physical examination noted on the screening exam under the heart body system but was not considered to be clinically significant by the Principal Investigator. No clinically significant changes were observed between the pre- and post- assessments.

Study Results for AQ-08-13

Forty-two subjects who received at least one dose of study medication were included in the safety population. One subject (No. 212) withdrew voluntarily for reasons unrelated to study drug before period six and received all treatments except treatment A (caplet under fasted conditions), whereas the other 41 subjects who completed the study were exposed to all six treatments. To account for this, the denominator for each treatment's AE incidence rate was based on the number of subjects exposed to the respective treatment.

Throughout the study, 23 (55%) subjects reported a total of 61 AEs. Eight subjects reported AEs in two periods, one subject in three periods, and one in four periods. The most common AEs among all treatment groups was nausea (nine instances across all treatments), followed by headache (eight incidences across four treatments; most of which were with the IBU/PE caplet fasted and Sudafed PE fasted treatment groups). All but eight AEs were rated as mild; the other eight were rated as moderate. Seventeen AEs were considered related to the study medication, all but two of the related AEs occurred with the combination caplet (7 in the fasted state and 8 in the fed state). Four to seven (9.5-16.7%) subjects reported AEs during each treatment arm. No notable differences were seen in the individual AE rates among the treatments.

There were no deaths, other serious or potentially serious AEs noted during the study. None of the subjects discontinued due to an AE.

At least one laboratory test was abnormal in 34 (81.0%) subjects during the screening evaluation, but none were clinically significant. No post-study laboratory tests were performed.

MO Comments: *Two subjects with normal baseline BPs became borderline hypertensive on their final reading. Subject #104 had a baseline BP of 120/87 with a heart rate of 88 and had a final BP of 141/96 and heart rate of 98 and received one Motrin IB tablet in the last treatment phase. Subject #109 had a baseline BP of 131/73 with a heart rate of 88 and had a final BP of 142/82 and heart rate went from 67 to 93 and received one IBU/PE combination tablet under fasted conditions. It is unclear as to whether these VS changes are related to study drug as measurements were made several half-lives after the drug was administered. In addition, subjects # 111 and # 113 with elevated systolic readings at baseline normalized their pressures on the final VS reading (one received Motrin IB and one received Sudafed PE in the last treatment phase).*

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Only PK studies were submitted. See Table 12 for common AEs among the PK studies.

7.2 Adequacy of Safety Assessments

Even though there were only 166 subjects exposed to the new combination drug product, there is a wide extent of exposure to the two single ingredients contained in this formulation. Therefore, there is sufficient safety information to characterize the safety profile of the proposed drug product.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

NA

7.2.2 Explorations for Dose Response

NA

7.2.3 Special Animal and/or In Vitro Testing

NA

7.2.4 Routine Clinical Testing

NA

7.2.5 Metabolic, Clearance, and Interaction Workup

NA

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

NA

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in the PK trials.

7.3.2 Nonfatal Serious Adverse Events

No serious events occurred in the PK trials.

7.3.3 Dropouts and/or Discontinuations

See section 4.4.3.

7.3.4 Significant Adverse Events

See section 7.1.2.

7.3.5 Submission Specific Primary Safety Concerns

NA

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported AEs associated with NSAID use involve the GI tract (e.g., dyspepsia, heartburn, nausea, abdominal pain); serious AEs such as peptic ulcer and GI bleeding can occur. CNS effects are also noted frequently (e.g., headache, dizziness, nervousness). Less

frequently, edema and fluid retention, renal effects, and dermatologic effects are reported. Renal failure and severe hypersensitivity reactions, like Steven's Johnson syndrome, can occur.

Sympathomimetic drugs are associated with adverse effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse. In therapeutic doses, phenylephrine PE causes little if any central nervous system stimulation, but may cause nervousness, restlessness, anxiety, dizziness, and tremor in some patients. As with other sympathomimetic drugs, PE should be used with caution in hypertensive subjects, hypothyroidism, diabetes mellitus, ischemic heart disease, or prostatic hypertrophy.

For the most common AEs seen in the PK trials, see section 7.1.2.

7.4.2 Laboratory Findings

No post-treatment laboratory labs were done.

7.4.3 Vital Signs

In study AQ-05-03, there were changes in vital sign data at the end of the study compared to baseline for a number of subjects. The Principal Investigator did not consider any of the changes to be clinically significant. There were five blood pressure readings outside the normal range (normal range for systolic blood pressure was taken as 90-139 mmHg; normal diastolic blood pressure was taken as 60-89 mmHg). Four of those readings were high systolic values, two at baseline and two at the post-treatment visit. The other abnormal blood pressure reading was a high post-treatment diastolic blood pressure. The highest systolic value was 142 and the highest diastolic value was 95.

In study AQ-08-13 two subjects with normal baseline BPs became borderline hypertensive on their final reading. Subject #104 had a baseline BP of 120/87 with a heart rate of 88 and had a final BP of 141/96 and heart rate of 98 and received one Motrin IB tablet in the last treatment phase. Subject #109 had a baseline BP of 131/73 with a heart rate of 88 and had a final BP of 142/82 and heart rate went from 67 to 93 and received one IBU/PE combination tablet under fasted conditions. It is unclear whether these VS changes are related to study drug, since measurements were made several half-lives after the drug was administered. In addition, subjects # 111 and # 113 with elevated systolic readings at baseline normalized their pressures on the final VS reading (one received Motrin IB and one received Sudafed PE in the last treatment phase). None of the readings at a given visit, and none of the changes from pre-study to final visit, were considered by the Principal Investigator to be clinically significant.

7.4.4 Electrocardiograms (ECGs)

No ECGs were performed for these PK trials.

7.4.5 Special Safety Studies/Clinical Trials

NA

7.4.6 Immunogenicity

NA

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The PK studies did not study multiple doses, so dose dependency for adverse events was not evaluated.

7.5.2 Time Dependency for Adverse Events

NA

7.5.3 Drug-Demographic Interactions

For gender effect, see clinical pharmacology review.

7.5.4 Drug-Disease Interactions

NA

7.5.5 Drug-Drug Interactions

Due to a potential hypertensive effect when phenylephrine is used with or shortly after a monoamine oxidase (MAO) inhibitor, the phenylephrine label warns patients not to use the product with, or for two weeks after, taking a MAO inhibitor.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There are no known carcinogenicity issues related to ibuprofen or phenylephrine.

7.6.2 Human Reproduction and Pregnancy Data

Ibuprofen (from Motrin prescription label)
In late pregnancy, as with other NSAIDs, ibuprofen tablets should be avoided because it may cause premature closure of the ductus arteriosus.

Teratogenic effects. Pregnancy Category C. Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Ibuprofen should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic effects. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.

Labor and Delivery. In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of ibuprofen tablets on labor and delivery in pregnant women are unknown.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human-milk and because of the potential for serious adverse reactions in nursing infants from MOTRIN tablets, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Phenylephrine (from Pharmacology Online)
Phenylephrine is classified as FDA pregnancy category C. It should be used during pregnancy with caution. Systemic phenylephrine must be used only when the benefit to the mother outweighs the risk to the fetus during late pregnancy, labor or obstetric delivery; when used during this time phenylephrine can cause fetal anoxia and/or bradycardia due to increased uterine contractility or decreased uterine blood flow.

It is not known whether phenylephrine is distributed into breast milk; however, the low molecular weight of the drug would suggest possible passage. However, since phenylephrine is generally poorly absorbed, the potential overall absorption of phenylephrine by an infant following breast-feeding may be minimal.

MO Comment: *The proposed label warns pregnant and breastfeeding women to ask a health professional before use, and warns pregnant women to not use ibuprofen in the last 3 months of pregnancy unless directed by a doctor to do so, since ibuprofen may cause problems in the unborn child or complications during delivery.*

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor requested a full waiver of pediatric studies in the 0 to less than 12 years age group and proposed that the label state "children under 12 years of age: consult a doctor". Subsequently, the Sponsor revised the label request to state "do not use in children under 12 years of age." The waiver request is based on the following assertions:

- The Advil Cold & Sinus PE product does not represent a meaningful therapeutic benefit over existing treatments for ages 0 to 12 years
- Caregivers are likely to select available existing treatment products, and the new product is not likely to be used in a substantial number of children
- Doses of ibuprofen and phenylephrine in the Advil Cold & Sinus PE product exceed the recommended doses for children under 12 years of age and may be inappropriate or unsafe for use in this age group
- Advil Cold & Sinus PE caplets need to be swallowed whole, and children may have difficulty swallowing them. Other formulations are preferred for the pediatric population and are available OTC.

There are a variety of cough and cold preparations combining pain reliever/fever reducer, nasal decongestant, and/or antihistamine specifically formulated for use in children, most of which are available OTC. The marketing of these products could be affected by potential new regulations arising from an Advisory Committee meeting that was held on October 18 and 19, 2007 to discuss the use of cough and cold drugs (including chlorpheniramine and phenylephrine) in pediatric age groups (0 to 6 years) in response to a Citizen Petition. The Committee recommended that cough and cold products should not be used below 2 years of age either as single ingredients or in combination. The Committee recommended assessing the clinical safety and efficacy of these ingredients in cough and cold products, including pharmacokinetic studies, in children aged 2 to 6 years. The Committee did not address use of cough and cold products in children 6 to <12 years of age.

The Agency has previously approved two ibuprofen/pseudoephedrine combination products for use in children down to the age of two. For the Children's Advil Cold oral suspension which is currently marketed OTC, efficacy in pediatric patients aged 2-12 was extrapolated from adults. Two PK studies, AQ-99-02 (consisting of 29 children 6 to <12 years) and AQ-00-04 (consisting of 23 children <6 years), and a safety study, AQ-99-03 (consisting of 104 children 2 to <12 years) supported the approval of this pediatric product.

MO Comments: *PREA is triggered for this new combination product. However, there are two arguments for granting a waiver.*

First, there are already two approved NDA nonprescription, age-appropriate ibuprofen/decongestant (pseudoephedrine) combination drug products, Children's Motrin Cold and Children's Advil Cold. Therefore, no additional pediatric studies are needed as this new combination drug product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients.

Second, the history behind this product development also has to be considered. Wyeth Consumer Healthcare (WCH) currently markets ibuprofen 200 mg/pseudoephedrine HCl 30 mg as a combination pain reliever/fever reducer and nasal decongestant under the trade name Advil Cold & Sinus caplets for adults and children 12 years and older (NDA 19-771). Although the latter product was approved for over-the-counter (OTC) use, it (as well as all pseudoephedrine-containing drug products) was moved behind the counter, in compliance with The Combat Methamphetamine Epidemic Act of 2005. WCH was advised by the Agency that phenylephrine could be substituted for pseudoephedrine in this combination product as long as pharmacokinetic studies demonstrate noninterference. In 2005, the FDA's policy was not to request any additional safety or efficacy data as long as pharmacokinetics of the new formulation was comparable to that of the single ingredients.

The Division believes that no additional pediatric studies are needed as this new combination drug product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients, and proposes that a waiver for pediatric studies be granted.

These issues will be discussed further during a PeRC meeting. In addition, legal counsel is being sought as to whether PREA or the monograph prevails for this situation.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In case of accidental ibuprofen overdose, use should be discontinued and professional assistance should be obtained. The signs and symptoms of overdose include vertigo, GI disorders (*e.g.,* abdominal pain, nausea, and vomiting), hepatic dysfunction, hyperkalemia, metabolic acidosis, CNS disorders (*e.g.,* dizziness, somnolence, headache, loss of consciousness), renal insufficiency/failure, dyspnea and respiratory depression, and hypotension.

It is not known if PE-containing products will eventually be able to be converted to illicit drugs.

We have no overdose, abuse, withdrawal, or rebound information for the combination of ibuprofen and phenylephrine.

7.7 Additional Submissions / Safety Issues

NA

8 Postmarket Experience

The Sponsor does not currently market a combination product containing IBU with PE anywhere in the world. Additionally, the proposed combination product containing IBU, 200 mg and PE, 10 mg is not marketed commercially anywhere by another Sponsor.

9 Appendices

9.1 Literature Review/References

The Sponsor retrieved literature on the combination of "ibuprofen" and "phenylephrine" from the Medline, Biosis Previews, and EMBASE databases, over the period from March 14, 2007 to February 28, 2009. The search did not result in any references concerning the safety of the ibuprofen-phenylephrine combination. The Sponsor performed a separate search for safety-related ibuprofen literature which yielded 24 references. The Sponsor concluded that there were no reports of any new or unexpected adverse events, and that there was no need to revise the label.

Cancer. There were two prospective cohort studies searching for an association between ibuprofen use and cancer. Kwan et al. 2007 found a marginally significant result that regular use of ibuprofen but not ASA, in a cohort of 2292 females, was associated with a reduction in breast CA (RR=0.56, 95% CI: 0.32-0.98). Genkinger et al. (2007) did not find an association between ibuprofen and bladder cancer in a cohort of 49,448 males followed for 18 years.

CV effects. The sponsor cited eight studies of cardiovascular effects. Each is summarized below.

Fosbol et al. 2009 performed a nationwide cohort study of individuals, totaling 1,028,437 participants >10 years of age, without previous hospital admissions or concomitant pharmacotherapy within 5 years of first claimed prescription for an NSAID. A dose-dependent increase in risk of death/myocardial infarction (MI) was found for rofecoxib (HR-2.13; 95%CI: 1.89, 2.41) and celecoxib (HR-2.01; 95%CI: 1.78, 2.27), but not for ibuprofen, or naproxen.

Rahme et al. 2007a performed a retrospective cohort study using health care records of 283,799 patients between the ages of 65 to 80 years, to evaluate the associations between rofecoxib, celecoxib, diclofenac, and IBU for a related but different endpoint from that of Fosbol et al.2009, the risk of a first hospitalization for acute MI (AMI). There were no statistically significant differences in pairwise comparisons between ibuprofen and any of diclofenac, rofecoxib (ROF) or celecoxib (CEL). In the direct two way adjusted comparison of each NSAID stratified by dose, the only statistically significant difference was with rofecoxib >25 mg/day versus celecoxib >200 mg/day. In this study there was no difference between AMI occurrence in elderly patients taking rofecoxib or celecoxib at recommended doses for chronic indications versus those taking ibuprofen/diclofenac.

Rahme and Nedjar. 2007b carried out a retrospective cohort study using health care records of 510,871 patients ≥ 65 years old who were prescribed ROF, CEL, or a nonselective NSAID and were hospitalized for AMI or GI bleeding. Acetaminophen (APAP) was used as the reference drug. The risks of first hospitalization for AMI and for GI bleed were not significantly different between ibuprofen and acetaminophen. An increased risk of GI bleed was found for naproxen compared with acetaminophen (HR-2.75; 95% CI= 2.05, 3.69).

Haag et al. 2008 performed a population-based cohort study of stroke associated with the use of NSAIDs, enrolling 7,636 participants ≥ 55 years of age (mean age 70.2 ±9.6 years) who were stroke free at baseline. During 70,063 person-years of follow-up (mean of 9.2 years), a total of 807 participants developed stroke (460 ischemic, 74 hemorrhagic, and 273 unspecified). Use of ibuprofen, diclofenac, and celecoxib were not associated with statistically significant increased risk of stroke. Naproxen (HR-2.63; 95% CI-1.47-4.72) and rofecoxib (HR-3.38; 95% CI-1.48-7.74) were associated with a greater risk of stroke.

Roumie et al. 2008 found similar results in a retrospective cohort study of stroke associated with the use of NSAIDs in Medicaid enrollees, following 336,906 persons aged 50-84 years without stroke in the year prior to cohort entry. After 989, 826 person-years of follow-up, there were 4354 stroke hospitalizations. Use of rofecoxib (HR-1.28; 95% CI-1.06- 1.53) and valdecoxib (HR-1.41; 95% CI-1.04-1.91) were associated with an increased risk of stroke compared to non-users of NSAIDs. Use of ibuprofen and other nonselective NSAIDs were not associated with increased risk of stroke.

Farkouh et al. 2007 studied cardiovascular events in a cohort of 18,325 osteoarthritis (OA) patients aged >50 years old who were taking aspirin and followed for 1 year, comparing lumiracoxib with naproxen and lumiracoxib with ibuprofen (at doses of 2400 mg/day, more than is allowed OTC). In high-risk patients receiving low dose ASA, the IBU group had a higher number of primary cardiovascular events than the lumiracoxib group (2.14% vs. 0.25%; HR = 9.08, 95% CI: 1.13-72.8; P = 0.038).

Hudson et al. 2007 performed a nested case-control cohort study of patients ≥ 66 years to determine whether there is a class effect among individual NSAIDs on the risk of CHF. Cases were defined as patients readmitted for congestive heart failure (CHF). There were 8,512 cases identified ,and 34,048 patients selected as controls. Cases had more renal disease (23%) than controls (16%). The odds of being readmitted for CHF was higher in patients exposed to indomethacin and rofecoxib compared to celecoxib but was similar for patients exposed to naproxen, diclofenac and ibuprofen compared to celecoxib.

Morrison et al. 2007 performed a meta-analysis of trials comparing nonselective NSAIDs in regard to effects on blood pressure. Compared to placebo, the risk ratio for hypertension was 2.85 (95% CI: 1.44, 5.65; p=0.003) in two ibuprofen trials. The mean change in blood pressure from baseline to the end of study in 5 trials of ibuprofen was 3.54 mm (CI 2.70, 4.39) for systolic blood pressure ($p<0.001$). The ibuprofen dosing in these trials was at 2400 mg/day for at least 4 weeks, above OTC dosing in amount and duration.

MO Comment: *Results did not indicate any new issues with ibuprofen safety in OTC use. The OTC label contains warnings that the risk of heart attack, stroke or GI bleed may increase if ibuprofen is used more than directed or for longer than directed, and it warns that ibuprofen may diminish the effectiveness of aspirin.*

Drug interactions. The sponsor provided three studies of drug interactions, of which two dealt with the ibuprofen-aspirin interaction that reduces the cardioprotective effect of aspirin from anti-platelet activity.

Gengo et al. 2008 reported on two studies of the ibuprofen-aspirin interaction. A three-way crossover study (aspirin 325 mg alone (ASA), ibuprofen 400 mg alone (IBU), then ibuprofen 400 mg, followed by ASA 325 mg 2 hours later) was performed in 10 healthy volunteers (aged 21-32) to determine the effect of IBU on ASA-induced inhibition of platelet aggregation. Co-administration of IBU with ASA significantly reduced the magnitude and duration of ASA on platelet aggregation ($P<0.007$). Inhibition of platelet aggregation was similar to that of IBU alone. In addition, a further observational study was performed in 28 patients with a history of stroke (mean age 64) who received ASA and who reported regular use of IBU or naproxen. Some of these individuals were also taking another antiplatelet agent, either dipyridamole or clopidogrel. All 28 patients showed platelet non-responsiveness to collagen or arachidonate. Of these, 18 patients agreed to either discontinue the NSAID (or take it at a time to avoid the interaction with ASA) and remain on ASA for 2-4 weeks. On follow-up, the platelet aggregation from collagen and from arachidonatre was significantly reduced. Thirteen of these 18 subjects (72%) were seen in clinic because they had experienced another cerebral ischemic event while concomitantly receiving ASA and the NSAID daily. The authors state that their data suggest that ibuprofen or naproxen when taken concomitantly with ASA reduces the anti-platelet aggregation due to ASA in as little as OTC doses. They support the FDA recommendation that patients who take immediate-release ASA should take IBU at least 30 minutes after or 8 hours prior to dosing with ASA.

Gladding et al. 2008 performed a randomized, double-blind, placebo-controlled, crossover study in 24 healthy volunteers (mean age 38 years) to determine the interaction of six NSAIDs (naproxen 550 mg, ibuprofen 400 mg, celecoxib 200 mg, indomethacin 25 mg, tiaprofenic acid 300 mg, and sulindac 200 mg) with antiplatelet effect of ASA 300 mg**.** Platelet function was measured 12 hours after the administration of each NSAID. The NSAID was then given 2 hours before aspirin 300 mg, and platelet function was reassessed 24 hours later. Naproxen and tiaprofenic acid (taken alone) both showed anti-platelet aggregation effect, but both also block the anti-platelet effect of aspirin. The authors found that IBU, indomethacin, naproxen and tiaprofenic acid all block the antiplatelet effect of ASA. The authors did not find this effect with sulindac or celecoxib.

Tornio et al. 2007 studied the effect of gemfibrozil on PK of ibuprofen. The interaction effect is stereoselective. The mean AUC of R-IBU was increased by 34%, and the $t_{1/2}$ increased by 54%, with no effects on C_{max} and t_{max}. The mean $t_{1/2}$ of S-IBU increased by 34% with no changes to the other PK parameters. The authors conclude that the gemfibrozil-ibuprofen interaction is of limited clinical significance.

MO Comments: *Ibuprofen reduces the anti-platelet aggregation activity of aspirin even when taken at OTC doses (Gengo et al. 2008). The anti-platelet effect of aspirin is also attenuated by indomethacin, naproxen, and tiaprofenic acid but not celecoxib and sulindac (Gladding et al. 2008). These results support the current OTC label warning to ask a doctor if also taking aspirin*

for heart attack or stroke, because ibuprofen may decrease the benefit of taking aspirin. This interaction is being further evaluated by the division for naproxen sodium.

GI effects. The sponsor provided a case study (Vidyasankar and Audun 2007) and a epidemiological simulation study (Varas-Lorenzo et al. 2007). Vidyasankar and Audun 2007 reported a case of NSAID enteropathy in a 42 year old female who self-medicated with ibuprofen three times a day for 7 months (dose unspecified). She was taken off ibuprofen and started on proton pump inhibitors, but after another year, during which she continued to take NSAID over the counter, she required surgery to remove 100 cm of proximal ileum with 30 strictures. The Varas-Lorenzo et al. 2007 simulation compared the GI and cardiovascular effects of celecoxib to those of diclofenac, ibuprofen and naproxen, finding a GI benefit of celecoxib (fewer peptic ulcer complications) that is not offset by cardiovascular events or mortality.

There were two case reports of overdoses reported by Marciniak et al. 2007 concerning a 14 year old male who ingested 50 g ibuprofen in a suicide attempt, and by Nelson et al. 2007 concerning a 28 year old male who ingested intentional overdoses of acetaminophen and ibuprofen which resulted in acute renal and fulminant liver failure complicated by rhabdomyolysis and necrotic bowel.

MO Comment: *NSAID enteropathy and bowel necrosis are rare complications of NSAID use.*

Exercise-Induced effects. The sponsor provided two studies of ibuprofen use with strenuous exercise. Dumke et al. 2007 studied the effect of a prescribed dose of IBU (600 mg the afternoon prior to race followed by 1200 mg on race day avoiding all other medication) on serum electrolytes in 63 subjects after a 160 km race. Study was not randomized (subjects entered the ibuprofen group or no medication group based on personal preference from previous practice), but found no effect of ibuprofen on serum electrolytes, CK, creatinine, uric acid, glucose, or bilirubin.

Other reports.

There was a case report describing aseptic meningitis and another case report describing a widespread vesicobullous eruption (lichen planus pemphogoides) that occurred in a person with lichus planus who received phototherapy, hormones, paracetamol and ibuprofen. (Bluth et al. 2007 and Maoz et al. 2008). Both patients, a 78 year old male and a 33 year old female respectively, recovered.

Neuman and Nicar 2007 reported a case of Stevens-Johnson syndrome in a 7 year old female, demonstrating effects of cell apoptosis in the liver and the skin.

Patel Raksha et al. 2008 conducted a cohort study in India of 200 patients (ranging from 1- 80 years old) presenting with cutaneous drug reaction. Out of the 200 cases followed, fixed drug eruption was the most common reaction seen in 61 patients followed by morbilliform rash in 37, pruritis 25, Stevens Johnson Syndrome 6, purpura 6. Cotrimoxazole was the most common drug

associated with cutaneous drug eruption (26 cases) followed by IBU (20 cases). Three severe cases of Stevens Johnson Syndrome were associated with IBU without fatality. The authors concluded that NSAIDs as a group were the most common drugs causing cutaneous reactions.

MO Comment. *These reports support the current warnings on OTC labeling concerning allergic reactions, hypersensitivity, rashes, and Steven's Johnson syndrome.*

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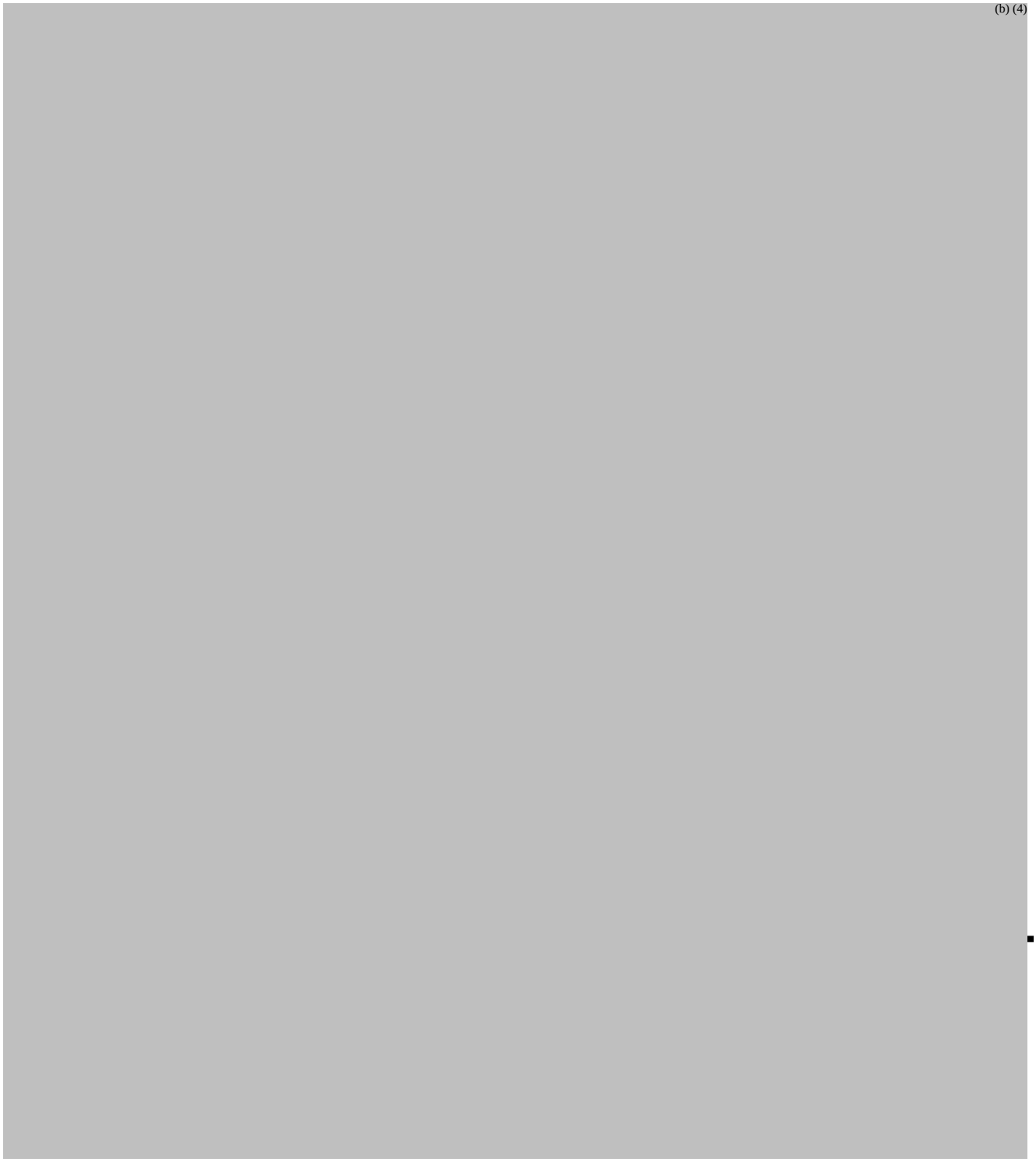
9.2 Labeling

LABELING HISTORY

WCH intends to market a size 20 count carton and 1-count pouches, which will be placed inside a dispensing carton.

2 pages of draft labeling has been withheld in full immediately following this page as B4 (CCI/TS)

(b) (4)



MO Comments: *It is recommended that the directions be revised to—"for best results, do not take with food", since under fed conditions, the lower bound of the CI for Cmax of free PE is outside the limits for bioequivalence (low) for the combination caplet.*

The Division of Medication Error Prevention and Analysis (DMEPPA) has also determined that the name Advil Cold & Sinus PE is unacceptable, They note that PE as a modifier does not sufficiently differentiate the proposed product from the currently marketed Advil Cold & Sinus product because the modifier 'PE' has been used for products that contain phenylephrine as well as pseudoephedrine DMEPPA has informed the Sponsor of this concern, and the Sponsor has subsequently provided a study protocol to assess this issue.

9.3 Advisory Committee Meeting

NA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22565	ORIG-1	WYETH CONSUMER HEALTHCARE	ADVIL COLD & SINUS PE(IBUPROFEN 200MG/PH

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/s/

LINDA S HU
12/28/2009

DAIVA SHETTY
12/28/2009

NDA 74-Day Fileability Meeting Checklist

NDA#: **22-565**
Product Name: **Advil Cold & Sinus PE**
Sponsor: **Wyeth**
Reviewer: **Linda Hu**
Date: **9/30/09**

Item	Yes	No
1. Is the clinical section of the NDA organized in a manner to allow substantive review to begin?	**X**	
2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	**X**	
3. Is the clinical section of the NDA legible so that substantive review can begin?	**X**	
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product through appropriately designed dose-ranging studies?	**NA**	
5. Do there appear to be the requisite number of adequately and well-controlled studies in the application?	**X**	
6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	**X**	
7. Are all data sets for pivotal efficacy studies complete for all indications requested?	**X**	
8. Do all pivotal studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**X**	
9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data and in the format agreed to previously by the Division?	**X**	
10. Has the application submitted a rationale for the applicability of foreign data (disease specific, microbiologic specific) in the submission to the U.S. population?	**NA**	
11. Has the applicant submitted all additional required case record forms, in addition to deaths and drop-outs, previously requested by the Division?	**X**	
12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	**X**	
13. Has the applicant presented the safety assessment based on all current world-wide knowledge regarding this product? (In a manner as previously agreed to by the Division)	**X**	

14. Has the applicant submitted adequate and well-controlled actual usage trial(s) within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**NA**	
15. Has the applicant submitted adequate and well-controlled labeling comprehension trial(s) within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**NA**	
Item	**Yes**	**No**
16. Has the applicant submitted draft labeling consistent with 201.5 and 201.56, current divisional policies, and the design of the development package?	**X**	
17. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	**X**	
18. Has PREA been addressed?	**See below**	
19. From a clinical perspective, is this NDA file-able? In no, please explain below.	**X**	

Reviewer Comments:
The application is filable. PREA has been triggered, and the Sponsor requests a waiver of pediatric studies for the (b) (4) old age group. The Sponsor will be notified that a waiver will not be granted and that pediatric studies will be required. The Sponsor will be asked to submit a pediatric plan.

Medical Officer
Division of Over-the-Counter Drug Products

Medical Team Leader
Division of Over-the-Counter Drug Products

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

/s/

LINDA S HU
09/30/2009

DAIVA SHETTY
09/30/2009