

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022113Orig1s000**

**OTHER REVIEW(S)**

### 505(b)(2) ASSESSMENT

Application Information		
NDA # 22113	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Advil Allergy and Congestion Relief Established/Proper Name: ibuprofen (IBU), phenylephrine HCl (PE), and chlorpheniramine (CHLOR) Dosage Form: tablet Strengths: IBU 200 mg, PE 10 mg, and CHLOR 4 mg		
Applicant: Pfizer Consumer Healthcare		
Date of Receipt: 6/21/2011		
PDUFA Goal Date: 12/21/2011	Action Goal Date (if different):	
Proposed Indication(s): temporary relief of symptoms associated with upper respiratory allergies and the common cold		

### 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: phenyephine	Pharmacokinetic data
CCABA Monograph: chlorpheniramine	Pharmacokinetic data
NDA 19012: Motrin IB	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 studies were conducted. The new combination product was compared to the single ingredient reference products Motrin IB, Sudafed PE, and Chlor-Trimeton; the latter two are monograph products. Study AD-08-10, using a revised and revalidated assay for PE, characterized the rate and extent of IBU, PE and CHLOR absorption under fasted conditions from IBU/PE/CHLOR 200/10/4 mg caplets compared to marketed Motrin IB (IBU 200 mg), Sudafed PE (PE 10 mg) and Chlor-Trimeton (CHLOR 4 mg) single entity products administered concomitantly. Additionally, the rate and extent of IBU, PE and CHLOR absorption from IBU/PE/CHLOR formulation was compared under fasted and fed conditions (i.e., food effect).

**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 and Chlorpheniramine maleate 4 mg (21 CFR 341)

d) Discontinued from marketing?

YES  NO

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 incorporation of phenylephrine HCl (10 mg) in this new product to replace pseudoephedrine HCl (30 mg) that is included in the currently marketed OTC product, Advil Allergy Sinus, NDA 22-441. The pseudoephedrine product was moved 'behind the counter' in compliance with the Combat Methamphetamine Epidemic Act of 2005 that restricted the sale of all pseudoephedrine (PSE) containing drug products over the counter.

*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) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not 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

*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):

<b>PATENT CERTIFICATION/STATEMENTS</b>
--

- 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):

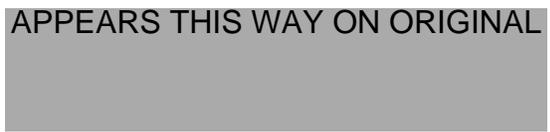
Date(s):

- (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

APPEARS THIS WAY ON ORIGINAL



-----  
**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  
12/21/2011

# Labeling Review for Advil Allergy and Congestion Relief *Draft Labeling*

---

---

**SUBMISSION DATES:** June 21 and November 23, 2011

**NDA/SUBMISSION TYPE:** 22-113/ Class 2 Resubmission

**ACTIVE INGREDIENTS:** 200 mg ibuprofen, 4 mg chlorpheniramine, 10 mg phenylephrine

**DOSAGE FORMS:** tablet

**SPONSOR:** Pfizer Consumer Healthcare  
Erica Sinclair

**REVIEWER:** Ayana K. Rowley, Pharm.D. ODEIV/DNRD

**TEAM LEADER:** Elaine Abraham, R.Ph. ODEIV/DNRD

---

---

## I. BACKGROUND

The sponsor has submitted labels for Advil Allergy and Congestion Relief as a Class 2 resubmission based on a Not Approvable letter sent on July 25, 2008. This is the first triple combination drug product consisting of chlorpheniramine 4 mg, ibuprofen 200 mg and phenylephrine 10 mg to treat symptoms associated with hay fever, upper respiratory allergies, and the common cold. This product is indicated for adults and children down to 12 years of age.

Submitted Labeling	Representative of Following SKUs
Outer carton (10-count)	N/A
Outer carton (20- count)	N/A
Outer carton (40-count)	N/A
Outer carton (50-count/dispenser bin)	N/A
Outer carton (Piggyback drug facts)	N/A
Immediate container (10- count blister)	N/A
Immediate container (1- count pouch FRONT)	N/A
Immediate container (1-count pouch BACK)	N/A

**REVIEWER'S COMMENTS****A. Outer carton 10-, 20-, 40-, 50-count carton labels and piggyback drug facts label.****i. Outer Carton Label Outside Drug Facts****(a) New Flag**

**Reviewer's comments:** The sponsor has added a "New" flag since this is the first triple combination drug product for chlorpheniramine 4mg, ibuprofen 200 mg and phenylephrine 10 mg. The "New" flag must be removed after 180 days from marketing. This is acceptable.

**(b) Proprietary Name**

**Reviewer's comments:** The proprietary name for this application is Advil Allergy and Congestion Relief. The Division of Medication Errors Prevention and Analysis (DMEPA) granted approval of this proprietary name on September 14, 2011. This is acceptable.

**(c) Review Team Comments:** The Division of Medication Errors Prevention and Analysis provided the following draft labeling comments on November 8, 2011 (see DMEPA review):

- (i) The dosage form is presented using two different terms [REDACTED] (b) (4) on the principal display of the carton, which is confusing. For consistency and clarity, change the banner [REDACTED] (b) (4) 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 [REDACTED] (b) (4) 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 led to consumer confusion or has resulted in any serious adverse events or safety concerns. During the labeling meeting held on November 14, 2011, this labeling concern was discussed with the review team. It was agreed upon with the review team not to make the labeling recommendation at this time. However if in the future, this becomes a serious safety issue DNRD will re-consider this recommendation.

- (ii) Highlight the active ingredient "phenylephrine" on the outer carton principal display panel and immediate container blister to distinguish the product from Advil Allergy Sinus in which the ingredients only differ by the decongestant.

**Reviewer's comments:** There are no regulatory requirements to highlight specific active ingredients to avoid consumer confusion with other Advil products, therefore DNRD requested the Division of Nonprescription

Clinical Evaluation (DNCE) input to address DMPEA's safety concerns. During the labeling meeting held on November 14, 2011, DNCE did not agree that the specific active ingredient needed to be highlighted with regards to DMEPA's safety concern. It was agreed upon with the review team not to make the labeling recommendation at this time. However if in the future, this becomes a serious safety issue DNRD will re-consider this recommendation.

- (iii) Highlight the active ingredient "phenylephrine" on the immediate container labels because they may be stored separately from the carton.

**Reviewer's comments:** There are no regulatory requirements to highlight specific active ingredients with regards to the immediate container being stored separately from the carton, therefore DNRD requested DNCE's input to address DMPEA's safety concerns. During the labeling meeting held on November 14, 2011, DNCE did not agree that the specific active ingredient needed to be highlighted with regards to DMEPA's safety concern. It was agreed upon with the review team not to make the labeling recommendation at this time. However if in the future, this becomes a serious safety issue DNRD will re-consider this recommendation.

**ii. Outer Carton Drug Facts Label (piggyback drug facts)**

- a. November 23, 2011 labeling amendment

**Review's Notes:** Following the mid-cycle team meeting held on September 19, 2011 the agency contacted the sponsor to recommend adding a general antihistamine warning to be compliance with the monograph regulation 21 CFR 341.72 (c) (1), that states that this product "may cause excitability especially in children." On November 23, 2011, the sponsor provided updated labels to include this warning. This is acceptable.

- b. Class 2 Resubmission

**Reviewer's Notes:** The following labeling comments were conveyed to the sponsor in a Not Approval Letter on July 25, 2008.

- (a) The label should convey a 7-day limit for duration of use (b) (4) in keeping with the monograph dosing for phenylephrine. Labeling should be changed under the "Warnings" and "Directions" sections.

**Reviewers' Comments:** This revision has been made. This is acceptable.

- (b) Under the subsection "Ask a doctor before use if you have", we agree with the inclusion of the term "asthma."

**Reviewer's comments:** This bulleted statement has been moved to the more prominent Allergy Alert section as a warning for all nonprescription ibuprofen containing drug products. This is acceptable.

- (c) Under the “Do not use” subsection of Warnings, we agree with adding the bulleted statement “in children under 12 years of age.” In addition, under Directions, we agree with changing the statement [REDACTED] (b) (4) [REDACTED] to read “children under 12 years of age: do not use.”

**Reviewer’s Comments:** The submitted labels are consistent with the above mentioned recommendations. This is acceptable.

c. Piggyback Drug Facts

**Review’s Comments:** The submitted labels are in accordance with current labeling regulations for this combination drug product. The labeled warnings, directions and uses sections are consistent with monograph and NDA drug products containing the three active ingredients (ibuprofen, chlorpheniramine and phenylephrine). 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 labels are acceptable.

**iii. Immediate Container Label (blister card and pouch)**

The submitted labels are in accordance with current labeling regulations for this combination drug product. The labeled warnings, directions and uses sections are consistent with monograph and NDA drug products containing the three active ingredients (ibuprofen, chlorpheniramine and phenylephrine). There are no deficiencies to be noted at this time. Therefore, the submitted labels are acceptable.

**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.

## II. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Advil Allergy and Congestion labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 10-count immediate container (blister card) and 10-, 20-, and 40- count outer carton labels submitted on June 21, 2011; AND 1-count FRONT and BACK immediate containers (pouch), 50-count (dispenser bin) carton and piggyback drug facts labels submitted on November 23, 2011.

Note: Please inform the sponsor that the “New” flag must be removed following 180 days of marketing.

## III. SUBMITTED LABELING

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

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**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  
11/29/2011

ELAINE E ABRAHAM  
11/29/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 22113 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Advil Allergy and Congestion Relief Established/Proper Name: ibuprofen, phenylephrine HCl, and chlorpheniramine Dosage Form: tablet Strengths: 200 mg, 10 mg, 4 mg		
Applicant: Pfizer Consumer Healthcare Agent for Applicant (if applicable):		
Date of Application: 09-25-2007 Date of Receipt: 09-25-2007 Date clock started after UN:		
PDUFA Goal Date: 07-25-2008		Action Goal Date (if different):
Filing Date: 2007		Date of Filing Meeting:
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): temporary relief of symptoms associated with upper respiratory allergies and the common cold		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>            and refer to Appendix A for further information.</i>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s):				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>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)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>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.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, 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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?				
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?				
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>	X			
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?				
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>	X			
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) 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...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>			X	
<b>Prescription Labeling</b>	<input checked="" type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>			X	
Is the PI submitted in PLR format? <sup>4</sup>				

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Outer carton label <input checked="" type="checkbox"/> Immediate container label <input checked="" type="checkbox"/> Blister card <input checked="" type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>			X	
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 3/19/2007  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**\*MEMO OF FILING MEETING**

**\*RPM Filing not documented in 2007; RPM completing filing review for this application cannot attest to occurrences during presumed filing meeting in 2007. Therefore, no action to the Memo of Filing Meeting is taken.**

**DATE:**

**BLA/NDA/Supp #:**

**PROPRIETARY NAME:**

**ESTABLISHED/PROPER NAME:**

**DOSAGE FORM/STRENGTH:**

**APPLICANT:**

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

**BACKGROUND:**

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:		
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:		
	TL:		
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial</i> )	Reviewer:		

<i>products)</i>			
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:		
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:		
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>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</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• 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?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b>	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

<input type="checkbox"/>	• notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

---

Regulatory Project Manager

Date

---

Chief, Project Management Staff

Date

## 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.

-----  
**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

11/17/2011

RPM Filing not documented in 2007; RPM completing filing review for this application cannot attest to occurrences during presumed filing meeting in 2007. Therefore, no action to the Memo of Filing Meeting is taken.

**MEMORANDUM**

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

---

DATE: November 10, 2011

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

FROM: Michael F. Skelly, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-113, Advil Allergy and  
Congestion Relief (Ibuprofen 200 mg, Phenylephrine HCl  
10 mg, and Chlorpheniramine Maleate 4 mg) tablets,  
sponsored by Pfizer Consumer Healthcare

At the request of Division of Clinical Pharmacology 2, the  
Division of Bioequivalence and GLP Compliance (DBGC) conducted  
inspections of the clinical and analytical portions of the  
following bioequivalence study:

**Study Number:** AD-08-10

**Study Title:** "A Four-Way Crossover, Bioavailability Study of a  
Caplet Formulation Containing Ibuprofen 200 mg,  
Phenylephrine Hydrochloride 10 mg and  
Chlorpheniramine Maleate 4 mg"

The clinical portions of the study were conducted at BioKinetic  
Clinical Applications (aka QPS BioKinetic Clinical Applications)  
Springfield, MO. An inspection was conducted at the site from  
July 21 through October 18, 2011. Following the inspection, no  
Form FDA-483 was issued for this study.

The analytical portions of the study were conducted at (b) (4)  
[REDACTED]. Following the inspection, no Form  
FDA-483 was issued.

**Conclusion:**

Following the above inspections, OSI recommends that the data for the clinical and analytical portions of study AD-08-10 may be accepted for Agency review.

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

Michael F. Skelly, Ph.D.  
Pharmacologist  
Bioequivalence Branch, DBGC, OSI

**Final Classifications:**

**NAI** - QPS BioKinetic Clinical Applications, Springfield, MO  
FEI: 1000511105

**VAI**

(b) (4)

cc:

OSI/Ball/Moreno

OSI/DBGC/Salewski/Dejernet

OSI/DBGC/BB/Haidar/Skelly

OTS/OCP/DCP2/Doddapaneni/Roy

OND/DNCE/Adams-King

HFR-SW3530/Cronenwett

HFR-CE2545/Milazzo

HFR-CE8585/Laufenberg

Draft: MFS 11/8/11

Edits: GP 11/8/11

DSI: File BE6237

O:\BIOEQUIV\EIRCOVER\22113a.Pfi.ibu.phen.chl.doc

FACTS: (b) (4)

Email: CDER DSI PM TRACK

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

/s/  
-----

MICHAEL F SKELLY

11/10/2011

Sam: You earlier approved a copy of this by e-mail.

SAM H HAIDAR

11/23/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: November 8, 2011

Reviewer(s): Lissa C. Owens, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh  
Division of Medication Error Prevention and Analysis

Deputy Director Kellie Taylor, PharmD, MPH  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name(s) & Strength: Advil Allergy & Congestion Relief  
(Ibuprofen, Chlorpheniramine, Phenylephrine HCL)  
Tablets, 200 mg/4 mg/10 mg

Application Type/Number: NDA 022113

Applicant/sponsor: Pfizer Consumer Healthcare

OSE RCM #: 2011-2381

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review summarizes DMEPA's evaluation of the labels and labeling of Advil Allergy & Congestion Relief to identify aspects that could contribute to medication errors.

### 1.1 REGULATORY HISTORY

On September 25, 2007, the Applicant submitted [REDACTED] (b) (4) as the proposed proprietary name for this product. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed name unacceptable because it "appears vulnerable to name confusion with the already marketed product, [REDACTED] (b) (4)

[REDACTED] is ambiguous and may be prone to confusion because it has been used to represent both pseudoephedrine and phenylephrine HCl and does not have a consistent meaning among consumers and healthcare professionals" (OSE RCM#2007-2497, date June 25, 2008).

The Division of Medication Error Prevention notes that the Applicant has submitted a 505(b)(2) application for that product, the application proposes to use the proprietary name "Advil Allergy and Congestion Relief". The Applicant currently has an approved NDA 021441 with the trade name "Advil Allergy Sinus" which was approved December 19, 2002. The currently marketed product contains ibuprofen 200 mg, pseudoephedrine HCl 30 mg and chlorpheniramine maleate 2 mg. Thus this product is kept behind the pharmacy counter as a result of the Combat Methamphetamine Epidemic Act of 2005. The proposed product "Advil Allergy & Congestion Relief" will utilize phenylephrine HCl 10 mg as the nasal decongestant ingredient. In addition, the products will also differ in the amount of chlorpheniramine maleate. The proposed product, Advil Allergy & Congestion Relief, contains 4 mg of chlorpheniramine maleate.

In our prior reviews of the proprietary names and labeling for this proposed product, one of the main concerns for medications errors identified for the proposed Advil Allergy & Congestion Relief product is healthcare provider and consumer confusion between Advil Allergy & Congestion Relief and Advil Allergy Sinus. Both of these products contain ibuprofen and chlorpheniramine co-formulated with a decongestant, and are used for symptomatic relief cold and flu. The main difference between these two products lies in the decongestant active ingredient: Advil Allergy & Congestion Relief contains phenylephrine while Advil Allergy Sinus contains pseudoephedrine. Because the active ingredients in the products differ, the products are dosed differently. Our previous reviews noted that because the applicant has elected to market both products using the Advil name, healthcare providers and consumers may not recognize that the products contain different active ingredients and dosing instructions if the proprietary names, carton labeling, and container labels are similar and fail to highlight the differences between the two products. We have determined that the proprietary name Advil Allergy & Congestion Relief provides adequate differentiation from Advil Allergy Sinus when used in isolation of the labeling, and this review evaluates the labels and labeling of Advil Allergy & Congestion Relief to ensure that the product is adequately different from Advil Allergy Sinus to help reduce errors related to confusion between the two products

## 1.2 PRODUCT INFORMATION

Advil Allergy & Congestion Relief is an over-the-counter combination product containing ibuprofen 200 mg, chlorpheniramine maleate 4 mg, and phenylephrine HCl 10 mg per tablet. The product is indicated for the following symptoms associated with hay fever or other respiratory allergies and common cold: runny nose, itchy and watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains and fever. The recommended dose is one caplet every four hours while symptoms occur. Patients should not use more than six caplets in any 24-hour period. Advil Allergy & Congestion Relief will be supplied in cartons of 10 count, 20 count, and 40 count containing either one, two, or four 10 count blister cards, respectively, Piggy Back carton of 10 count, and Dispenser Bin 1s X 50 count.

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 21, 2011
- Carton Labeling submitted June 21, 2011

Additionally, since the root name Advil is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Advil. The AERS search conducted on July 20, 2011 used the following search terms: MedDRA High Level Group Terms (HLGT): “Medication Errors”, High Level Term (HLT): “Product Label Issues”, and Preferred Term (PT): “Product Quality Issue” along with the Trade Name “Advil” and verbatim term “Advi%”. A date limit of February 1, 2011 to July 20, 2011 was used because a previous review evaluated AERS cases through January 31, 2011.

We also conducted a separate search of ‘Advil Congestion Relief’ to try to capture any safety issues with the modifier. This AERS search was conducted on September 9, 2011 and used the following search terms: MedDRA High Level Group Terms (HLGT): “Medication Errors”, High Level Term (HLT): “Product Label Issues”, and Preferred Term (PT): “Product Quality Issue” along with the Trade Name “Advil Congestion Relief” and verbatim term “Advil Congestion Reli%.” A date limit of February 1, 2011 to July 20, 2011 was used because a previous review evaluated AERS cases through January 31, 2011.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error (e.g. product quality issues), adverse events unrelated to labeling, and intentional overdoses.

Following exclusions we had no cases relevant to this review. Additionally, there were no cases involving drug name confusion.

---

<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Given our concern of possible confusion between Advil Allergy Sinus and Advil Allergy & Congestion Relief, for comparison, we also reviewed the labels and labeling for the currently marketed Advil Allergy Sinus obtained from the annual reports dated May 17, 2011 (see Appendix D)

### **3 DISCUSSION OF DEFICIENCIES IDENTIFIED**

The Advil Allergy & Congestion Relief carton labeling appears different from Advil Allergy Sinus. The labeling design uses a different background color [REDACTED] (b) (4) and a call out box in the corner of the principal display alerts the public that this is a new product.

With respect to the container labels, the labels of Advil Allergy & Congestion Relief also appear different from Advil Allergy Sinus since the container labels use the same design elements as the carton labeling. However, we have concern that the principal display panel of the carton and the single dose container labels do not sufficiently highlight phenylephrine. We are concerned that as presented there is not attention drawn to the unique ingredient and consumers may store the single dose packets separately from the shelf carton, and if the phenylephrine is overlooked consumers may mistakenly assume the product contains pseudoephedrine and dose the product incorrectly. Given our concern, we recommend that the Applicant highlight the active ingredient and format the statement of identity in a manner that clearly and prominently indicates the active ingredients contained in the product. We also recommend that the call out box in the corner of the principal display contains the active ingredients to alert the public that this is a different product.

We note that on all container labels and carton labeling each component of the name ‘Advil Allergy & Congestion Relief’ should be expressed in the same prominence to avoid ambiguity between the Advil product line. As currently expressed the word ‘Advil’ has more prominence than ‘Allergy & Congestion.’ We acknowledge that this format was accepted previously and realize that it may not be implemented. However, from a safety perspective this may alert consumers that these products contain additional ingredients and therefore may contribute to medication errors.

Lastly, there is inconsistent terminology used on the principal display panel for the carton labeling. The dosage form is described as a “coated tablets” and [REDACTED] (b) (4). Such inconsistency may confuse consumers. Since “coated tablets” is the term used throughout the remainder of the labels and labeling, we recommend that [REDACTED] (b) (4) be revised to “coated tablets”.

### **4 CONCLUSIONS AND RECOMMENDATIONS**

The proposed label and labeling introduce vulnerability that can lead to medication errors because of the lack of prominence of phenylephrine. Thus leading to potential consumer confusion with the currently marketed product containing pseudoephedrine. Since the dosing of these products differ, we recommend the following:

1. The dosage form is presented using two different terms [REDACTED] (b) (4) on the Principal Display Panel of the carton, which is confusing. For consistency and clarity, change the banner [REDACTED] (b) (4) to read "1 tablet dosage".
2. On the Principal Display Panel, Drug Facts section, and blister label we recommend highlighting the active ingredient, ‘phenylephrine’ to further distinguish the product from Advil Allergy Sinus in which the ingredients only differ by the decongestant.

3. On the single dosage packet container labels, we recommend highlighting the active ingredient, phenylephrine, since the packets may be stored separately from the carton.

If you have further questions or need clarifications, please contact Cheryle Milburn, project manager, at 301-796-2084.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

LISSA C OWENS  
11/08/2011

CARLOS M MENA-GRILLASCA  
11/08/2011

CAROL A HOLQUIST  
11/08/2011

MEMORANDUM

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

---

DATE: July 28, 2011

TO: Director, Investigations Branch  
Kansas District Office (KAN-DO)  
11630 West 80th Street  
Lenexa, KS 66214-3383

Director, Investigations Branch  
Baltimore District Office (BLT-DO)  
6000 Metro Drive Suite 101  
Baltimore, MD 21215

From: Martin K. Yau, Ph.D.  
Acting Team Leader - Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

SUBJECT: FY 2011, **High Priority NDA Pre-Approval Data  
Validation Inspection**, Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 22-113  
DRUG: Advil Allergy and Congestion Relief  
SPONSOR: Pfizer Consumer Healthcare  
5 Giralda Farms  
Madison, NJ 07940

This memo requests an inspection of both the clinical and analytical portions of the following bioequivalence study. **Per the request of the Review Division, these inspections should be completed before October 7, 2011.**

**Study Number:** AD-08-10

**Study Title:** A Four-Way Crossover, Bioavailability Study Of A  
Caplet Formulation Containing Ibuprofen 200 Mg,  
Phenylephrine Hydrochloride 10 Mg And  
Chlorpheniramine Maleate 4 Mg

**# of subjects:** 56

**Clinical Site:** Bio-Kinetic Clinical Applications  
1816 W. Mount Vernon  
Springfield, MO 65802  
Telephone: (973) 660-5137  
Facsimile: (973) 660-7162

**Clinical**  
**Investigator:** Thomas J. Legg, D.O.

Please check the batch numbers of the test and reference formulations used in the studies with the descriptions in documents submitted to the Agency. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63. Samples of the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening.

Please have the records for at least 50% of subjects in study AD-08-10 audited. The subject records in the submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Please confirm the presence of 100% of the signed and dated informed consent forms, and comment on this informed consent check in the EIR. Please determine if the subjects met the protocol inclusion/exclusion criteria. Also, please verify that the subjects were compliant with the trial regimen.

**Analytical Site:**

**Analytical**  
**Investigators:**



**Analytical Methods:** Chlorpheniramine - LC/MS/MS  
Phenylephrine - LC/MS/MS  
Ibuprofen - HPLC/UV absorbance detection

All pertinent items related to the analytical methods (LC/MS/MS for chlorpheniramine and phenylephrine; and HPLC for ibuprofen) should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. For each analytical method, the validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator, background material will be forwarded directly. **A scientist from DBGC, OSI (formerly DSI) with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise.** Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspection.

Headquarters Contact Person: Seongeun Julia Cho, Ph.D.  
(301) 796-5032

CC:

CDER DSI PM TRACK

OSI/DBGC/Salewski/Haidar/Yau/Cho/Dejernet/CF

HFR-SW300/Gerald D. Bromley Jr. (DIB)

HFR-SW300/Carl J. Montgomery/ John "Larry" Stevens (BIMO)

HFR-CE250/Christine Smith (DIB)

HFR-CE250/Cynthia Harris (BIMO)

OCP/Suresh Doddapaneni/Partha Roy

DNCE/Janice Adams-King

Draft: SC 7/28/2011

Edit: MKY 8/1/2011

DSI: (b) (4) O:\BE\assigns\bio22113.doc

FACTS: (b) (4)

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

/s/  
-----

SEONGEUN CHO  
08/02/2011

MARTIN K YAU  
08/02/2011

<b>DSI CONSULT</b> <b>Request for Biopharmaceutical Inspections</b>
--

**DATE:** July 11, 2011

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

**THROUGH:** Director, Division of Clinical Pharmacology 2, HFD-870

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

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 022113  
Advil Allergy and Congestion Relief (ibuprofen 200 mg, phenylephrine HCl 10 mg, and chlorpheniramine maleate 4 mg) tablets  
Pfizer 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)
<b>Study AD-08-10</b>	The Principal Investigator of this study was: Thomas J. Legg D.O. The study was conducted at: <b>Bio-Kinetic Clinical Applications</b> <b>1816 W. Mount Vernon</b> <b>Springfield, MO 65802</b>	(b) (4)

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

\_\_\_\_\_ There is a lack of domestic data that solely supports approval;

\_\_\_\_\_ Other (please explain):

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by October 21, 2011. We intend to issue an action letter on this application by December 21, 2011.

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

Concurrence:

Clinical Pharmacology Team Leader: Suresh Doddapaneni

Clinical Pharmacology Reviewer: Partha Roy

-----  
**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  
07/12/2011



**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: June 25, 2008

To: Andrea Leonard-Segal, MD  
Director, Division of Nonprescription Clinical Evaluation

Through: Todd Bridges, RPh, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention

From: Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator  
Division of Medication Error Prevention

Subject: Proprietary Name, Label and Labeling Review (b) (4)  
(b) (4)

Drug Name(s): (b) (4) (Chlorpheniramine Maleate, Ibuprofen,  
Phenylephrine HCl) (b) (4) 4 mg/200 mg/10 mg

Submission Number: NA

Application Type/Number: NDA # 22-113

Applicant: Wyeth Healthcare Products

OSE RCM #: 2007-2497

# CONTENTS

EXECUTIVE SUMMARY .....	1
1 BACKGROUND .....	1
1.1 Introduction .....	1
1.2 Regulatory History .....	1
1.3 Product Information .....	1
2 METHODS AND MATERIALS .....	2
2.1 Proprietary Name Risk Assessment .....	3
2.2 Label and Labeling Risk Assessment .....	10
3 RESULTS.....	10
3.1 Proprietary Name Risk Assessment .....	10
3.2 Label and Labeling Risk Assessment .....	13
4 DISCUSSION .....	13
4.1 Proprietary Name Risk Assessment .....	13
4.2 Label and Labeling Risk Assessment .....	15
5 CONCLUSIONS .....	15
6 RECOMMENDATIONS .....	16
7 REFERENCES .....	18
APPENDICES .....	20

## EXECUTIVE SUMMARY

The Proprietary Name Risk Assessment findings indicate that the proposed name, (b) (4) appears vulnerable to name confusion with the already marketed product, Advil Allergy Sinus and could lead to medication errors (b) (4) is ambiguous and may be prone to confusion because it has been used to represent both pseudoephedrine and phenylephrine HCl and does not have a consistent meaning among consumers or healthcare professionals (b) (4) contain different amounts of chlorpheniramine maleate. Therefore, the Division of Medication Error Prevention objects to the use of the name (b) (4).

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton labeling appears to be vulnerable to confusion that could lead to medication errors. We are specifically concerned that packaging, trade dress and principle display panel for Advil Allergy Sinus and (b) (4) appear almost identical. These similarities compound the risk of name confusion between these two products. We believe the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6.2 that aim at reducing the risk of medication errors.

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review was written in response to a request from the Division of Nonprescription Clinical Evaluation, for assessment of the proprietary name, (b) (4) regarding potential name confusion with other proprietary or established drug names. Additionally, the carton labeling and container label were provided for evaluation to identify areas that could lead to medication errors.

### 1.2 REGULATORY HISTORY

The Division of Medication Error Prevention notes that the Applicant has submitted a 505(b)(2) application proposing the proprietary name (b) (4). The Applicant currently has an approved NDA 21-441 with the trade name "Advil Allergy Sinus" which was approved December 19, 2002. The currently marketed product contains ibuprofen 200 mg, pseudoephedrine HCl 30 mg and chlorpheniramine maleate 2mg. Thus this product is kept behind the pharmacy counter as a result of the Combat Methamphetamine Epidemic Act of 2005. The proposed product (b) (4) will utilize phenylephrine HCl 10 mg as the nasal decongestant ingredient. In addition, the products will also differ in the amount of chlorpheniramine maleate. The proposed product, (b) (4) contains 4 mg of chlorpheniramine maleate.

### 1.3 PRODUCT INFORMATION

(b) (4) is an over-the-counter combination product containing chlorpheniramine maleate 4 mg, ibuprofen 200 mg and phenylephrine HCl 10 mg per caplet. The product is indicated to temporarily relieve the symptoms associated with hay fever or other upper respiratory allergies, and the common cold. These symptoms include: runny nose, itchy and watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains and fever. The recommended dose is one caplet every four hours while symptoms occur. Patients should not use more than six caplets in any 24-hour period. (b) (4) will be supplied in cartons of 10 count and 20 count containing either one or

two 10 count blister cards, respectively. The table below details the currently approved and marketed Advil product line.

<b>Drug name*</b>	<b>Active ingredients</b>	<b>Dosing Frequency</b>
Advil	Ibuprofen 200 mg tablets/caplets/gel caps	One (or two) every 4 to 6 hours as needed
Advil Allergy Sinus	Ibuprofen 200 mg Pseudoephedrine HCl 30 mg Chlorpheniramine maleate 2 mg caplets	One caplet every 4 to 6 hours while symptoms persist
Advil Cold and Sinus	Ibuprofen 200 mg Pseudoephedrine HCl 30 mg caplets	One (or two) caplets every 4 to 6 hours while symptoms persist
Advil Liqui-Gels	Solubilized Ibuprofen 200 mg capsules	One (or two) capsules every 4 to 6 hours while symptoms persist
Advil Migraine	Solubilized Ibuprofen 200 mg capsules	Two capsules for migraine (not to exceed 2 capsules in 24 hours)
Advil PM	Ibuprofen 200 mg Diphenhydramine citrate 38 mg caplets	Two caplets at bedside (not to exceed 2 capsules in 24 hours)
Children's Advil	Ibuprofen 100 mg/5 mL suspension Ibuprofen 50 mg tablets	Dosed per weight/age every 6-8 hours if needed
Children's Advil Allergy Sinus	Ibuprofen 100 mg Chlorpheniramine maleate 1 mg Pseudoephedrine HCl 15 mg suspension	Dosed per weight/age every 6 hours while symptoms persist
Children's Advil Cold	Ibuprofen 100 mg Pseudoephedrine HCl 15 mg suspension	Dosed per weight/age every 6 hours while symptoms persist
Children's Advil-Flavored	Ibuprofen 100 mg/5 mL suspension	Dosed per weight/age every 6-8 hours if needed
Junior Strength Advil	Ibuprofen 100 mg tablet	Dosed per weight/age every 6-8 hours if needed
Pediatric Advil	Ibuprofen 100 mg/2.5 mL suspension drops	Dosed per weight/age every 6-8 hours if needed

\*All products are available over-the-counter

## 2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the Division of Medication Error Prevention medication error staff conducting a proprietary name risk assessment (see Section 2.1) and label, labeling, and/or packaging risk assessment (see Section 2.3). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate

medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

## 2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, (b) (4) and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency. The Division of Medication Error Prevention also considered the appropriateness (b) (4). Additionally, these modifiers were assessed for resemblance to any numbers, dosing instructions, or medical abbreviations. Furthermore, the Division of Medication Error Prevention considered the potential for the modifier's omission or misinterpretation and verified that the modifiers do not appear on the error-prone abbreviation list maintained by the Institute of Safe Medication Practices (ISMP).

For the proprietary name, (b) (4) the medication error staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Section 2.1.1) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see Section 2.1.1.2). We also conducted internal CDER prescription analysis studies (see Section 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>2</sup> FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

---

<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, the Division of Medication Error Prevention staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.<sup>3</sup>

### 2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'A' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.<sup>4,5</sup>

To identify drug names that may look similar to (b) (4), Advil, or (b) (4) the Staff also considers the orthographic appearance of the name on lined and unlined orders.

(b) (4)

(b) (4)

(b) (4) considers these alternate appearances when identifying drug names that may look similar to (b) (4)

<sup>3</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

<sup>4</sup> Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

<sup>5</sup> Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

When searching to identify potential names that may look or sound similar (b) (4) the Medication Error Staff search for names with similar number of syllables (b) (4) stresses (b) (4) and placement of vowel and consonant sounds. Additionally, several letters in (b) (4) may be pronounced similarly to other letters, 'Ad' may sound like 'Ab', and 'v' may sound like 'b'; 'all' may sound like 'al'; 'er' may sound like 'ir'; 'gy' may sound like 'gi' or 'ge'; and 'si' may sound like 'sigh', 'ci' or 'sy'. Therefore, the Staff considers names these alternative sounds when identifying drug names that sound similar (b) (4). The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (b) (4), the established name (chlorpheniramine maleate, ibuprofen, and phenylephrine HCl), proposed indication (temporary relief of symptoms associated with hay fever or other respiratory allergies and the common cold), strength (4 mg/200 mg/10 mg), dose (one caplet), frequency of administration (every 4 hours), route (oral) and dosage form of the product (caplet). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

#### **2.1.1.1 Database and information sources**

The proposed proprietary name, (b) (4), was provided to the medication error staff of the Division of Medication Error Prevention to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to (b) (4) using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

#### **2.1.1.2 CDER Expert Panel Discussion**

An Expert Panel Discussion is held by the Division of Medication Error Prevention to gather CDER professional opinions on the safety of the product and the proprietary name, (b) (4). Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Error Prevention

staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

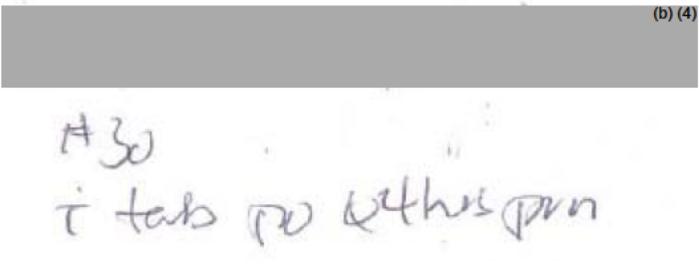
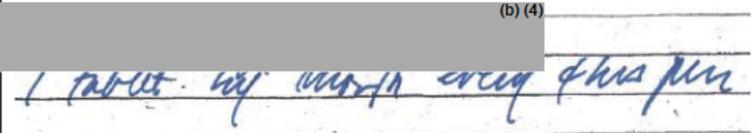
The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

### 2.1.2 CDER Prescription analysis studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of (b) (4) with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of (b) (4) in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff.

**Figure 1.** (b) (4) **Study (conducted on January 3, 2008)**

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Outpatient Prescription:</u></p> <p>(b) (4)</p> 	<p>(b) (4)</p> <p>#30</p> <p>Take 1 tablets by mouth every 4 hours prn"</p>
<p><u>Inpatient Medication Order :</u></p> <p>(b) (4)</p> 	

### 2.1.3 FDA Adverse Event Reporting System (AERS) Database

Since the Advil product line is currently in the marketplace, the FDA Adverse Event Reporting System (AERS) was searched for post-marketing safety reports related to these products which could potentially cause confusion with the introduction of [REDACTED] (b) (4). The following criteria were used: MedDRA High Level Group Term (HLGT) “Medication Errors” and Preferred Term (PT) “Pharmaceutical Product Complaint” with the trade name “Advil” and the verbatim letter string of “Advi%”. The time frame searched was from December 6, 2006 through May 1, 2008. This time frame was chosen because it represents the ending date from the previous Division of Medication Error Prevention search for medication errors involving the Advil product line.

### 2.1.4 Division of Medication Error Prevention Review Search

Our post-marketing medication errors reviews were searched for any information pertaining to the use of [REDACTED] (b) (4) to represent phenylephrine and/or pseudoephedrine. The phrase “phenylephrine and pseudoephedrine” was searched.

### 2.1.5 Internet Search

In order to see if there have been any complaints of confusion between [REDACTED] (b) (4) being used to distinguish between pseudoephedrine and phenylephrine, the internet was searched using the website [www.google.com](http://www.google.com) and the phrase ‘phenylephrine and pseudoephedrine’.

### 2.1.6 Institute of Safe Medication Practices (ISMP) Search

[REDACTED] (b) (4)

### 2.1.7 [REDACTED] (b) (4)

[REDACTED] (b) (4)

### 2.1.8 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>6</sup> When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where

<sup>6</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: “Is the name [REDACTED] (b) (4) convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?” An affirmative answer indicates a failure mode and represents a potential for [REDACTED] (b) (4) to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the name possesses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking “Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?” The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The Division of Medication Error Prevention will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator’s Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. The Division of Medication Error Prevention identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that the Division of Medication Error Prevention objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use of the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then the Division of Medication Error Prevention will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including The Institute of Medicine, The World Health Organization, The Joint Commission and The Institute for Safe Medication Practices. These organizations have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, the Division of Medication Error Prevention contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, the Division of Medication Error Prevention believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If the Division of Medication Error Prevention objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. The Division of Medication Error Prevention is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

## 2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>7</sup>

Because the Division of Medication Error Prevention staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The Division of Medication Error Prevention uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Division submitted on December 5, 2007, the following labels and labeling for our review (see Appendix L and M):

Container label: Blister 10 count

Carton labeling: 10 count

Although the Division did not request a review of the existing Advil Allergy Sinus labeling, in order to evaluate any confusion that the proposed product (b) (4) labels may cause upon introduction into the Advil product line, we evaluated the Advil Allergy Sinus labels found in the February 19, 2008 annual report (See Appendix N) by providing a side-by-side comparison of the two products.

Carton labeling: 20 count

## 3 RESULTS

### 3.1 PROPRIETARY NAME RISK ASSESSMENT

#### 3.1.1 Database and information sources

The Division of Medication Error Prevention conducted a search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug names which sound-alike or look-alike to (b) (4) to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. In total 15 names were identified as having some similarity to the name (b) (4)

All fifteen names (Children's Advil, Children's Advil Allergy Sinus, Advil Allergy Sinus, Advil PM, Advil Liqui-Gels, Advil Migraine Liqui-Gels, Pediatric Advil, Junior Strength Advil, Advil Cold and Sinus, Children's Advil Cold, Advil, Children's Advil Oral Suspension, Advil Cold &

---

<sup>7</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Sinus Plus, Advil Flu and Body Ache and Advil Multi-Symptom Cold were thought to look and sound similar to (b) (4).

In addition, a search of the USAN Stem List on April 29, 2008, identified no USAN Stems within the proposed name, (b) (4).

### 3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention staff (see Section 3.1.1.), and noted no additional names thought to have orthographic or phonetic similarity to (b) (4) and have the potential for confusion. The panel questioned what the (b) (4) stood for and advised to check AERS for any medication errors associated with the already marketed product, Advil. The panel also questioned if the current Advil Allergy Sinus would continue to be marketed and if there were any problems with other products with the (b) (4).

DDMAC had no comments regarding the proposed name from a promotional perspective as this product is available over the counter.

### 3.1.3 CDER Prescription analysis studies

A total of 35 practitioners responded. The majority of the respondents (n=31) interpreted the name correctly as (b) (4),” with correct interpretation occurring more frequently in the written studies. The remainder of the respondents misinterpreted the drug name. The majority of misinterpretations occurred in the written inpatient prescription study. Two (n=2) of the respondents in the written studies (b) (4) and thus the name overlapped with the currently marketed drug name Advil Allergy Sinus. One (n=1) of the respondents in the verbal study omitted the word “Allergy” and the remaining misinterpretation (n=1) was of the letter ‘-y’ being interpreted as ‘-en’ in the inpatient written study. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

### 3.1.4 FDA Adverse Event Reporting System (AERS) Medication Error Cases

The AERS search yielded twenty cases involving Advil. However, none of these cases involved confusion within the Advil product line. The cases retrieved involved intentional overdose (n=7), accidental exposure (n=3), drug administration error/accidental overdose (n=8) and pharmaceutical product complaint (n=2). There was no causality stated in any of the drug administration error cases.

### 3.1.5 Division of Medication Error Prevention Review Search

(b) (4)

### 3.1.6 Internet Search

Our internet search found an FDA Drug Topics April 2, 2007 article on the FDA Safety Page entitled: "Helping patients understand OTC labeling", (b) (4)

### 3.1.7 Institute of Safe Medication Practices (ISMP) Search

(b) (4)

(b) (4)

### 3.1.9 Safety evaluator risk assessment

An independent search by the primary Safety Evaluator identified six (6) additional names (Benadryl Maximum Strength Severe Allergy & Sinus Headache, Walgreens Wal-Dryl Maximum Strength Severe Allergy & Sinus Headache, Benadryl Allergy & Sinus Headache, Walgreens Wal-Dryl-D Allergy & Sinus, Walgreens Wal-dryl Allergy & Sinus Headache, and Benadryl-D Children's Allergy & Sinus) thought to look and/or sound similar (b) (4) and represent a potential source of drug name confusion.

As such a total of twenty-one (21) names were evaluated to determine if the drug names could be confused with (b) (4) or any component (b) (4) and if the drug name confusion would likely result in a medication error. Additionally, (b) (4) was evaluated to determine if it could present a source of confusion.

All of the identified names were determined to have some orthographic and/or phonetic similarity to (b) (4) and thus determined to present some risk of confusion. Additionally, because they contain the family trade name, Advil, there was potential for confusion within the product line. Failure modes and effects analysis (FMEA) was then applied to determine if the

---

<sup>8</sup> <http://www.medilexicon.com/medicalabbreviations.php>

proposed name, (b) (4), could potentially be confused with any of the twenty-one names or if the modifier representing phenylephrine could also be confused leading to medication error.

This analysis determined that the name similarity between (b) (4) and the identified names was unlikely to result in medication error for twenty (20) product names. Eleven names were not considered further because they do not contain (b) (4) (Appendix C). Even though they share the root name Advil, they lack convincing orthographic and/or phonetic similarities with (b) (4). Six names share one of the Allergy and/or Sinus Modifiers but the root name is different from Advil thus decreasing the orthographic and/or phonetic similarities with (b) (4). One name (Advil Cold and Sinus Plus) was a foreign name and was not considered further because it is not marketed in the U.S. (see Appendix D). For two (2) of the names (Children’s Advil Allergy Sinus and Advil Cold and Sinus) it was determined that although these names shared the root name, “Advil”, with the proposed name and may have overlapping product characteristics, a medication error was unlikely in the usual practice setting because Children’s Advil Allergy Sinus will generally be stored in the pediatric medication section and the carton labeling for both products are clearly differentiated (i.e., specifically identifies pediatric dosing). Although the proposed product and Advil Cold and Sinus share the modifier ‘Sinus’, there is minimal chance of confusion because the modifier, “Cold and” appears distinctly different from “Allergy” and the carton labeling of both products are clearly differentiated. (Appendix E). The remaining name (Advil Allergy Sinus) was found to likely result in confusion leading to medication error (b) (4)

### 3.2 LABEL AND LABELING RISK ASSESSMENT

The carton labeling of the proposed product, (b) (4) looks similar to the carton labeling of the currently marketed product, Advil Allergy Sinus.

## 4 DISCUSSION

### 4.1 PROPRIETARY NAME RISK ASSESSMENT

Post-marketing evidence has shown that introduction of a new product into an established product line is often a source of confusion. Errors introduced by product line extensions are multi-factorial in nature and can stem from the similarity of product names, overlapping product characteristics coupled with the low level of awareness or knowledge of the product profile by healthcare professionals and patients. In this case, (b) (4) will be added to an existing product line, Advil. However, the strength of the chlorpheniramine maleate will be different; as the currently marketed Advil Allergy Sinus has 2 mg of chlorpheniramine maleate, and the proposed product, (b) (4) contains 4 mg of chlorpheniramine maleate. Additionally, the proposed product will contain phenylephrine whereas the currently marketed product contains pseudoephedrine. The Applicant’s proposal is that these ingredient and strength differences will be differentiated (b) (4) (Advil Allergy Sinus vs. (b) (4)

(b) (4)

Compounding the potential confusion between Advil Allergy Sinus and (b) (4) is the differences in chlorpheniramine maleate strength. The amount of chlorpheniramine maleate is double in the proposed product (4 mg vs. 2 mg) than in the currently marketed product. Although the differences in these products are clearly listed in the Drug Facts section (b) (4)

(b) (4) does not convey the differences between the Advil Allergy Sinus (b) (4). Thus, using the name (b) (4) will likely lead to confusion resulting in medication errors.

Therefore, we contend that (b) (4) is ambiguous, does not help to distinguish Advil Allergy Sinus from (b) (4), and furthermore it contradicts the goals set forth by healthcare practitioners, the IOM, and NCC MERP. In the July 20, 2006, Institute of Medicine (IOM) Report “Preventing Medication Errors” recommendation number four, urges FDA to standardize abbreviations, acronyms, and terms to the extent possible. FDA also participated in a meeting sponsored by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) entitled “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. We heard from practicing health care practitioners at this meeting to stop approving drug name modifiers that are ambiguous and error prone. (b) (4) (b) (4) does not help to distinguish Advil Allergy Sinus from (b) (4).

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, the Division of Medication Error Prevention believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, the Division of Medication Error Prevention recommends that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

## 4.2 LABEL AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment found that the presentation of information on carton labeling appears to be vulnerable to confusion that could lead to medication errors. We noted the carton labeling for the proposed product, (b) (4) looks almost identical to the carton labeling of the currently marketed product, Advil Allergy Sinus. When compared side-by-side, the cartons for Advil Allergy Sinus and (b) (4) appear almost identical despite the (b) (4) 'New Formula' banner, and the red arrow containing the 'One pill...' dosage statement. Both products share the same layout and color scheme of a green background with yellow and white lettering (see Appendix N). The visual similarity of the carton labeling further compounds the potential for confusion and likelihood of medication errors between the two products.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

## 5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, (b) (4) appears to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention objects to the use of the proprietary name, (b) (4) for this product.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

## 6 RECOMMENDATIONS

### 6.1. Comments to the Division

The Division of Medication Error Prevention does not recommend the use of the proprietary name, (b) (4). Based upon our assessment of the proprietary name, labels, and labeling, we have identified areas needed of improvement. We have provided recommendations in Section 6.2 and request this information be forwarded to the Applicant.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy Division of Medication Error Prevention on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cherye Milburn, project manager, at 301-796-2084.

### 6.2. Comments to the Applicant

#### 6.2.1 Proprietary name

The Division of Medication Error Prevention does not recommend the use of the proprietary name, (b) (4). The proposed name appears to be vulnerable to name confusion that could lead to medication errors with Advil Allergy Sinus.

Post-marketing evidence has shown that introduction of a new product into an established product line is often a source of confusion. Errors introduced by product line extensions are multi-factorial in nature and can stem from the similarity of product names, overlapping product characteristics coupled with the low level of awareness or knowledge of the product profile by healthcare professionals and patients. In this case, (b) (4) will be added to an existing product line, Advil. However, the strength of the chlorpheniramine maleate will be different; as the currently marketed Advil Allergy Sinus has 2 mg of chlorpheniramine maleate, and the proposed product, (b) (4), contains 4 mg of chlorpheniramine maleate. Additionally, the proposed product will contain pheynylephrine whereas the currently marketed product contains pseudoephedrine. Your proposal is that these ingredient and strength differences will be differentiated (b) (4) (Advil Allergy Sinus vs. (b) (4)

(b) (4)

Compounding the potential confusion between Advil Allergy Sinus and (b) (4) is the differences in chlorpheniramine maleate strength. The amount of chlorpheniramine maleate is double in the proposed product (4 mg vs. 2 mg) than in the currently marketed product. Although the differences in these products are clearly listed in the Drug Facts section, (b) (4)

(b) (4) Adding the (b) (4) does not convey the differences between the Advil Allergy Sinus and (b) (4). Thus, using the name (b) (4) will likely lead to confusion resulting in medication errors.

Therefore, we contend that the (b) (4) is ambiguous, does not help to distinguish Advil Allergy Sinus from (b) (4), and furthermore it contradicts the goals set forth by healthcare practitioners, the IOM, and NCC MERP. In the July 20, 2006, Institute of Medicine (IOM) Report “Preventing Medication Errors” recommendation number four, urges FDA to standardize abbreviations, acronyms, and terms to the extent possible. FDA also participated in a meeting sponsored by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) entitled “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. We heard from practicing health care practitioners at this meeting to stop approving drug name modifiers that are ambiguous and error prone. (b) (4) does not help to distinguish Advil Allergy Sinus from (b) (4)

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

**6.2.2 Labels and Labeling**

Ensure (b) (4) packaging, trade dress and principle display panel colors are clearly differentiated from the currently marketed product, Advil Allergy Sinus.

## 7 REFERENCES

### 1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

### 2. *Micromedex Integrated Index (<http://weblern/>)*

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

### 3. *Phonetic and Orthographic Computer Analysis (POCA)*

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention, FDA.

### 4. *Drug Facts and Comparisons, online version, St. Louis, MO (<http://weblern/>)*

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

### 5. *AMF Decision Support System [DSS]*

DSS is a government database used to track individual submissions and assignments in review divisions.

### 6. *Division of Medication Errors and Technical Support proprietary name consultation requests*

This is a list of proposed and pending names that is generated by THE DIVISION OF MEDICATION ERROR PREVENTION from the Access database/tracking system.

### 7. *Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)*

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved [brand name](#) and [generic drugs](#) and [therapeutic biological products](#); [prescription](#) and [over-the-counter](#) human drugs and [therapeutic biologics](#), [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

**8. Electronic online version of the FDA Orange Book**  
(<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

**9. WWW location** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

**10. Clinical Pharmacology Online** (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

**11. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at** [www.thomson-thomson.com](http://www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

**12. Natural Medicines Comprehensive Databases** (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

**13. Stat!Ref** (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

**14. USAN Stems** (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

**15. Red Book Pharmacy's Fundamental Reference**

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

**16. Lexi-Comp** ([www.pharmacist.com](http://www.pharmacist.com))

A web-based searchable version of the Drug Information Handbook.

**17. Medical Abbreviations Book**

Contains commonly used medical abbreviations and their definitions.

## APPENDICES

### Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, Division of Medication Error Prevention will consider the Sponsor’s intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, Division of Medication Error Prevention also considers a variety of pronunciations that could occur in the English language.

**Table 1.** Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic similarity	Similar spelling Length of the name	<ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to</li> </ul>

		<p>Upstrokes</p> <p>Downstrokes</p> <p>Cross-strokes</p> <p>Dotted letters</p> <p>Ambiguity introduced by scripting letters</p> <p>Overlapping product characteristics</p>	<p>drug name confusion in written communication</p>
Sound-alike	Phonetic similarity	<p>Identical prefix</p> <p>Identical infix</p> <p>Identical suffix</p> <p>Number of syllables</p> <p>Stresses</p> <p>Placement of vowel sounds</p> <p>Placement of consonant sounds</p> <p>Overlapping product characteristics</p>	<ul style="list-style-type: none"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>

**Appendix B:**

CDER Prescription Study Responses

(b) (4)



**Appendix C: Names lacking convincing look-alike and/or sound-alike similarities with** (b) (4)

<b>Proprietary Name</b>	<b>Similarity</b> (b) (4)
Advil	Look and Sound
Advil PM	Look and Sound
Advil Liqui-Gels	Look and Sound
Advil Migraine Liqui-Gels	Look and Sound
Advil Flu & Body Ache	Look and Sound
Advil Multi-Symptom Cold	Look and Sound
Children's Advil Oral Suspension	Look and Sound
Children's Advil	Look and Sound
Children's Advil Cold	Look and Sound
Junior Strength Advil	Look and Sound
Pediatric Advil	Look and Sound
Benadryl Maximum Strength Severe Allergy & Sinus Headache	Look and Sound
Walgreens Wal-Dryl Maximum Strength Severe Allergy & Sinus Headache	Look and Sound
Benadryl Allergy & Sinus Headache	Look and Sound
Walgreens Wal-Dryl-D Allergy & Sinus	Look and Sound
Walgreens Wal-dryl Allergy & Sinus Headache	Look and Sound
Benadryl-D Children's Allergy & Sinus	Look and Sound

**Appendix D:** Proprietary names used only in Foreign Countries

Proprietary Name	Similarity to (b) (4)	Country
Advil Cold & Sinus Plus	Look	Canada

**Appendix E:** Names that *do* overlap in strength and/or orthographic similarity to (b) (4)

Failure Mode: Name confusion	Causes (could be multiple)	Effects
(b) (4) (chlorpheniramine maleate/ibuprofen/phenylephrine HCl) 200 mg/4 mg/ 10 mg caplet		<b>Usual dose: 1 caplet every four hours while symptoms occur; Not to exceed 6 caplets in a 24 hour period</b>
Advil Allergy Sinus (Ibuprofen/Chlorpheniramine maleate/Pseudoephedrine HCl) 200 mg/2 mg/30 mg	Orthographically and phonetically the same because of shared root name and modifier (“Advil Allergy Sinus”)  Overlapping strength (200 mg) and dosing (1 caplet every 4 to 6 hours)	Medication error likely to occur in the usual practice setting. <i>Rationale:</i> (b) (4)
Children’s Advil Allergy Sinus (Ibuprofen/Chlorpheniramine maleate/Pseudoephedrine HCl) 100 mg/1 mg/15 mg	Orthographically and phonetically the same because of shared root name and modifier (“Advil Allergy Sinus”)	Medication error unlikely to occur in usual practice setting. <i>Rationale:</i> The additional modifier “Children’s” helps to differentiate the names. The products differ in strength and usual dose, as the children’s product is dosed by weight. Furthermore, Children’s Advil Allergy Sinus will typically be stored with the pediatric medication and the carton labeling clearly conveys that the product is for children. As a result, confusion between these two names is unlikely to occur.

<p>Advil Cold and Sinus (Ibuprofen/Pseudoephedrine HCl) 200 mg/30 mg</p>	<p>Orthographically and phonetically the same because of shared root name (“Advil”) and the modifier (“Sinus”)  Overlapping strength (200 mg) and dosing (1-2 tablets every 4 to 6 hours)</p>	<p>Medication error unlikely to occur in usual practice setting. <i>Rationale:</i> The words in the modifier, “Cold and” appears distinctly different from “Allergy” and the carton labeling of both products are clearly differentiated making confusion unlikely.</p>
--	---	---

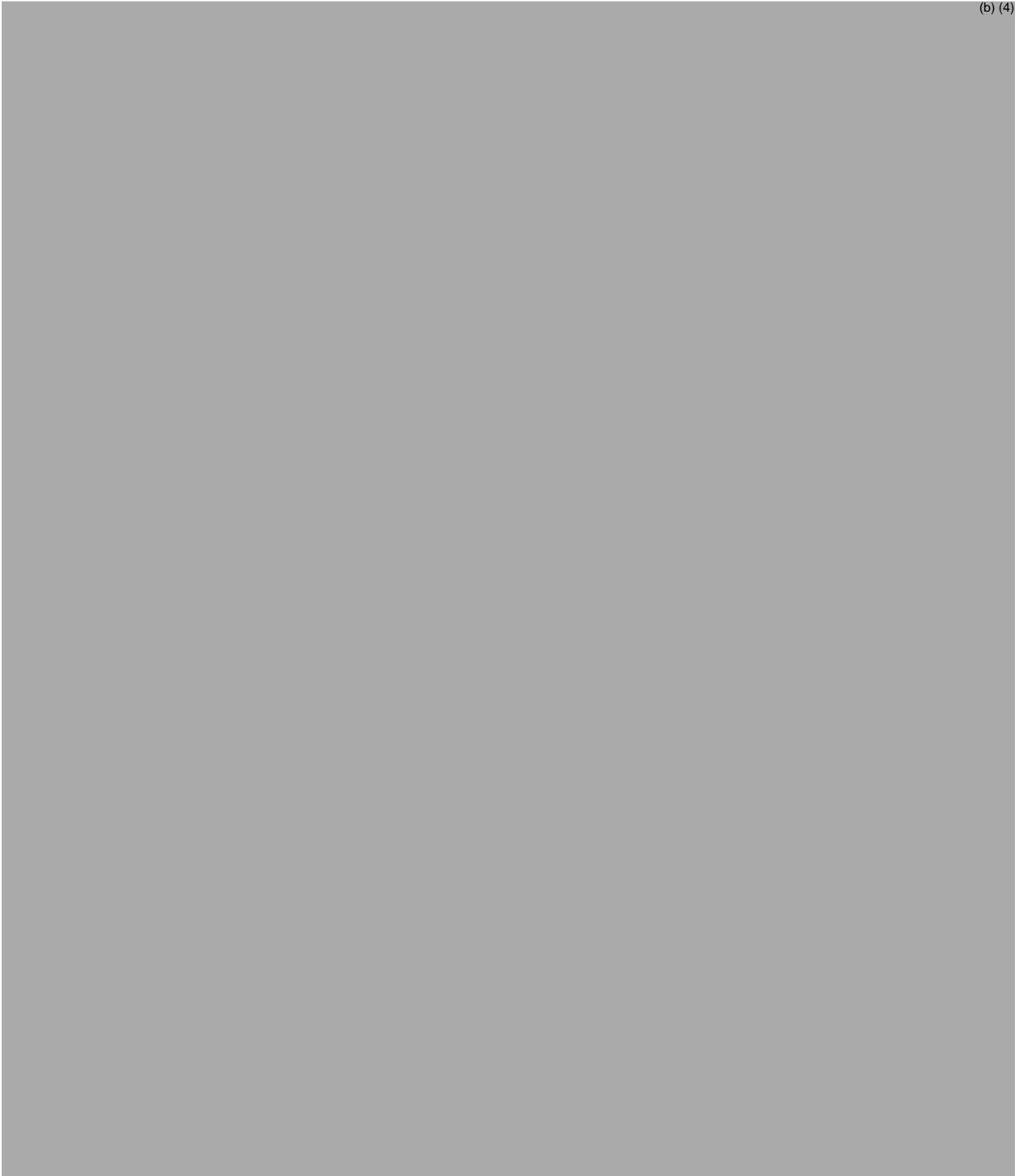
(b) (4)





**Appendix H: Sudafed Post Marketing Safety Review**

(b) (4)



8 Pages have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

**Appendix I : FDA Drug Topics : Helping Patients understand OTC Labeling**

**Helping patients understand OTC labeling**

COPYRIGHT MATERIAL WITHHELD



**Appendix J: ISMP Medication Safety Alert: Separation Anxiety**

COPYRIGHT MATERIAL WITHHELD



COPYRIGHT MATERIAL WITHHELD

**Appendix K: U.S Pharmacist: Separation Anxiety**

COPYRIGHT MATERIAL WITHHELD



COPYRIGHT MATERIAL WITHHELD

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

-----  
Deveonne Hamilton-Stokes  
6/25/2008 08:04:18 AM  
DRUG SAFETY OFFICE REVIEWER

Todd Bridges  
6/25/2008 08:12:17 AM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
6/25/2008 12:44:23 PM  
DRUG SAFETY OFFICE REVIEWER

OTC Drug Labeling Review (b) (4)  
(chlorpheniramine maleate 4 mg, ibuprofen 200 mg, phenylephrine HCl 10 mg)  
Office of Nonprescription Products  
Center for Drug Evaluation and Research • Food and Drug Administration

**NDA 22-113**

**SUBMISSION DATE:** September 25, 2007  
January 31, 2008

**REVIEW DATE:** May 20, 2008

**NDA (SUBMISSION TYPE)** Labeling for previously unmarketed product

**SPONSOR CONTACT:** Neil J. Napolitano  
Assistant Director  
Global Regulatory Affairs  
Wyeth Consumer Healthcare  
Five Giralda Farms  
Madison, NJ 07940  
973-660-5725

**DRUG PRODUCT:** (b) (4)

**ACTIVE INGREDIENTS:** chlorpheniramine maleate 4 mg,  
ibuprofen 200 mg,  
phenylephrine HCl 10 mg

**INDICATIONS:** temporarily relieves these symptoms  
associated with hay fever or other upper  
respiratory allergies and the common  
cold:

- runny nose
- itchy, watery eyes
- sneezing
- itching of the nose or throat
- nasal congestion
- headache
- sinus pressure
- minor aches and pains
- fever

**PHARMACOLOGIC CATEGORY:** antihistamine, pain reliever/fever reducer,  
and nasal decongestant

**LABELING SUBMITTED:**

Carton in 10- and 20- counts  
Container consisting of blister back label in  
packs of 10 blisters per card

**BACKGROUND:**

On March 9, 2006, the Combat Methamphetamine Epidemic Act of 2005 (CMEA) was signed into law regulating among other things OTC sales of pseudoephedrine, ephedrine and phenylpropanolamine. On September 25, 2007, sponsor submitted annotated labeling to substitute phenylephrine HCl for pseudoephedrine HCl in Advil Allergy Sinus under NDA 21-441. The substitution was prompted by the CMEA being signed into law.

Phenylephrine HCl (PE) and pseudoephedrine HCl (PSE) are both monograph nasal decongestant active ingredients (21 CFR part 341). When used as an oral nasal decongestant, the statement of identity (21 CFR 341.80(a)), the indications (21 CFR 341.80(b)), and the warnings (21 CFR 341.80(c)) for both PE and PSE are identical. For adults and children 12 years of age and over, the directions for use (21 CFR 341.80(d)) for PE and PSE differ only in that a monograph dose of PSE may be taken every 4 to 6 hours, while a monograph dose of PE may be taken every 4 hours. For children under 12 years of age, the monograph indicated “consult a doctor” for both PSE and PE products.

In July, 2005, FDA sent an information request (IR) letter, which included labeling templates, to all non-prescription non-steroidal anti-inflammatory drugs (NSAIDs) NDA/ANDA holders, requesting revisions of their “Drug Facts” labeling to include adverse event symptoms for Steven Johnson Syndromes and cardiovascular warnings. The IR request included ibuprofen.

The labeling submitted by the sponsor includes all of the elements in the July 2005 IR letter, along with the necessary PE monograph labeling from 21 CFR part 341.

On January 31, 2008, sponsor proposed to amend labeling to include (1) a Warning that recommends asking a doctor before use if you have asthma, and (2) statements under the Warnings and Directions sections of Drug Facts to emphasize that the product should not be used in children under 12.

## REVIEWER'S COMMENTS

Strikethrough is used for deletions and redline is used for additions.

### I. Carton

#### A. Principal Display Panel, Top and Bottom Panels

(b) (4)

**Reviewer's Comment:** Chlorpheniramine maleate, an antihistamine is associated with drowsiness. (b) (4)

#### B. Back Panel Drug Facts

##### 1. Warnings

Ask a doctor before use if you have [bullet] asthma

Do not use [bullet] in children under 12 years of age

**Reviewer's Comment:** These statements are currently under review.

Stop use and ask a doctor if

(b) (4)

**Reviewer's Comment:** Inconsistencies exist between the number of days to take this product and the number of days to take this product for the intended treatment. Since this product is intended for treatment of symptoms of cold and flu, the warning for pain can be deleted.

##### 2. Directions

(b) (4)

**Reviewer's Comment:** Change is needed for consistency with the number of days for the intended treatment.

[bullet] children under 12 years of age: do not use

**Reviewer's Comment:** This statement is currently under review.

Adults and children 12 years and over: take 1 caplet every 4 hours while symptoms persist

**Reviewer's Comment:** The Pediatric Research Equity Act (PREA) defines the pediatric age range as from birth to 17 years. Many monographs, including that for phenylephrine, indicate that the drugs are for "adults and children 12 years of age and over." This statement for ages 12-17 is typically not based on studies in that age group, but instead, is based on the historical belief that 12-17 year olds are the same as adults. This is clearly not consistent with the underlying rationale for PREA and the consequent standards for study requirements in 12-17 year olds. The agency is currently reviewing the approach to labeling in ages 12-17.

3. Questions or comments

(b) (4)

**Reviewer's Comment:** Encourage inclusion of days of the week and time of day to be available.

II. Container label

**Reviewer's comment:** Blister pack labeling is appropriate per 21 CFR 201.10(h)(2)(i).

**RECOMMENDATIONS:**

A. Labeling is "approvable." Inform sponsor to revise labeling as follows:

1. Principal Display Panel, Top and Bottom Panels

a. Remove the term (b) (4)

2. Back Panel Drug Facts

a. Remove (b) (4) under the Warning "Stop use and ask a doctor if."

b. Under the Directions, change (b) (4) to "Do not take longer than 7 days, unless directed by a doctor (see Warnings)" to be consistent with the number of days for the intended treatment.

B. In addition to the above revisions, we are reserving further recommendations of the “Drug Facts” labeling until other disciplines/agency have/has completed their/its reviews for the following issues:

- Addition of an "asthma" warning to "Ask a doctor before use if you have" subsection of the Warnings
- Adding the statement “in children under 12 years of age” warning to the “Do not use” sub-section Warnings
- Changing the statement [REDACTED] (b) (4) to read “children under 12 years of age: do not use”
- Whether the dosing directions should be “adults and children 17 and above”, as per PREA, or as stated in the monograph (i.e. Adults and children 12 and above)

C. Inform sponsor that we encourage inclusion of appropriate times when phones will be answered under the "Questions or comments" heading.

D. Inform sponsor that the phrase [REDACTED] (b) (4) must be deleted from the principal display, top, and bottom panels, six months after introduction of the product into the OTC marketplace.

E. Project manager: This labeling review is incomplete. Further recommendations regarding “Drug Facts” labeling may be necessary to relate to the sponsor pending other disciplines' completion of their reviews, including resolution of the PREA-monograph issue, and we have a chance to incorporate their recommendations and/or conclusions in the labeling.

---

Michael T. Benson, R.Ph., J.D.  
Regulatory Review Pharmacist

---

Marina Chang, R.Ph.  
Team #1 Leader, Concurrence

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

/s/

-----  
Michael Benson  
5/21/2008 01:46:12 PM  
INTERDISCIPLINARY

Marina Chang  
5/22/2008 09:45:48 AM  
INTERDISCIPLINARY

MEMORANDUM

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

DATE: May 2, 2008

FROM: Jacqueline A. O'Shaughnessy, Ph.D.  
Mark J. Seaton, Ph.D.  
Samuel Chan, Pharm.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: CT. Viswanathan, Ph.D.  
Associate Director - Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-113 (b) (4)  
(b) (4) (Ibuprofen 200 mg/Phenylephrine  
HCl 10 mg/Chlorpheniramine Maleate 4 mg) (b) (4),  
Sponsored by Wyeth Consumer Healthcare

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

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

**Protocol AD-05-05:** A Three-Way Crossover, Food Effect/ Formulation Effect, Bioavailability Study of a Caplet Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 10 mg, and Chlorpheniramine Maleate 4 mg

The clinical and analytical portions of this study were conducted (b) (4)

Inspection of the (b) (4) clinical site (b) (4) and the (b) (4) analytical site (b) (4) did not reveal any significant deficiencies; Form 483 was not issued at either site. Following the inspection at the (b) (4) facility in (b) (4), Form 483 was issued. DSI received (b) (4) response to the Form 483 on April 8, 2008. The objectionable

items and our evaluation are the following:

**1. The bioanalytical method for total phenylephrine is flawed and the reported subject sample concentrations are not accurate.**

Subsequent to the conduct and reporting of Study AD-05-05, (b) (4) determined that their method (LCMS 257 version 2) significantly underestimated the concentration of total phenylephrine (PE) present in the subject samples. Neither Wyeth nor (b) (4) informed the Agency that the reported results were not accurate prior to the DSI inspection. The bioanalytical method for Study AD-05-05 measured total PE. This involved enzyme hydrolysis of PE conjugates (sulfate, glucuronide) present in plasma samples from subjects dosed with PE (i.e., incurred samples). (b) (4) determined that their method was flawed following an investigation initiated in June 2007.<sup>1</sup> (b) (4) investigation found that total PE concentrations were not accurately measured due to incomplete hydrolysis of the PE-conjugates and instability of unconjugated PE under the hydrolysis conditions (Attachment 1). The inspection also found that the quality control (QC) samples used for run acceptance were different from the subject samples in that the QCs were spiked with unconjugated PE only.

Because accuracy was not assured, the reported total PE concentrations for Study AD-05-05 are not reliable. Please note that this finding applies to all studies conducted with (b) (4) method LCMS 257 version 2 for total PE, including Wyeth Study AQ-05-03 submitted to (b) (4)

2

According to (b) (4), the PE method was subsequently optimized (LCMS 257 version 3.01). On September 7, 2007 Wyeth requested reanalysis of a subset of subject samples from Study AD-06-06

---

<sup>1</sup> The investigation was initiated to evaluate non-reproducibility observed between original and repeat results (i.e., pharmacokinetic repeats) for subject samples from a different Wyeth study (**not** Study AD-05-05 from NDA 22-113). Email correspondence provided (b) (4) indicated that (b) (4) informed Wyeth of the method problem and investigation on July 19, 2007.

<sup>2</sup> Please refer to DSI memo dated April 10, 2008. Please note that (b) (4) also conducted studies (b) (4) with the flawed method.

with the method optimized for PE glucuronide.<sup>3</sup> (The DSI inspection did not audit data related to the revised method). The original results were significantly underestimated compared to the repeat results, with differences ranging from approximately 100-4300% (Attachment 2). Wyeth did not request reanalysis of the three other studies that (b) (4) conducted for them with the flawed method (Studies AQ-05-03, AD-05-05, and AQ-06-08).

Contrary to Wyeth's assessment of this issue submitted after the DSI inspection, extrapolating the outcome of the reanalysis for Study AD-06-06 to other studies that used the flawed method is not justified as accuracy was not assured for the total PE concentrations reported from the flawed method. The claim made by (b) (4) and Wyeth that the degree of total PE concentration underestimation within a batch of samples processed together was consistent (i.e., that with-in batch samples underwent similar levels of hydrolysis) is not supported by the repeat data from Study AD-06-06 (Attachment 2). Specifically, the difference in original and repeat results **between samples within a subject** was highly variable. For example, the 0.25-8 hour samples for subjects 101 and 204 had differences ranging from 213-318% and 179-315%, respectively, between the original and repeat results. This does not demonstrate a similar level of underestimation within a batch. Furthermore, it should be noted that samples beyond 8 hours had even greater differences. In our view, extrapolating the results of reanalysis of a subset of subject samples from Study AD-06-06 to Study AD-05-05 and other Wyeth studies that were analyzed using the flawed original method is not justified.

In response to the Form 483, (b) (4) stated that they have amended and reissued to sponsors all final reports that used the flawed method to note the inaccuracy of the method. In the future, (b) (4) intends to notify FDA if they discover that

---

<sup>3</sup>The optimized method included QCs spiked with PE-glucuronide and a surrogate incurred plasma QC pool (prepared with plasma and incurred urine containing both PE-sulfate and PE-glucuronide) with an analytically determined concentration of total PE to quantitatively evaluate assay performance. In contrast, the original method used a QC spiked with unconjugated PE, and an incurred plasma QC pool for a qualitative measure of hydrolysis. According to (b) (4), PE-glucuronide was not available commercially when they developed the original method, and PE-sulfate is not currently available commercially. The percentage of hydrolysis of PE-sulfate is not known absolutely.

previously reported study data is subsequently found to be unreliable.

**2. The chlorpheniramine method was not evaluated for potential interference from concomitantly administered phenylephrine.**

In response to the Form 483, (b) (4) submitted the results of recently completed interference testing. No interference was noted (Attachment 3).

**3. Chromatography integration parameters for several runs were changed multiple times without documenting the interim changes made.**

The audit trail for the chromatography software (Analyst 1.2) documented that changes were made but did not capture the actual parameters altered with each interim modification. Because the firm's procedures include setting integration parameters prior to calculating the resulting sample concentrations and applying the parameters across the run as a whole, the incomplete documentation should not have a significant impact.

In response to the Form 483, the firm stated that they currently use a revised version of the software (Analyst 1.4.2) that captures the details of interim changes.

**4. The storage temperature of samples used to demonstrate the stability of chlorpheniramine in extracted samples was not documented. Some runs were injected the day after extraction.**

In response to the Form 483, (b) (4) repeated the extract stability experiment. No stability problem was noted for the storage duration of the study sample extracts (Attachment 4).

## **Conclusions**

For the reasons stated above, the Division of Scientific Investigations concludes that the accuracy of total PE concentrations reported for Study AD-05-05 was not demonstrated. In this regard, the reliability of the reported total PE data for a bioequivalence assessment has not been assured.

In addition, it is objectionable that neither Wyeth nor (b) (4) informed FDA prior to the inspection that the assay used for Study AD-05-05 was flawed although this information was available before the original NDA submission.

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

Jacqueline A. O'Shaughnessy, Ph.D.  
Mark J. Seaton, Ph.D.  
Samuel Chan, Pharm.D.

Attachment 1: (b) (4) investigation, draft report  
Attachment 2: Repeat result comparison, Wyeth Study AD-06-06  
Attachment 3: Interference assessment for chlorpheniramine  
Attachment 4: Extract stability for chlorpheniramine

**Final Classification**

(b) (4)

cc:

HFD-45/Vaccari

HFD-48/Himaya/O'Shaughnessy/Seaton/Chan/CF

OCP/DCP2/Partha Roy

ONP/DNCE/Robin Anderson

HFR-SW1575/Lorenz

HFR-CE8585/Laufenberg

HFR-CE2545/Milazzo

Draft: JAO 4/24/08

Edit: MJS/SC/SS

DSI 5825 O:\BE\eircover\22113we.phe.doc

FACTS (b) (4)

56 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

-----  
Jacqueline OShaughnessy  
5/2/2008 03:19:13 PM  
PHARMACOLOGIST

Samuel Chan  
5/2/2008 03:58:39 PM  
DRUG SAFETY OFFICE REVIEWER

Mark Seaton  
5/2/2008 04:15:05 PM  
CSO

Martin Yau  
5/5/2008 04:26:59 PM  
CSO

## **DSI CONSULT**

### **Request for Biopharmaceutical Inspections**

**DATE:** December 5, 2007

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

**THROUGH:** Andrea Leonard-Segal, M.D.  
Director, Division of Nonprescription Clinical Evaluation

**FROM:** Robin Anderson, Regulatory Project Manager, DNCE

**SUBJECT: Request for Biopharmaceutical Inspection**  
NDA 22-113  
(b) (4) (ibuprofen 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate 4 mg)

#### **Study/Site Identification:**

The following studies/sites pivotal to approval have been identified for inspection:

<b>Study #</b>	<b>Clinical Site (name, address, phone, fax, contact person, if available)</b>	<b>Analytical Site (name, address, phone, fax, contact person, if available)</b>
Study AD-05-05 AD-05-05: A Three-Way Crossover, Food Effect/Formulation Effect, Bioavailability Study of a Caplet Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 10 mg, and Chlorpheniramine Maleate 4 mg	PPD Development 7551 Metro Center Blvd., Suite 200 Austin, TX 78744	(b) (4)

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **May 23, 2008**. We intend to issue an action letter on this application by **July 25, 2008**. This is our division's pilot CDTL NDA, so review timelines have been scheduled to comply with that initiative.

Should you require any additional information, please contact Robin Anderson at (301) 796-0534.

Concurrence: (Optional)  
Partha Roy, Ph.D., Clinical Pharmacology Reviewer

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

/s/

-----  
Robin E Anderson  
12/6/2007 12:25:31 PM

LABELING FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 22-113      **Applicant:** Wyeth Consumer Healthcare      **Stamp Date:** 09/25/07

**Drug Name:** Ibuprofen (200 mg)  
 Phenylephrine HCl (10 mg)  
 Chlorpheniramine Maleate (4 mg)      **NDA Type:** 505(b)(2)

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

	Content Parameter	Yes	No	Comments
1	Is Index sufficient to locate necessary labeling?	X		
2	Has labeling for all SKUs been submitted (e.g., blister card, pouch, immediate container, carton label, package insert labeling, etc.)?	X		
3	Does the submission contain the annotated specifications for the “Drug Facts” label?	X		
4	Is a new trade name being proposed? If multiple trade names, is the RLD trade name identified?	X		

Any additional comments:

The product introduced by this NDA is a triple combination of monograph active ingredients. The sponsor already has approved NDA 21-441 (Advil Allergy Sinus) with a similar triple combination. The only difference is that for this NDA, phenylephrine HCl is replacing pseudoephedrine HCl. Phenylephrine and pseudoephedrine are both antihistamine active ingredients with identical monograph labeling. The labeling proposed by this NDA has all the elements in the labeling approved in NDA 21-441. In addition, it also has new warnings that have been implemented or proposed since the first approved labeling for 21-441.

Michael Chasey	11/15/07
Reviewing Interdisciplinary Scientist	Date

Marina Chang	11/26/07
Supervisor/Team Leader	Date

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

/s/

-----  
Michael Chasey  
11/26/2007 11:42:36 AM  
CHEMIST

Marina Chang  
11/26/2007 11:44:28 AM  
INTERDISCIPLINARY