CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-565

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 17, 2010

TO: Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation (DNCE)

FROM: Carol M. Rivera-Lopez, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 6/17/10
Acting Team Leader, Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Second Addendum to the Review of EIRs Covering NDA 22-565, Advil® Cold & Sinus PE (Ibuprofen 200 mg/Phenylephrine HCl 10 mg) caplets, sponsored by Wyeth Consumer Healthcare.

At the request of the Division of Nonprescription Clinical Evaluation (DNCE), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

Study # AQ-08-12
Title: "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 # AQ-08-13
Title: "A Six-Way Crossover, Food Effect/Drug Interaction, Bioavailability Study of a Caplet Formulation of Ibuprofen 200 MG and Phenylephrine Hydrochloride 10 MG"

Following our evaluation of Form FDA-483 observations for Bio-Kinetic Clinical Applications and (b)(4), and their responses, DSI submitted a review on 1/28/10 and a review addendum on 2/23/10. DSI concluded that the clinical and analytical data from both studies are acceptable for Agency review.

This second addendum is to inform DNCE that DSI received a second response from (b) (4) (dated April 9, 2010). This response contains freeze/thaw and long term stability data using samples containing both ibuprofen and phenylephrine, to mimic the storage and handling conditions of study samples. These data suggest that there is no significant effect when the two analytes are present in combination. Therefore, DSI's recommendation to accept the data remains unchanged.

Conclusion:

Studies AQ-08-12 and AQ-08-13 are acceptable for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Carol M. Rivera-Lopez, Ph.D.

Final Classification:

VAI - (b) (4)

FEI: (b) (4)

cc:
DSI/Ball
DSI/GLPBB/Rivera-Lopez/Yau/Haidar/CF
OCP/DCP2/Ying Fan
OND/DNCE/Adams-King
HFR-CE2545/Milazzo
Draft: CRL 6/17/10
Edit:
DSI file: 6008
O:\BIOEQUIV\EIRCOVER\22565wye.ibupe.add2.doc
FACTS: (b) (4)

Email:
CDER DSI PM TRACK

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22565	ORIG-1	WYETH CONSUMER HEALTHCARE	Advil Congestion Relief

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

/s/

CAROL M RIVERA-LOPEZ
06/17/2010
Dr. Yau signed the paper copy on 6/17/10. Original signed copies are available in the DSI file.

505(b)(2) ASSESSMENT

Application Information		
NDA # 22565	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Advil® Congestion Relief Established/Proper Name: Ibuprofen / Phenylephrine HCl Dosage Form: Tablet Strengths: 200 mg / 10 mg		
Applicant: Wyeth Consumer Healthcare		
Date of Receipt: July 28, 2009		
PDUFA Goal Date: May 28, 2010	Action Goal Date (if different): May 27, 2010	
Proposed Indication(s): Temporarily relieves symptoms associated with cold and flu: headache, fever, sinus pressure, nasal congestion, minor aches and pain, reduces swelling of the nasal passages, temporarily restores freer breathing through the nose		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
CCABA Monograph: Phenylephrine	Pharmacokinetic data
NDA 19012: Motrin IB	Pharmacokinetic data
Literature`References (EDR Section 5.4 of NDA 22565)	Pharmacokinetic data

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Bioequivalence and bioavailability studies conducted. A total of 2 pivotal human pharmacokinetic studies (study AQ-08-12 and study AQ-08-13) have been submitted in support of this NDA. Study AQ-08-12 is a three-way crossover, formulation effect and drug interaction bioavailability study and Study AQ-08-13 is a six-way crossover, food effect and drug interaction, relative bioavailability study of the to-be-marketed formulation ibuprofen 200 mg/phenylephrine 10 mg.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Motrin IB	NDA 19012	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph: Phenylephrine HCl 10 mg (21 CFR 341)

d) Discontinued from marketing?

YES ☐ NO X

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for the change from the Motrin single ingredient product to a new combination of ibuprofen and phenylephrine.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES NO X

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): 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)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22565	ORIG-1	WYETH CONSUMER HEALTHCARE	Advil Congestion Relief

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

/s/

JANICE Adams
06/02/2010

Labeling Review for
Advil Congestion Relief
Draft Labeling 2nd Addendum

SUBMISSION DATES:	May 11, May 18 and May 26, 2010
NDA/SUBMISSION TYPE:	22-565 (PA)
ACTIVE INGREDIENTS:	200 mg ibuprofen and 10 mg phenylephrine HCL
DOSAGE FORMS:	Tablet
SPONSOR:	Wyeth Consumer Healthcare Erica Sinclair, Senior Manager, Global Regulatory Affairs
REVIEWER:	Ayana K. Rowley, Pharm.D., DNRD, ODEIV
TEAM LEADER:	Marina Y. Chang, R.Ph., DNRD, ODEIV

I. BACKGROUND

This is an addendum draft labeling review. Previous labeling reviews were completed on November 4 and December 4, 2009. This addendum draft labeling review is to address the labeling revision negotiations that were conducted between the Agency and the sponsor on May 13th, 20th and 24th. The sponsor submitted revised labels on May 11th, 18th and 26th. This label review reflects the labels submitted on May 26, 2010.

PROPRIETARY NAME CHANGED: The sponsor has revised their carton and container labels in response to the agency's denial of the initial proposed proprietary name, "Advil Cold and Sinus PE". The sponsor re-submitted revised carton and container labels (see chart below) on May 11, 2010 with a new proposed proprietary name, "Advil Congestion Relief".

NOTE: In the December 4, 2009 labeling review, it was recommended to revise the following bulleted statement under the "Directions" heading: "for best result, do not take with a full meal" to state "for best results, do not take with food". The rationale for this revision was to enhance the clarity of the label by providing the consumer with consistent language in the drug facts panel regarding a potential food effect. However, the food effect concern was re-addressed by the clinical review team and it was concluded that the food effect was not clinically meaningful. Thus, the sponsor was asked to delete the statement "for best results, do not take with a full meal" in the "Directions", and no further revisions to this statement were needed.

Submitted Labeling	Representative of Following SKUs
Outer Carton (20-count)	N/A
Outer Carton - Piggy Back Drug Facts	N/A
Immediate Container - Individual Foil Blister Pouch (Front and Back)	N/A
Immediate Container -Blister Card (10-count)	N/A
Outer Carton-Dispenser Bin (50-count)	N/A

REVIEWER'S COMMENTS
This addendum draft label review includes a brief summary of the May 11, May 18th and May 26, 2010 labeling submissions and revisions.

May 11, 2010 Submission
The sponsor re-submitted their revised carton (20- and 50-count) and immediate container (blister card and pouch) labels in response to the agency's denial of their initial proprietary name proposal, Advil Cold and Sinus PE. The sponsor has included an alternative proprietary name; Advil Congestion Relief, on their revised labels. The agency provided the following draft label comments to the sponsor as an information request (via email) on May 13, 2010:

1. Annoted Font Specifications are missing.

2. On the principal display panel, the sponsor uses the phrase "caplet". The agency does not recognized this as an official dosage form. The sponsor must revise the label to include the definition of a "caplet" on the principal display panel as a recognized dosage form. For example, a "Caplet" is a "Capsule-Shaped Tablet". The sponsor must make this denotation at least once on the principal display panel on all of their SKU. This can be provided by creating an asterisk following the term "caplet" and then closely followed below/beside the definition (capsule-shaped tablet) with an asterisk preceding the definition. Also, please confirm with the sponsor that their product meets the definition of a "caplet" which is a "capsule-shaped tablet".

3. We would prefer that there is no interruption of the Trade name with promotional statements. Currently, the statement "Non-Drowsy" interrupts "Advil" and "Congestion Relief" on the principal display panel.

May 18, 2010 Submission
The sponsor provided revised labels in response to the agency's May 13, 2010 information request, which included the following revisions.

1. The inclusion of the annotated font specifications

2. The revision of the dosage form descriptor to an officially recognized dosage form (from "caplet" to "tablet").

3. The relocation of "Non-Drowsy" on the principal display panel so that it no longer interrupts the proposed trade name.

Reviewer's Comments: The above mentioned revisions were acceptable, however the sponsor removed " [bullet] pain gets worse or lasts more than 7 days" warning statement from the subheading "Stop use and ask a doctor if". The agency notified the sponsor via email on May 20th that this statement should be included in the label.

May 24, 2010 Teleconference

The agency held a teleconference with the sponsor informing them of an additional label revision under the subheading, "Do not use". The agency requested that the sponsor revise the current statement "[bullet] in children under 12 years of age" to read "[bullet] this product contains too much medication for children under 12 years of age'.

Reviewer's Comments: The agency has asked the sponsor to revise this warning to be in compliance with the Pediatric Research Equity Act (PREA) (505B(a)(4)(D)); when a pediatric wavier request is granted. The statue states that if FDA grants a waiver "…because there is evidence that a drug…would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug."

On May 25, 2010, the sponsor provided the agency with a draft annotated label for the drug facts panel via email. The following revisions were included:

1. Under the subheading "Do no use" the statement (b) (4) was revised to" [bullet] in children under 12 years of age because this product contains too much medication for children under this age.

2. Under the Heading directions the statemen (b) (4) was revised to (b) (4)

Reviewer's Comments: The agency informed the sponsor that the proposed changes were acceptable however, in order to keep the same format under "Directions", the agency requested that the sponsor to revise the statement as follows: "Children under 12 years of age: do not use because this product contains too much medication for children under this age". This label revision was communicated to the sponsor on the same day.

May 26, 2010 Submission (Formal Labeling Review)

A. Carton (20-count), Carton-Piggy Back Drug Facts, Immediate Container -Foil Blister Pouch, Immediate Container-Blister Card, Carton -Dispenser Bin (50-count)

i. Outer Carton Label Outside Drug Facts

The labels submitted on May 26, 2010 are in accordance with the current labeling regulations for this product. There are no deficiencies to be noted at this time. Therefore, the submitted labeling is acceptable.

Note: The Division of Medication Error Prevention Analysis (DMEPA) provided the following draft labeling comment concerning the outer carton label on May 26, 2010 (see DMEPA review): *The dosage form is presented using two different terms (pill, tablet) on the principal display panel of the carton, which is confusing. For consistency and clarity, change the banner that states "1 pill dosage" to read "1 tablet dosage.*

Reviewer's Comments: The Division of Nonprescription Regulation Development (DNRD) recognizes the inconsistency in the terminology presented on the principal display panel; however, the term "pill" is commonly used to convey to the consumer a variety of dosage forms (tablet, capsule, etc.). This term exists on other nonprescription products in the marketplace and the division is unaware that this inconsistency has lead to consumer confusion or has resulted in any adverse events or safety concerns. DNRD will allow the banner statement to remain "1 pill dosage".

ii. Outer Carton Drug Facts Label

The labels submitted are in accordance with current labeling regulations for this product. The annotated font specifications are acceptable and in accordance with 21 CFR 201.66. There are no deficiencies to be noted at this time. Therefore, the submitted labeling is acceptable.

iii. Immediate Container Label (Blister Card and pouch)

The labels submitted are in accordance with current labeling regulations for this product. There are no deficiencies to be noted at this time. Therefore, the submitted labeling is acceptable.

Note: DMEPA provided the following draft labeling comments concerning the immediate container (pouch) label on May 26, 2010 (see DMEPA review).

1. *On the single dosage packet container labels, the Applicant has included the statement of identity in the highlighted yellow box, which is helpful. Given that these packets may be stored separate from the shelf carton, we also recommend that the Applicant consider highlighting phenylephrine with the colors red and white (as presented on the carton).*

Reviewer's Comments: The division appreciates the comments provided by DMEPA to further enhance the readability of the immediate container label. However, there is no regulation that requires color differentiation for each ingredient in a combination product. The division will not recommend the sponsor to highlighting phenylephrine with a different color at this time but

will take this recommendation in consideration on the applicability of highlighting individual active ingredients on the immediate containers of combination products in a later date.

2. *On the single dosage packet container labels, the statement of identity is confusing because the active ingredients are not directly linked with their pharmacological category (e.g. pain reliever/fever reducer and nasal decongestant). Consider reverting to the previous presentation and extending the highlighted yellow box to include the active ingredient and purposes section (immediately above "uses").*

Reviewers Comments: The division appreciates the comments provided by DMEPA to further enhance the immediate container label, however due to the small spatial parameters of the packaging, the division does not agree that the spacing provided will allow for such a revision without reducing the font size or cause additional crowding. The division will allow the current alignment of the statement identity and pharmacological categories on to remain as is.

iv. Consumer Information Leaflet or Package Insert

The sponsor did not provide a consumer information leaflet or package insert with this application. This is acceptable.

v. Proprietary Name Review

The sponsor resubmitted an alternative proprietary name, **Advil Congestion Relief** on May 11, 2009. DMEPA approved this proprietary name on May 25, 2010.

II. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Advil Congestion Relief labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: Carton (20-count), Carton-Piggy Back Drug Facts, Immediate Container -Foil Blister Pouch (front and back), Immediate Container-Blister Card, and Carton -Dispenser Bin (50-count) labels submitted on May 26, 2010 date.

III. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

11 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22565	ORIG-1	WYETH CONSUMER HEALTHCARE	Advil Congestion Relief

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

/s/

AYANA K ROWLEY
05/27/2010

MARINA Y CHANG
05/27/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 17, 2010

TO: Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation (DNCE)

FROM: Carol M. Rivera-Lopez, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 2/19/10
Acting Team Leader, Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Addendum to the Review of EIRs Covering NDA 22-565, Advil® Cold & Sinus PE (Ibuprofen 200 mg/Phenylephrine HCl 10 mg) caplets, sponsored by Wyeth Consumer Healthcare.

At the request of the Division of Nonprescription Clinical Evaluation (DNCE), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

Study # AQ-08-12
Title: "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 # AQ-08-13
Title: "A Six-Way Crossover, Food Effect/Drug Interaction, Bioavailability Study of a Caplet Formulation of Ibuprofen 200 MG and Phenylephrine Hydrochloride 10 MG"

Following evaluation of the Form FDA-483 observations for Bio-Kinetic Clinical Applications (clinical portion of study AQ-08-12) and (b)(4) (analytical portion of both studies) and Bio-kinetic's response, DSI submitted an inspection summary memo to DNCE on January 28, 2010. DSI concluded that the clinical and

analytical data from both studies are acceptable for Agency review.

This addendum is to inform DNCE that DSI received (b) (4) response (dated January 21, 2010) on February 1st, 2010. Following evaluation of the firm's response, DSI recommendation remains unchanged.

Conclusion:

Studies AQ-08-12 and AQ-08-13 are acceptable for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Carol M. Rivera-Lopez, Ph.D.

Final Classification:

(b) (4)

FEI: (b) (4)

cc:
DSI/GLPBB/Rivera-Lopez/Yau/CF
OCP/DCP2/Ying Fan
OND/DNCE/Adams-King
HFR-CE2545/Milazzo
Draft: CRL 2/12/10
Edit:
DSI file: 6008
O:\BIOEQUIV\EIRCOVER\22565wye.ibupe.add.doc
FACTS: (b) (4)

Email:
CDER DSI PM TRACK

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/

CAROL M RIVERA-LOPEZ

02/23/2010

Dr. Yau signed the paper copy on 2/19/10. Original signed copies are available in the DSI file.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 28, 2010

TO: Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation (DNCE)

FROM: Carol M. Rivera-Lopez, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. _____
Acting Team Leader, Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-565, Advil® Cold & Sinus PE (Ibuprofen 200 mg/Phenylephrine HCl 10 mg) caplets, sponsored by Wyeth Consumer Healthcare.

At the request of the Division of Nonprescription Clinical Evaluation (DNCE), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

Study # AQ-08-12
Title: "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 # AQ-08-13
Title: "A Six-Way Crossover, Food Effect/Drug Interaction, Bioavailability Study of a Caplet Formulation of Ibuprofen 200 MG and Phenylephrine Hydrochloride 10 MG"

The clinical portion of Study AQ-08-12 was conducted at Bio-Kinetic Clinical Applications in Springfield, MO. The clinical portion of Study AQ-08-13 was conducted at PPD Development in Austin, TX. The analytical portion for both studies was conducted (b) (4) Following the inspection of PPD Development, Austin, TX (December 8-16, 2009), no significant findings were noted and no Form FDA 483 was issued.

Following inspections of Bio-Kinetic Clinical Applications, Springfield, MO (November 18-24, 2009) and (b) (4) (January 4-8, 2010), Form FDA 483 was issued (Attachments 1 and 2, respectively). DSI received Bio-Kinetic's response to Form 483 on January 15, 2009. DSI has not yet received (b) (4) response to Form 483. Our evaluation of the 483 observations and Bio-Kinetic's response follows:

Bio-Kinetic Clinical Applications, Springfield, MO (Clinical portion Study AQ-08-12)

1. **An investigation was not conducted in accordance with the investigational plan. Specifically,**

   a. **You failed to document the time the blood samples for IBU and PHE analysis were taken from the centrifuge, the rpm's used and temperature for the centrifuge in the source documents to ensure compliance with the protocol for Study No. AQ-08-12. The protocol states the blood samples for IBU assay are to be centrifuged at (b) (4) and the blood samples for PHE assay are to be centrifuged at approximately (b) (4)**

   b. **Your review of the protocol deviations for blood draw time points which were submitted to the Institutional Review Board on 9/15/08 failed to identify 22 additional blood draw time point deviations. These additional protocol deviations were submitted to the Institutional Review Board by you on 11/17/09.**

Although Bio-Kinetic failed to document the times and conditions of centrifugation mentioned in observation 1a, at the inspection they claimed that they actually complied with the protocol requirements. Although they did not report the deviations to the IRB, DSI believes it is unlikely that subject safety was compromised by blood sampling deviations. The deviations were properly reported to the sponsor and included in the final study report with appropriate adjustments to pharmacokinetic parameter calculations. In their response, the firm acknowledged the findings and documented corrective actions for future studies. DSI concludes that these deviations do not affect the study data.

(b) (4) **(Analytical)**

(b) (4)

(b) (4)

Conclusions:

Following the above inspections, the Division of Scientific Investigations recommends the following:

- Studies AQ-08-12 and AQ-08-13 are acceptable for Agency review.

Please note that DSI has not yet received (b) (4) response to the Form 483 observations. We will submit our evaluation of the response soon after receipt.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Carol M. Rivera-Lopez, Ph.D.

Final Classifications:

NAI – PPD Development, Austin, TX
FEI: 1643420
VAI – Bio-Kinetic Clinical Applications, Springfield, MO
FEI: 1000511105
VAI – (b) (4)
FEI: (b) (4)

cc:
DSI/GLPBB/Rivera-Lopez/Yau/Salewski/CF
OCP/DCP2/Ying Fan
OND/DNCE/Adams-King
HFR-CE2545/Milazzo
Draft: CRL 1/25/10, 1/28/10
Edit: MFS 1/27/10
DSI file: 6008
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FACTS: (b) (4)

Email:
CDER DSI PM TRACK

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/

CAROL M RIVERA-LOPEZ
01/28/2010

MICHAEL F SKELLY
01/28/2010
signed on behalf of Dr. Martin Yau

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 3, 2009
To:	Andrea Leonard-Segal, M.D., Director Division of Nonprescription Clinical Evaluation
Through:	Kellie Taylor, Pharm.D., M.P.H., Team Leader Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Advil Cold & Sinus PE (Ibuprofen and Phenylephrine Hydrochloride) Caplets 200 mg/10 mg
Application Type/Number:	NDA 022565
Applicant:	Wyeth Consumer Healthcare
OSE RCM #:	2009-1591

CONTENTS

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a request from the Division of Nonprescription Clinical Evaluation (DNCE) for evaluation of the labels and labeling of Advil Cold & Sinus PE to identify areas that could contribute to medication errors. The Applicant submitted proposed container labels and carton labeling for our review.

1.2 REGULATORY HISTORY

On August 26, 2009, the Applicant submitted "Advil Cold & Sinus PE" as the proposed proprietary name for this product. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed name unacceptable because the "PE" modifier may not provide adequate differentiation from the currently marketed Advil Cold & Sinus product, which contains pseudoephedrine (see RCM# 2009-1586; dated November 6, 2009). Subsequently, we notified the Applicant of our decision in a letter dated November 16, 2009. As of the date of this review, DMEPA has not received additional information from the Applicant regarding the proprietary name for this product.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and carton labeling submitted August 26, 2009 (see Appendix A).

For the purpose of comparison, we also reviewed the labels and labeling for the currently marketed Advil Cold & Sinus products (Liqui-Gels and Caplets) obtained from the annual reports dated July 24, 2009 and November 18, 2008, respectively (see Appendix B).

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

Since Advil Cold & Sinus liqui-gels and caplets are currently marketed products, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to retrieve any medication errors involving risks that might relate to Advil Cold & Sinus PE caplets. AERS was searched using the trade name terms *"Advil Cold & Sinus" and "Advil Cold & Sinus PE",* and the verbatim terms *"Advil Cold%" and "Advil Sinus %* with the MedDRA high level group term "Medication Errors" and preferred term "Product Quality Issue". We selected the option to include combination products.

The cases were manually reviewed to determine if medication errors occurred involving the labels/labeling. Those cases that did not describe a medication error were excluded from further analysis.

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

The search of the Adverse Event Reporting System retrieved eight reports. However, only two involved medication errors as follows: one report described accidental ingestion by a child and the other described an overdose which resulted in an adverse event, but the cause is unclear. Of the remaining six reports, four involved intentional misuse of the product resulting in overdose and two described adverse events.

4 RECOMMENDATIONS

Our evaluation noted areas where the presentation of information on the container labels and carton labeling can be improved to minimize the potential for medication errors. *Section 4.2 Comments to the*

Applicant contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Karen Townsend, Regulatory Project Manager, at 301-796-5413.

4.1 COMMENT TO THE DIVISION

DMEPA found the proposed proprietary name "Advil Cold & Sinus PE" unacceptable for this product and subsequently notified the Applicant. The proprietary name remains a pending issue for this application.

4.2 COMMENTS TO THE APPLICANT

A. General Comments for All Labels and Labeling

1. Please submit revised labels and labeling reflecting the approved proprietary name for this product, when available, for our review.

B. Container Labels (Blister Cards – (b) (4) 1 x 10 caplets; Single Dose Packets)

No comments at this time.

C. Carton Labeling (Package of 20 caplets; Package of 50 single dose packets)

1. We note that the tradedress for Advil Cold & Sinus PE is very similar to that of the currently marketed Advil Cold & Sinus products which contain pseudoephedrine. While the "PE" at the end of the name is highlighted in bright yellow, the similarities may lead to confusion with the Advil Cold & Sinus products if this ibuprofen/phenylephrine product is managed using an Advil tradename. Changes in background color and font style may result in improved differentiation.
2. Ensure the flag that states "New formula" located in the upper left hand corner of the principal display panel remains on the labeling for no more than 6 months after the initial product launch.
3. We note that the dosage form is presented using two different terms (pill, caplet) on the principal display panel, which is confusing. For consistency and clarity, change the banner that states "1 pill dosage" to read "1 caplet dosage".

10 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

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/

TARA P TURNER
12/02/2009

KELLIE A TAYLOR
12/04/2009

CAROL A HOLQUIST
12/04/2009

OTC Drug Labeling Review Addendum

Advil Cold and Sinus PE

Office of Nonprescription Drug Products

Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATE: September 28, 2009

REVIEW DATE: December 1, 2009

NDA: 22-565

SUBMISSION TYPE: BLA

SPONSOR/CONTACT: Wyeth Consumer Healthcare
5 Giralda Farms
Madison, NJ 07940

Erica Sinclair,
Senior Manager,
Global Regulatory Affairs

DRUG PRODUCT (BRAND NAME): Advil Cold and Sinus PE coated caplets

ACTIVE INGREDIENT(S): ibuprofen 200 mg and phenylephrine 10 mg

PHARMACOLOGICAL CATEGORY: analgesic and nasal decongestant

LABELING SUBMITTED (SKU):

1. Carton (20 – count)
2. Piggy back drug facts carton
3. Individual foil pouch
(b) (4)
5. Blister card (10 – count)
6. Dispenser bin (50 – count)

PROJECT MANAGER: Janice Adams-King, RN

REVIEWER'S NAME: Ayana K .Rowley, Pharm.D.

BACKGROUND

This is an amendment to the October 29, 2009 labeling review, which was put in DARRTS on November 4, 2009. This review addresses additional labeling comments and revisions discussed with the review team during the mid-cycle meeting on November 30, 2009.

REVIEWER'S COMMENT

I. Drug Facts Panels

The Office of Clinical Pharmacology has determined that food affects the pharmacokinetics of this product. Therefore, to inform the consumer that the product should not be taken with food we recommend the following revisions.

A. Remove the following statement located under the heading "Warnings" and the subheading When using this product: *"take with food or milk if stomach upset occurs".*

B. Revise the following located under the heading "Directions" from "for best results, do not take with a full meal" to state, *"for best results, do not take with food."*

RECOMMENDATIONS

1) We recommend a "Discipline Review Letter" for the following labels in this submission:

Piggy back drug facts carton
Individual foil pouch
Dispenser bin (50 – count)

2) Inform the sponsor the following revisions MUST be made to the proposed labeling for the above mentioned labels prior to the action due date and resubmit as addendum to this supplement:

a) Remove the following statement located under the heading "Warnings" and the subheading When using this product: *"take with food or milk if stomach upset occurs".*
b) Revise the following statement located under the heading "Directions" from "for best results, do not take with a full meal" to state, *"for best results, do not take with food."*

Ayana K. Rowley, Pharm.D.
Reviewer's name

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/

AYANA K ROWLEY
12/04/2009

DEBBIE L LUMPKINS
12/04/2009

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-565 (formerly 22-112) BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Advil Cold and Sinus PE Established/Proper Name: Ibuprofen and Phenylephrine Dosage Form: Capsules Strengths: Ibuprofen 200 mg and Phenylephrine 10 mg		
Applicant: Wyeth Consumer Healthcare Agent for Applicant (if applicable):		
Date of Application: July 28, 2009 Date of Receipt: July 28, 2009 Date clock started after UN:		
PDUFA Goal Date: May 28, 2009	Action Goal Date (if different): January 28, 2010	
Filing Date: Date of Filing Meeting: Sept 22, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Pain Reliever, Fever Reducer, Nasal Decongestant		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***		☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☒ Formerly NDA 22-112 Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☒ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR

	601.42)
Collaborative Review Division (*if OTC product*): DAARP	
List referenced IND Number(s):	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments: Resubmission of nonapprovable application that was submitted and accepted for filing without identification of listed drug**	☐ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☒ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☐ YES # years requested: ☒ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ **Not applicable** ☐ YES ☒ NO ☐ YES ☒ NO ☐ YES ☒ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☒ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**: Submitted as amendments upon information request	☒ YES ☐ NO ☐ YES ☒ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☒ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must***	☒ YES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☒ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**: Requested pediatric plan in 74-day letter	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☒ **Not applicable** ☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☐ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☐ Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**:	☐ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☐ Not Applicable ☐ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**: 20-count carton, carton drug facts piggy back label, individual foil pouch, 8-count blister card, 10- count blister card and 50-count dispenser bin	☐ **Not Applicable** ☒ Outer carton label ☐ Immediate container label ☒ Blister card ☒ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☒ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**: None	☒ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**: None	☒ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**: None	☒ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**: None	☒ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☐ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 22, 2009

NDA/BLA #: 22-565

PROPRIETARY/ESTABLISHED NAMES: Advil Cold and Sinus PE

APPLICANT: Wyeth Consumer Healthcare

BACKGROUND: A combination of the OTC analgesic ibuprofen (IBU) with the nasal decongestant pseudoephedrine HCl (PSE) was approved as a solid, oral dosage form on September 19, 1989 (Advil Cold & Sinus, NDA 19771), as a suspension on April 18, 2002 (NDA 21373), and as a liquid-filled capsule on May 30, 2002 (NDA 21374). The solid, oral dosage form product is being reformulated with the substitution phenylephrine HCl for PSE. This application is a 505(b)(2) application for a new combination of IBU 200 mg and PE 10 mg to provide an alternative to the IBU 200 mg and PSE 30 mg product currently marketed under the trade name Advil Cold & Sinus, NDA 19771.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Janice Adams-King	Y
	CPMS/TL:	Melissa Furness	Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Linda Hu	Yes
	TL:	Daiva Shetty	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:	Ayana Rowley	Y
	TL:	Marina Chang	Y
OSE	Reviewer:	Tara Turner	Y
	TL:	Kellie Taylor	Y

Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ying Fan	Y
	TL:	Dakshina Chilukuri	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:	Paul Brown	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Gene Holbert	Y
	TL:	Shulin Ding	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers	Robert Shibuya (DAARP)		Y

OTHER ATTENDEES: Shaw Chen, Leah Christl, Andrea Leonard-Segal, Joel Schiffenbauer, Karen Townsend

505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☒ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☒ NO ☐ YES ☐ NO

FACILITY (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Janice Adams-King

GRMP Timeline Milestones: 9/22 Filing Meeting; 11/30 Mid-Term Meeting; 1/4/10 Wrap-Up Meeting; 1/6/2010 PeRC Meeting; 1/28/2010 (Proposed Action Date)

Comments: Complete Response to NDA 22-112

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/

JANICE Adams
11/13/2009

OTC Drug Labeling Review
Advil Cold and Sinus PE

Office of Nonprescription Drug Products
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATE: September 28, 2009

REVIEW DATE: October 29, 2009

NDA: 22-565

SUBMISSION TYPE: BLA

SPONSOR/CONTACT: Wyeth Consumer Healthcare
5 Giralda Farms
Madison, NJ 07940

Erica Sinclair,
Senior Manager,
Global Regulatory Affairs

DRUG PRODUCT (BRAND NAME): Advil Cold and Sinus PE

ACTIVE INGREDIENT(S) [ESTABLISHED NAME(S)]: ibuprofen and phenylephrine

PHARMACOLOGICAL CATEGORY: analgesic and nasal decongestant

LABELING SUBMITTED (SKU):

1. Carton (20 – count)
2. Piggy back drug facts carton
3. Individual foil pouch
(b) (4)
5. Blister card (10 – count)
6. Dispenser bin (50 – count)

PROJECT MANAGER: Janice Adams-King, RN

REVIEWER'S NAME: Ayana K .Rowley, Pharm.D.

BACKGROUND

Wyeth Consumer Healthcare has submitted this application to address the deficiencies noted in the non-approval letter sent to them on May 8, 2007 under NDA 22-112 Advil Cold and Sinus PE. The sponsor has re-submitted NDA 22-112 as NDA 22-565 due to administrative requirements. The sponsor has submitted the following labels for Advil Cold and Sinus PE under NDA 22-565 on July 28, 2009: 20-count carton, piggyback drug facts label, blister card (b) (4) 10-count), individual foil pouch and a 50-count dispenser bin.

REVIEWER'S COMMENT

This review will highlight the revisions made by the sponsor that addresses the labeling deficiencies noted in the non-approval letter for NDA 22-122 as well as any additional changes made to the labels.

(b) (4)

I. Carton Label (20-count and 50-count dispenser bin)

A. Principal display and side panel (s)

1. The "New Formula" flag must be removed following 180 days of marketing.

2. "See New Warnings Information" has been added in bold type and in prominent prize size on the principal display panel to inform consumers of the new warnings concerning the Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use Final Rule published on April 29, 2009.

   Reviewers' Comment: This revision is acceptable. This statement must remain on the label for 12 months after the effective date of the final rule as stated in 201.326 (b).

3. Proprietary name review; The sponsor has proposed the trade name: Advil Cold and Sinus PE.

   Reviewer's Comment: The acceptability of this trade name is pending the Division of Medication Error and Prevention Assessment's review. We will reserve further comment until their review has been completed.

4. "Ibuprofen 200 mg Pain Reliever/Fever Reducer (NSAID)" is in bold type and one-quarter as large as the size of the most prominent printed matter on the principal display panel.

   Reviewer's Comment: This revision has been made to be in accordance with 21 CFR 201.326 (a)(2)(i) and this is acceptable.

II. Drug Facts Panels 0

A. Under the Heading: Uses. The sponsor has added the following two new indications for this product: "Reduces swelling of the nasal passages" and "Temporarily restores freer breathing through the nose".

   Reviewer's Comment: These indications are listed as acceptable phrases in the monograph (see 21 CFR 341.80(b)). This is acceptable.

B. Under the heading: Warnings.
   a. Subheading: Do not use. The sponsor has added the phrase (b) (4)

   Reviewer's Comment: This issue is currently under review by the Division of Nonprescription Clinical Evaluation and Regulatory Policy Staff (RPS). We will reserve comment until their reviews have been completed.

   b. Subheading: Ask a doctor before use if. The sponsor has added the term "asthma". This revision was made to address the labeling deficiency noted in NDA 22-112.

   Reviewer's Comment: This revision is acceptable as it alerts consumers with pre-existing asthma to talk to their health provider to address the agency's concerns about NSAID-induced asthma.

   c. Subheading: Stop use and ask a doctor if. The sponsor has revised the statement (b) (4) to "pain gets worse or last more than 7 days" This revision was made to address the labeling deficiency noted in the non-approval letter for NDA 22-122.

   Reviewer's Comment: This revision is acceptable since a cold product should not be taken longer than 7 days.

C. Under the heading: Directions. The sponsor has revised the statement from (b) (4) to "do not take longer than 7 days, unless directed by a doctor (see Warnings)". This revision was made to address the labeling deficiency noted in the non-approval letter for NDA 22-122.

Reviewer's Comment: This revision is acceptable to be consistent with the number of days for the intended treatment.

D. Under the heading: Other information. The sponsor has added the (b) (4) times of day that are appropriate for the consumer to call regarding any questions or comments for this product. This revision was made to address the labeling deficiency noted in the non-approval letter for NDA 22-112.

Reviewer's Comment: This revision is acceptable and in accordance with 21 CFR 201.66 (c)(9).

III. Drug Facts Panel for Dispenser Bin (50- count)

A. Under the subheading: Other information. The phrase "Keep Carton" has been omitted.

Reviewer's Comment: This is acceptable since full drug facts information has been provided on the individual foil pouches.

IV. Immediate Container Label (as noted in the previous labeling review for NDA 22-112).

Reviewer's Comment:

1. Blister pack labeling is appropriate, per 21 CFR 201.10(h)(2)(i)
2. Non-child resistant packaging for "1 caplet" dose is appropriate
3. One count foil pouch with full labeling is acceptable

V. All annotated specifications for carton and container labels are acceptable.

RECOMMENDATIONS

1. We will make our final recommendation for the following carton and container labels:

1. Carton (20 – count)
2. Piggy back drug facts carton
3. Individual foil pouch
4. Blister card (10 – count)
5. Dispenser bin (50 – count)

Pending the outcome of the reviews of the trade name and whether this product should be labeled as "Adults and children 12 years of age and older" (b) (4) and "Do not use in children under **12** (b) (4) years of age" due to the PREA.

2. Inform the sponsor the "New Formula" flag on the principal display and side panels needs to be deleted from the 20- count carton and 50- count dispenser bin labels after 180 days of marketing.

3. Remind the sponsor that the statement "See New Warnings Information" must remain on the label for 12 months after the effective date of the Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use Final Rule published on April 29, 2009 as stated in 201.326 (b).

4. Pending the review of the following, issues:

   A. Trade name Review- The sponsor has proposed the trade name: Advil Cold and Sinus PE. The acceptability of this trade name is pending Division of Medication Errors and Prevention Assessment's review. We will reserve comment until the review has been completed.

   B. Under the subheading: The sponsor has added the phrase (b) (4) This issue is currently under review the Division of Nonprescription Clinical Evaluation and Regulatory Counsel staff. We will reserve comment until the review has been completed. If any further changes are needed to the label we will amend our review.

Ayana K. Rowley, Pharm.D.
Reviewer's name

Marina Chang, R.Ph
Team Leader concurrence

5 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

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/

AYANA K ROWLEY
11/04/2009

MARINA Y CHANG
11/04/2009

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: October 16, 2009

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Director, Division of Pharmaceutical Evaluation

FROM: Janice Adams-King**,** Regulatory Project Manager,
Division of Nonprescription Clinical Evaluation, HFD-560

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-565
Advil® Cold & Sinus PE (ibuprofen 200 mg/phenylepherine HCl 10 mg) caplets
Wyeth Consumer Healthcare

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
AQ-08-12	Study title: A Three-Way Crossover, Formulation Effect and Drug Interaction, Bioavailability Study Of A Caplet Formulation Of Ibuprofen 200 MG And Phenylephrine Hydrochloride 10 MG Principal Investigator: Donald Burkindine, D.O. Clinical site: Bio-Kinetic Clinical Applications, LLC 1816 W. Mt. Vernon Springfield, MO 65802	(b) (4)
AQ-08-13	Study title: A Six-Way Crossover, Food Effect/Drug Interaction, Bioavailability Study of a Caplet	(b) (4)

	Formulation of Ibuprofen 200 MG and Phenylephrine Hydrochloride 10 MG Principal Investigator: Aziz Laurent, M.D. Clinical site: PPD Development Clinic 7551 Metro Center Blvd, Suite 200 Austin TX 78744	

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by December 1, 2009. We intend to issue an action letter on this application by January 28, 2010.

Should you require any additional information, please contact Janice Adams-King, Regulatory Project Manager, at 301-796-3713.

Concurrence: (Optional)
Ying Fan, Ph.D., Clinical Pharmacology Reviewer
Partha Roy, Ph.D., Clinical Pharmacology Acting Team Leader

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/

JANICE Adams
10/16/2009

LABELING FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: **22-565 (22-112)**	**Applicant:** **Wyeth Consumer Healthcare**	**Stamp Date:** 07/28/09
Drug Name: **Advil Cold &Sinus PE**	**NDA Type:** NDA	

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comments
1	Is Index sufficient to locate necessary labeling?	X		Section 1.14 Labeling
2	Has labeling for all SKUs been submitted (e.g., blister card, pouch, immediate container, carton label and package insert labeling, etc)?	X		1) 20 - count carton 2) Drug facts piggyback label 3) Individual foil pouch (b) (4) 5) 10 - count blister card 6) 50 - count dispenser bin
3	Does the submission contain the annotated specifications for the "Drug Facts" label?	X		All labels have annotated specifications.
4	Is a new trade name being proposed? If multiple trade names, is the RLD trade name identified?	X		New Trade Name: Advil Cold & Sinus PE

Additional Comments:
A non-approvable letter was initially sent to sponsor on May 8, 2007 for NDA 22-112 Advil Cold & Sinus PE (ibuprofen 200 mg/ phenylephrine HCL 10 mg) caplets. The sponsor has resubmitted their application for approval under a new NDA number 22-565.

Internal Notes:

- The sponsor only submitted one count size for the carton, which is a 20–count container. What is the purpose of the (b) (4)
- The sponsor has indicated that this product target population will include the pediatric age group (12-16). A full pediatric development plan has not been included in this submission to support the use of this product in this patient population. Further labeling changes may be required to address the age limitations/restrictions for children less than 17 years of age.

Ayana K. Rowley, Pharm.D. — September 22, 2009
Reviewing Interdisciplinary Scientist — Date

Marina Y. Chang, R.Ph.
Supervisor/Team Leader — Date

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/s/

AYANA K ROWLEY
10/02/2009

MARINA Y CHANG
10/05/2009