

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022113Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22113 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Advil Allergy and Congestion Relief Established/Proper Name: ibuprofen, 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate, 4mg Dosage Form: tablets		Applicant: Pfizer Consumer Healthcare Agent for Applicant (if applicable):
RPM: Janice Adams-King		Division: Nonprescription Clinical Evaluation
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Motrin IB</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input checked="" type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on (explain) NDA 19012: Motrin IB</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 12/21/2011</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 21, 2011</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None CR 07/25/2008

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 4</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input checked="" type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 12/21/11; CR 7/25/2008
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	06/21/2011 and 11/23/2011
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Acceptability -- 09/16/2011 Reviews: 09/14/2011
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 11/08/2011; 06/25/2008 <input type="checkbox"/> DMPP/PLT (DRISK) <input type="checkbox"/> ODPD (DDMAC) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 11/29/2011
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	11/17/2011
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 11/21/2011 <input type="checkbox"/> Not a (b)(2) 12/21/2011
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>09/14/2011</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	9/16/11; 03/07/11; 2/16/10; 12/02/09;
❖ Internal memoranda, telecons, etc.	9/19/07;
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 3/19/07
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	2/26/08
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/20/2011
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/02/2011
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 12/21/2011
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	12/02/2011
• Clinical review(s) <i>(indicate date for each review)</i>	11/18/2011
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	11/18/11
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i>	
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	
• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 11/23/2011
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 11/16/11; 06/05/08
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 11/16/11; 06/06/08
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None 11/23/11; 05/08/08
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 10/28/11; 7/11/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 12/05/11
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 11/23/11; 06/11/08
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	06/11/08
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 08/10/11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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
07/10/2012

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-113

NAME OF APPLICANT / NDA HOLDER

WYETH CONSUMER HEALTHCARE, A
DIVISION OF WYETH

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

(b) (4)

ACTIVE INGREDIENT(S)

IBUPROFEN
PHENYLEPHRINE HYDROCHLORIDE
CHLORPHENIRAMINE MALEATE

STRENGTH(S)

200 mg
10 mg
4 mg

DOSAGE FORM

CAPLET

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
6/27/2007



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
MICHAEL LEE

Address
FIVE GIRALDA FARMS

City/State
MADISON, NEW JERSEY

ZIP Code
07940

Telephone Number
973-660-7681

FAX Number (if available)
973-660-7151

E-Mail Address (if available)
LEEM4@WYETH.COM

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PATENT CERTIFICATION
(NDA 22-113)

Pursuant to 21 CFR 314.50 Wyeth Consumer Healthcare, a division of Wyeth, hereby certifies that in its opinion and to the best knowledge, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

WYETH CONSUMER HEALTHCARE

 6/27/07

Michael Lee
Patent Counsel

EXCLUSIVITY SUMMARY

NDA # 22113

SUPPL #

HFD # 560

Trade Name Advil Allergy and Congestion Relief

Generic Name 200 mg ibuprofen, 4 mg chlorpheniramine, 10 mg phenylephrine

Applicant Name Pfizer Consumer Healthcare

Approval Date, If Known 12/21/2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Relative bioavailability studies under fed and fasted states were provided for the combination product and each individual ingredient. No efficacy studies were performed.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22565	Advil Congestion Relief
NDA# 19012	Motrin IB
NDA# 21441	Advil Allergy Sinus

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

YES
Explain:

! NO
! Explain:

Investigation #2

!
!

YES
Explain:

! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Janice Adams-King
Title: Regulatory Health Project Manager
Date: January 3, 2012

Name of Office/Division Director signing form: Joel Schiffenbauer
Title: Deputy Director, Division of Nonprescription Clinical Evaluation

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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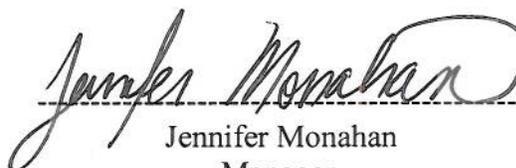
/s/

JANICE ADAMS
02/07/2012

JOEL SCHIFFENBAUER
02/13/2012

1.3.3 DEBARMENT CERTIFICATION

Pfizer Consumer Healthcare hereby certifies that it did not and will not use in any capacity the service of any person debarred under section 306 of the Federal Food and Drug and Cosmetic Act in connection with the application, NDA 22-113 Advil Allergy & Congestion Relief.

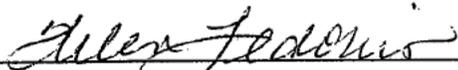
A handwritten signature in cursive script, reading "Jennifer Monahan", is written over a horizontal dashed line.

Jennifer Monahan
Manager
Development Quality and Compliance

DEBARMENT CERTIFICATION STATEMENT

Wyeth Consumer Healthcare 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 Cosmetics Act in connection with this application, [REDACTED] (b) (4)

NDA 22-113 [REDACTED] (b) (4)



Helen Fedoriw, RPh.
Director
Development Quality & Compliance
Wyeth Consumer Healthcare



NDA 022113

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Pfizer Consumer Healthcare
Attention: Erica M. Sinclair, MBA
Senior Manager, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Ms. Sinclair:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advil® Allergy and Congestion Relief (ibuprofen 200 mg/ phenylephrine HCl 10 mg/ chlorpheniramine maleate 4 mg) tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

¹ These violations include studies conducted by [REDACTED] (b) (4) specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Janice Adams-King, Regulatory Project Manager, at (301) 796-3713.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Division Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

MELISSA H FURNESS

09/16/2011

Signing for Dr. Andrea Leonard-Segal



NDA 022113

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pfizer Consumer Healthcare
5 Giralda Farms
Madison, New Jersey 07940

Attention: Erica Sinclair, MBA
Senior Manager, Regulatory Affairs

Dear Ms. Sinclair:

Please refer to your New Drug Application (NDA) dated September 25, 2007, received September 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and the Class 2 Resubmission dated June 21, 2011 for Ibuprofen, Chlorpheniramine, and Phenylephrine HCl Tablets, 200 mg/4 mg/10 mg.

We also refer to your June 21, 2011, correspondence, received June 21, 2011, requesting review of your proposed proprietary name, Advil Allergy & Congestion Relief. We have completed our review of the proposed proprietary name, Advil Allergy & Congestion Relief, and have concluded that it is acceptable.

The proposed proprietary name, Advil Allergy & Congestion Relief, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable we will notify you.

If any of the proposed product characteristics as stated in your June 21, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Janice Adams-King at (301) 796-3713.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
09/16/2011



NDA 022113

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Pfizer Consumer Healthcare
Attention: Erica Sinclair, MBA
Senior Manager, Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Ms. Sinclair:

We acknowledge receipt on June 21, 2011 of your June 21, 2011 resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Advil® Allergy and Congestion Relief (ibuprofen 200 mg, phenylephrine HCl 10 mg, and chlorpheniramine maleate 4 mg) tablets.

We consider this a complete, class 2 response to our July 25, 2008, action letter. Therefore, the user fee goal date is December 21, 2011.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-3713.

Sincerely,

{See appended electronic signature page}

Janice Adams-King, RN, BSN, MS
Regulatory Health Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

JANICE ADAMS
06/30/2011

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	(b) (6)		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Emanuel Troullos, D.M.D.	TITLE Senior Director Clinical Research
FIRM/ORGANIZATION Pfizer Consumer Healthcare	
SIGNATURE 	DATE (mm/dd/yyyy) 02/18/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850



NDA 022113

**PROPRIETARY NAME REQUEST
INCOMPLETE**

Pfizer Consumer Healthcare
5 Giralda Farms
Madison, New Jersey 07940

ATTENTION: Erica Sinclair
Senior Manager, Regulatory Affairs

Dear Ms. Sinclair:

Please refer to your New Drug Application (NDA), dated and received September 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate (b) (4) 200 mg/10 mg/4 mg.

We also refer to your December 22, 2010, correspondence, received December 22, 2010, requesting a review of your proposed proprietary name, (b) (4).

As noted in the Agency's Not Approvable letter, dated July 25, 2008, in order to start a new review cycle you must fully address all the deficiencies listed. Since your Request for Proprietary Name Review, did not accompany a Complete Response to the Not Approvable letter, your Request for Proprietary Name Review cannot be reviewed at this time.

If you intend to submit a new Request for Proprietary Name Review at this time; submit it to an applicable Investigational New Drug (IND) application. Alternatively, your Request for Proprietary Name Review may accompany your Complete Response to the Not Approvable letter.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Janice Adams-King, at (301) 796-3713.

Sincerely,
{See appended electronic signature page}

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DENISE P TOYER
01/24/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: January 3, 2011
TO: NDA 022113 Administrative File
FROM: Doris J. Bates, Ph.D.
SUBJECT: **Telecon with Pfizer Consumer Health**
Re: Proprietary Name Submission, December 22, 2010
(b) (4)

Background. Wyeth Consumer Healthcare submitted NDA 022113 to DNCE in September 2007 (proposed proprietary name (b) (4)). The proprietary name was rejected in June, 2008 (review); the NDA received a Not Approvable letter in July, 2008.

In October, 2009, Wyeth was acquired by Pfizer and discussions with DNCE towards planning a resubmission continued. A new proposed proprietary name was submitted and received under the NDA on December 22, 2010 (SD 29, sequence number 0017).

The cover letter for this submission indicates that the firm plans to submit the remaining components of a Complete Response in March, 2011. However, since this submission was made after the NDA received an NA letter, it technically cannot be reviewed until the remaining Complete Response components have also been received.

Telephone Contacts with Sponsor. I contacted Pfizer Consumer Health on Monday, December 27 (Erica Sinclair, 973-660-6431), and left a voicemail explaining the technical situation. On December 29, I was contacted by Suzanne Brabant (973-660-5164) and followed up with her to explain.

I explained that Pfizer could incorporate the existing proprietary name submission (NDA 022113, December 22, 2010) into their upcoming complete response NDA resubmission by cross-reference; at that time we will be able to initiate the review.

I also clarified that any changes in the product, labeling, etc. should also be included in the upcoming resubmission and referenced at that time.

Pfizer understands the technical situation. OSE can issue an incomplete letter for this submission, which I have drafted to include a summary of the recommendations above.

Doris J. Bates, Ph.D.
Team Leader
OSE Project Management

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/s/

DORIS J BATES
01/07/2011



NDA 22-113

INFORMATION REQUEST LETTER

Wyeth Consumer Healthcare
Attention: Neil Napolitano
Assistant Director, Global Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Mr. Napolitano:

Please refer to your new drug application (NDA) dated September 25, 2007, received September 25, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (ibuprofen 200 mg/ phenylephrine HCl 10 mg/ chlorpheniramine maleate 4 mg) tablets.

We also refer to your submissions dated December 18, 2007, March 5, 2008 and April 18, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submissions and have the following comments and information requests. We request a prompt written response by May 19, 2008, in order to continue our evaluation of your NDA:

1. We remind you that the drug product expiration date should start from the manufacturing date of the bulk tablets.
2. We have concluded that the stability data and other relevant information provided to-date in the application can support only one month of holding time for the bulk tablets. However, if you commit to the following, you may hold the bulk tablets up to three months:
 - Perform full release testing on the final dosage form (i.e., tablets in blister or pouch) for each batch.
 - Ensure that the bulk tablets are stored at 20°C – 25°C/60% RH during the holding period.
 - Submit information (name and address of the supplier, and reference to the appropriate indirect food additives regulation) on the inner liner of the bulk packaging (drug contact surface) to ensure the drug product quality during the storage of the bulk tablets.

3. The stability data provided in the amendment dated April 18, 2008, indicate that ^{(b) (4)} has been identified with concentration up to ^{(b) (4)} relative to phenylephrine hydrochloride. Please add ^{(b) (4)} to the drug product specification as a specified impurity and do not include it in the calculation for unspecified impurities. The limit for ^{(b) (4)} should be set at NMT ^{(b) (4)} per ICH Q3B unless the degradant has been qualified at a higher level.
4. Please explain the meaning of symbol “N” in the stability summary report.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
5/8/2008 05:57:54 PM
Chief, Branch III



Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Neil J. Napolitano
Assistant Director, Regulatory Affairs
Tel: 973.660.5725
Fax: 973.660.8071
E-mail: napolin@wyeth.com

ORIGINAL

NEW CORRESP

18Apr2008

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED

APR 21 2008

CDER COR

Re: New Drug Application 22-113: Information Amendment

Products: (b) (4) (ibuprofen 200mg/phenylephrine HCl 10mg/chlorpheniramine maleate 4mg) (b) (4)

Indications: Temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor body aches and pains, fever.

Sponsor: Wyeth Consumer Healthcare ("WCH")

Dear Dr. Segal:

Reference is made to:

1. NDA 22-113, submitted 25Sep2007
 - o Specifically, the Pre-NDA Meeting Minutes dated 19Mar2007, in which WCH agreed to provide updated stability data
2. CMC amendment dated 18Dec2007, wherein WCH informed the Agency of an additional degradant known as (b) (4)
3. 26Feb2008 Meeting Minutes dated 15Mar2008, which captures a discussion between WCH and FDA regarding degradants, stability and toxicology studies included the subject NDA.

Accordingly, this amendment includes:

1. Updated stability data for the formulation with propyl gallate (PG).
2. A specification for (b) (4), based on data generated through 12 months, including documentation to support the establishment of the specification.
3. Updated toxicology information.

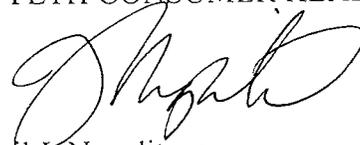
The e-CTD sections are organized as follows (please refer to the table in Attachment 1 for a detailed list of changes including whether the impacted sections will be replaced or appended):

Module 1	Regional Administrative Information
1.1.2	Form FDA 356h
1.2	Cover Letter
1.3.2	Field Copy Certification
1.6.3	Correspondence regarding meetings
Module 2	Quality Information
2.2	Introduction (reference to 2.4, 2.6.6 and 2.6.7)
2.3.1	Quality Overall Summary
2.4	Nonclinical Overview (reference to 2.6.6, 2.6.7 and 4.2.3)
2.6	Nonclinical written and tabulated summaries <ul style="list-style-type: none"> ▪ 2.6.6 Toxicology written summary ▪ 2.6.7 Toxicology tabulated summary
Module 3	Quality Information
3.2.P.5.1	Specifications
3.2.P.5.4	Batch Analysis
3.2.P.5.5	Characterization of Impurities
3.2.P.5.6	Justification of Specifications
3.2.P.8.1	Stability Summary and Conclusion
3.2.P.8.2	Post-Approval Stability Protocol and Stability Commitment
3.2.P.8.3	Stability Data
Module 4	Nonclinical Study Reports
4.2.3.7.6	Toxicology; Other toxicity studies; Impurities <ul style="list-style-type: none"> ▪ 14-day Toxicology study (AD-07-09) ▪ Chromosomal Aberration (AD-07-08) ▪ Ames Test (AD-07-07) ▪ Lab Validation

Please note the megabyte size, presentation (e.g. in CD-ROM form) and virus scan information is appended to this letter.

If you have any questions or comments regarding this submission, please contact the undersigned at (973) 660-5725, or Lauren Quinn, at (973) 660-6167.

Sincerely,
WYETH CONSUMER HEALTHCARE



Neil J. Napolitano
Assistant Director
Global Regulatory Affairs

cc: Robin Anderson, R.N., M.B.A., Regulatory Project Manager (NDA 22-113)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: April 14, 2008

From: Hari Cheryl Sachs, MD, Medical Officer
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD, OND Associate Director
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff

To: Andrea Leonard-Segal
Director, Office of Generic Drugs

Re: (b) (4)
(b) (4) (ibuprofen 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate 4 mg), NDA 22-113

Consult question:

Please advise whether the Sponsor (Wyeth Consumer Healthcare) should be required to perform pediatric studies for this combination product.

Regulatory Background:

Ibuprofen, although marketed over-the-counter (OTC) is an NDA product. Ibuprofen is approved for the treatment of fever down to 6 months of age. However, there is a proposed rule to add ibuprofen as a GRASE active ingredient (67FR54139, published August 2002). The proposed rule (68FR33429, June 2003) would permit ibuprofen 200 mg to be marketed via monograph for “the relief of pain and fever in adults and children 12 years of age and older.”

Phenylephrine and chlorpheniramine are already monograph products. Phenylephrine, like pseudoephedrine is an oral nasal decongestants which act systemically “to reduce nasal congestion caused by acute or chronic rhinitis” [21CFR 341.3(f)]. Multiple

phenylephrine products are approved and marketed as either single ingredient or combination products via monograph with dosing down to 2 years of age. Phenylephrine has replaced pseudoephedrine in many cough and cold preparations due to the Combat Methamphetamine Epidemic Act 2005 (Title VII of the USA Patriot Improvement and Reauthorization Act of 2005, P.L. 109-177). Chlorpheniramine, is approved as an antihistamine used for allergic rhinitis via monograph "to temporarily relieve runny nose, sneezing, itching of the nose or throat due to hay fever or allergic rhinitis." Multiple chlorpheniramine single ingredient or combination products include dosing down to age 6 years and professional labeling for ages 2 to 6 years.

Reviewer comment: although the nasal symptoms related to allergic rhinitis certainly overlap those of the common cold, the monograph does not include labeling for the common cold per se for antihistamines.

Approval for both phenylephrine and chlorpheniramine was based in part on recommendations by an FDA Advisory Review Panel. Note that dosing was determined by simply fractionating adult dose (e.g., one-half the adult dose for children 6 to 12 years of age and one-quarter the adult dose for children 2 to 6 years of age).

Approved dosing via monograph is as follows:

For phenylephrine hydrochloride (every 4 hours)

- Adults and children 12 years of age and older: 10 mg (maximum 60 mg in 24 hours)
- Children 6 to 12 years: 5 mg (maximum 30 mg in 24 hours)
- Children 2 to 6 years: 2.5 mg (maximum 14 mg in 24 hours)

For chlorpheniramine maleate (every 4 to 6 hours)

- Adults and children 12 years of age and older : 4 mg (maximum 24 mg in 24 hours)
- 6 to 12 years: 2 mg (maximum 12 mg in 24 hours)
- 2 to 6 years: 1 mg (maximum 6 mg in 24 hours) [professional labeling]

Combination products containing ibuprofen and pseudoephedrine were approved for adults and children 12 years of age and older in 1989 and subsequently as a suspension in 2000 for children 2 year of age and older (Children's Motrin Cold, NDA 21-128) and as a liquegel on May 30, 2002 (Advil cold and Sinus, NDA 21-374). The triple combination of ibuprofen, pseudoephedrine and chlorpheniramine ((b) (4), NDA 21-441) was approved on December 19, 2002. A pediatric formulation, Children's Advil Allergy Sinus (NDA 21-587) was approved on February 24, 2004.

Due to abuse of pseudoephedrine, Combat Methamphetamine Epidemic Act restricted the use of pseudoephedrine to behind the counter. Industry has been advised that due to this Act, phenylephrine could be substituted for pseudoephedrine as long as pharmacokinetic studies demonstrate noninterference.

Two recent citizen petitions in regard to cough and cold products in children (October 18-19, 2007) and the use of higher doses of phenylephrine (December 14, 2007) have prompted discussion at Advisory Committee meetings that impact these products. At the October AC, the committee recommended more studies and data in children to evaluate the efficacy of monograph cough/cold products for the common cold (see Flash Minutes).

At the December AC (see Flash Minutes), the committee recommended additional trials for the 10 and 25 mg dose of phenylephrine (PEH).

- *A multi-center, parallel, randomized, double blind, placebo-controlled trials, preferably with an active control such as pseudoephedrine, to evaluate nasal congestion scores and symptom relief. The trials need to have sufficient sample size to evaluate efficacy and safety according to key characteristics such as age, gender, race, and severity of symptoms;*
- *Characterization of the PEH dose response and the effect of dosing interval, formulation, type of delivery system, and potentially, genetic factors, on safety and efficacy endpoints;*
- *Comparison of the pharmacokinetics of single-ingredient products versus multiple-ingredient products;*
- *Safety evaluation of the effects of PEH on blood pressure and cardiovascular and use of PEH in patients with important comorbidities such as BPH, hypertension, or diabetes mellitus.*

In response to the discussions and recommendations at the October AC and an internal review of the data regarding the safety of these medications in children, FDA issued a PHA January 17, 2008 strongly recommending that over-the counter cough and cold medications not be given to infants and children under two years of age because of the risk of life-threatening adverse events. According to the PHA, "FDA has not completed its review of information about the safety of OTC cough and cold medicines in children 2 through 11 years of age."

An internal memo from Dr. Jenkins indicates that "pk, efficacy and safety data from adequate and well controlled studies are needed to demonstrate the efficacy of each ingredient in children and permit the assessment of the benefit/risk profile." In the interim, as these studies are conducted, Dr. Jenkins recommends that efforts should be initiated to remove the indications for pediatric use from the cough and cold monograph, develop a communication plan to publicize these conclusions and strongly recommend that CHPA to voluntarily change the product labeling to reflect "do not use" less than age 6 years and "use only if recommended by a physician" in ages 6 to 12 years. However, a final decision has not yet been made by Agency officials regarding the most appropriate course of action.

Safety reviews of AEs for cough and cold products in children 6 years and older are in progress and have not been completed.

Reviewer comment: Raw counts based on an AERs query by this reviewer on 1/25/2008 revealed a total of 276 AEs related to phenylephrine in patients 0 to 16; 168 were serious and 33 were fatal. Most of the fatalities in children older than 6 years of age appeared to be confounded by exposure to phenylpropanolamine or other agents. However, the serious AEs included reports of seizures, stroke, hypertension and arrhythmias.

Summary of Proposal:

Wyeth proposes the following indication

(b) (4)

(b) (4)

- NDA 22-113 (ibuprofen, phenylephrine, and chlorpheniramine): adults and children 12 year and older "temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies and the common cold: runny nose, itch watery eyes,

itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor body aches and pains, fever.”

The proposed dosing is as follows:

- (b) (4)
- NDA 22-113: one caplet (200 mg ibuprofen, 10 mg phenylephrine and 4 mg chlorpheniramine) q 4 hours, not to exceed 6 doses in 24 hours.
Reviewer comment: note that the amount of phenylephrine (10 mg) and chlorpheniramine (4 mg) in each tablet exceeds monograph dosing for children less than 12 years of age.

The sponsor is requesting a waiver of studies in the 0 to 12 year age group because:

- The product does not represent a meaningful therapeutic benefit over numerous existing treatments
- The product is not likely to be used in a substantial number of children as “caregivers are likely to select readily available existing treatment products”
- The dosing exceeds current monograph doses for children less than 12 year of age
- The caplets need to be swallowed whole and may be inappropriate for children ages 0 to 12 years

Note that since the waiver would be in a subpopulation, the Sponsor is actually requesting a partial waiver of pediatric studies. If the drug product is approved for patients 12 years and older based on the monograph and previous agreement to substitute phenylephrine for pseudoephedrine, these products would be considered to be adequately labeled in pediatric patients 12 years and older. However, since pharmacokinetic data is not available for phenylephrine (see Pediatric meeting consult: phenylephrine extended release, (b) (4) Feb 2008), pK information is needed to confirm dosing.

Studies performed thus far:

The studies submitted for (b) (4) NDA 22-113 (Sept 25, 2007) consist of bioavailability study for each of the combination products compared with the single ingredient products administered concomitantly in adults.

Reviewer comment: Due to the agreement regarding the substitution of phenylephrine for pseudoephedrine, clinical studies were not performed for the ibuprofen/phenylephrine or ibuprofen/phenylephrine/chlorpheniramine combinations. However, efficacy trials were performed for the (b) (4) triple combination product containing ibuprofen/pseudoephedrine /chlorpheniramine products (NDA 21-441). The efficacy trials for the triple product did include adolescent patients, while efficacy of the pediatric formulations (NDA 21-128, 21-373 and 21-587) in younger pediatric patients (2 to 12 years) appears to be extrapolated from adults or older adolescents in combination with supporting pK and safety data obtained in children ages 4 to 12 years of age. Of interest, pK studies revealed that the bioavailability of chlorpheniramine is lower and clearance faster in children than in adults (NDA-587, Daiva Shetty). Somnolence was the most common AE noted in the trials (NDA- 21-128, NDA373). The safety reviews for patients 12 years and older (NDA-374) and 2 to 12

years (NDA 21-128) suggested that "no drug effect" was the most common AE reported from postmarketing analysis.

Discussion:

This NDA product is a new combination product (i.e., a new active ingredient and triggers PREA. Concerns have been raised regarding the safety and efficacy of cough and cold products in general. External advisors (Pediatric Advisory Committee) recommend that studies be performed in the pediatric population for cough and cold products. Moreover, the efficacy of current monograph dosing of phenylephrine has also been challenged. External advisors recommend additional studies for phenylephrine as well. The internal cough/cold working group also recommends that studies be performed in pediatric patients. Pediatric pharmacokinetic data are not available for phenylephrine and safety data for combinations containing phenylephrine and ibuprofen are not available for pediatric patients.

Cough and cold products are used in millions of pediatric patients who are otherwise essentially healthy. Cough and cold products provide symptomatic relief for an otherwise self-limited disease. These products have not been shown to alter the course of the common cold, prevent transmission to others or prevent complications. The tolerance for adverse events in an otherwise healthy population is low as evidenced by FDA actions on vaccines. For example, the vaccine against rotavirus (Rotashield), which was at least 90% effective at reducing hospitalizations due to rotavirus gastroenteritis, was withdrawn from the market for reports of intussusception, a complication which occurred at a frequency of approximately 1 case per 10,000 doses. Similarly, inactivated polio vaccine has replaced oral polio vaccine due to rare reports of paralysis after oral vaccination at a rate of one case in 750,000 to 1.2 million doses (MMWR 1999)

In contrast, safety concerns with cough and cold products include the large number of emergency room visits related to adverse events (Schaefer 2008, MMWR 2007). The estimated number of emergency room visits related to cough and cold products exceed 7,000 annually. Although many of these emergency room visits and AEs appear to be related to unsupervised ingestions or overdoses, up to 18% of cases in 2 to 5 year olds and 55% of cases in the 6 to 12 year olds involve supervised settings without apparent medical error (Schaeffer 2008). Therefore, due to the lack of data on combination products containing phenylephrine and ibuprofen in pediatric patients and these safety concerns, pediatric studies are needed for all age groups.

Waivers can be granted under PREA if one or more of the following apply:

1. Necessary studies are impossible or highly impracticable
2. Evidence strongly suggests that the drug product would be ineffective or unsafe in that age group.
3. The drug does not represent meaningful therapeutic benefit AND is not likely to be used by a substantial number of patients.
4. Reasonable attempts to produce an age-appropriate formulation have failed. This process must be documented.

Furthermore, if a waiver is granted based on evidence the drug is unsafe or ineffective, the information must appear in the product labeling.

Wyeth is requesting a waiver based on the dual criteria (lack of meaningful benefit AND unlikely to be used), as well as two formulation issues. However, these reasons are not valid for the proposed products.

Use data for cough and cold products contradicts the Sponsor's first statement (unlikely to be used). Upper respiratory infections are common and cough and cold products are used in millions of pediatric patients. Thus, an age-appropriate formulation of a new cough and cold product would most likely be widely used. Therefore, the Sponsor cannot claim that the drug would not likely be used by a substantial number of pediatric patients. Furthermore, with respect to not representing a meaningful therapeutic benefit, a combination product containing ibuprofen may have some advantages over products containing acetaminophen. The duration of action for ibuprofen is longer and permits less frequent dosing (q 6 to 8 hours vs. q 4 to 6 hrs. for acetaminophen). Many physicians recommend (and many parents choose) to alternate acetaminophen and ibuprofen to treat fever (Sarrell 2006). In addition, comparative studies in the literature suggest that ibuprofen tends to have a stronger effect reducing fever (Perrott 2004, Autret-Leca 1007) and musculoskeletal pain (Clark 2007). Review of AAPCC data (1994-2000) suggests that ibuprofen may have a wider therapeutic margin than acetaminophen (Linda Hu, Medical Officer Review NDA 21-373).

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Reviewer comment: The strength of this analysis is that the data reflect single product use (before combination products containing ibuprofen were widely available). However, one weakness of the analysis is that most of the exposures occurred in adults. Finally, the initial reviews supporting the approval of the combination products containing ibuprofen/pseudoephedrine (NDA 21-374) suggested that review of AEs from multiple post-marketing sources (i.e., AAPCC, AERs) suggested more AEs in single use products used concomitantly than from combination products (Andrea Leonard Segal, NDA 21-374). Therefore, combination products containing ibuprofen may be considered by consumers (Autret-Leca 2007) and health care providers to be superior to products containing acetaminophen.

The Sponsor asserts that two formulation issues should permit a waiver of studies, namely that children less than 12 years of age are unlikely to be able to swallow a pill and that the amount of phenylephrine and/or chlorpheniramine in each tablet exceeds monograph doses. However, PREA requires the development of an age-appropriate formulation. In direct contrast to the Sponsor's assertion, the majority (90%) of children

6 to 12 years of age appear to be able to be taught to swallow a pill (Meltzer 2006). Therefore, a tablet containing appropriate doses of these products for children 6 to 12 years would be needed. In addition, an age-appropriate formulation for patients less than 6 years or those who may be unable to swallow a tablet or capsule must be developed. The challenge for the Sponsor will be to develop an age-appropriate formulation that provides an appropriate dose at an appropriate dosing interval for each component of the product. If the Sponsor is unable to do so, PREA 2007 now requires that efforts to develop a formulation must be documented and posted.

Reviewer comment: Since many children would be capable of swallowing a capsule or tablet, consideration should be given to including in the labeling a statement that indicates the dose provided by the proposed formulation exceeds the recommended (monograph) dose for children less than 12 years of age.

The need for pediatric studies must be addressed for all age groups. Due to the various issues for different pediatric subpopulations (0 to <2 years of age, 2 years to <12 years and 12 to 17 years old), these age groups will be discussed separately.

0 to less than 2 years of age

Safety concerns provide the primary factor impacting the decision to waive or defer studies in this age group. Based on the safety concerns raised by OSE, the deliberations at the October 2007 Advisory Committee and the Public Health Advisory issued by the FDA, a partial waiver of studies in pediatric patients in patients less than 2 years of age is appropriate. Since the waiver in this age group is due primarily to safety concerns, labeling must reflect these safety concerns.

An argument can be made to defer studies, since nasopharyngitis is common in this age group, and the risk/benefit might change if pediatric studies establish safety and efficacy in older children. However, studies thus far in children of cough and cold products do not inspire optimism that future studies will demonstrate that these products will be effective. Therefore, due to the safety concerns and existing data which do not currently support efficacy in children, studies should be waived. If efficacy was indeed established in older pediatric patients in the future, the decision to waive studies in this age group can be reconsidered.

2 to less than 12 years of age

Pediatric studies are required for this age group under PREA and can be deferred since adult studies are ready for approval. PREA requires development of an age-appropriate formulation since the proposed formulations are inappropriate for this age group. A pediatric plan must be submitted by the Sponsor. Efficacy in this age group has been previously been extrapolated from older patients, as evidenced by extrapolation of efficacy from the adequate and well controlled studies of the two pseudoephedrine and ibuprofen- containing combinations. However, since there would be no "adequate and well-controlled" studies of the ibuprofen and phenylephrine combination products in older pediatric patients or adults to extrapolate from, efficacy and safety studies would be required in this age group. In addition, pharmacokinetic data for phenylephrine to establish appropriate dosing needs to be obtained. Moreover, even if these studies were

available, in order to extrapolate, according to the FDA algorithm, one would need to show that “it is reasonable to assume that children, when compared to adults, have a similar response to intervention.” That assumption is no longer appears to be warranted given existing data which do not support the efficacy and safety of these products in children.

12 to 17 years of age

Since pharmacokinetic data is not available for phenylephrine and safety data is not available for the ibuprofen/phenylephrine or ibuprofen/phenylephrine/chlorpheniramine combinations, pharmacokinetic and safety studies are needed in adolescents. Adolescents have traditionally been included in efficacy studies of these products, as evidenced by the studies of the ibuprofen and pseudoephedrine combinations. In addition, efficacy could only be extrapolated from “adequate and well-controlled trials in adults” for the specific product which have not been performed. Therefore, efficacy studies would be needed as well. Requiring studies is inconsistent with the monograph determination and the Agency’s policy for relying on labeled findings of safety and efficacy without reassessing supporting efficacy data to support generic products. Thus, the mechanism for obtaining studies in this age group rests on the regulatory action chosen by the Division for this specific product and the Agency’s recommendation on the best approach to reconciling the previous determination of GRAS/E status conferred by the existing monographs when pediatric information is lacking and would be required under PREA due to safety concerns or scientific necessity.

If the Division decides to approve the product down to age 12 years based on the monograph and agreements related to the Combat Methamphetamine Epidemic Act that appropriate bioequivalent studies have been performed, the product would be adequately labeled in adolescents. Since pharmacokinetic data is not available for phenylephrine and safety data is not available for the ibuprofen/phenylephrine combinations in adolescents, pharmacokinetic, efficacy and safety studies in this age group should be required as a post-marketing requirement. This approach is somewhat unsatisfactory in that doses ultimately identified from pharmacokinetic studies potentially could differ from those in the monograph, efficacy might not be demonstrated or significant safety concerns could arise, necessitating withdrawal of the approval in this age group.

If the Division decides to approve the product only in adults, pediatric studies would be deferred in pediatric patients 2 years and older. A pediatric plan must be submitted by the Sponsor.

Conclusions and Recommendations:

Pediatric studies are required under PREA for this NDA product. Pediatric studies in children age 2 to 12 years of age should be deferred if the product is approved down to age 12. In that case, studies in adolescents should be required as a PMR depending on the Agency’s recommendation on the best approach to reconciling the previous determination of GRAS/E status conferred by the existing monographs when pediatric information is lacking. If the product is approved in adults only, pediatric studies should

be deferred for patients ages 2 to 17 years. A pediatric plan must be submitted by Wyeth. The waiver decision, deferrals and plan must be discussed at PERC before an approval action is taken.

A partial waiver may be granted for children less than 2 years of age. Labeling must reflect the safety concerns in this age group. Labeling should also indicate that the dose provided by the proposed product is too high for children less than 12 years of age.

The challenge for the Sponsor will be to develop an age-appropriate formulation that permits the proper dosing of each component in this combination product. If ultimately, Wyeth cannot develop an age-appropriate formulation, efforts must be documented and posted as required under PREA.

REFERENCES

- Suspension of rotavirus vaccine after reports of intussusception- United States, 1999. *MMWR* 2004; 53(34): 786-789.
- Infant deaths associated with cough and cold medications- two states, 2005. *MMWR* 2007; 56(1): 1-4.
- Autret-Leca E, Gibb I, and Goulder M. Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study. *Curr Med Res Opin* 2007; 23(9): 2205-2011.
- Clark E, Plint A, Correll R, et al. A randomized, controlled trial of acetaminophen, ibuprofen and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics* 2007; 119(3): 460-467.
- Meltzer E, Welch M and Ostrom N. Pill swallowing ability and training in children 6 to 11 years of age. *Clin Pediatr* 2006; 45(8): 725-733.
- Pernott D, Piira T, Goodenough B, et al. Efficacy and safety of acetaminophen vs. Ibuprofen for treating children's pain or fever: a meta-analysis. *Arch Pediatr Adolesc Med* 2004; 158(6): 521-526.
- Sarrell E, Wielunsky E, and Cohen H. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen or both alternating in a randomized, double-blind study. *Arch Pediatr Adolesc Med* 2006; 160: 197-202.
- Schaefer M, Shehab N, Cohen A, et al. Adverse events from cough and cold medications in children. *Pediatrics* 2008; 121(4): 783-787.

MATERIAL REVIEWED

Flash Minutes: Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee October 18-19, 2007

Summary minutes of the Nonprescription Drugs Advisory Committee Meeting December 14, 2007

Pediatric meeting consult: phenylephrine extended release (b) (4) Feb 2008)

Pediatric consult: (b) (4), March 2007)

Public Health Advisory: January 17, 2008 cough and cold products

OND Memo March 4, 2008 OTC Cough and Cold Medications: Recommendations for Next Steps

Medical Officer Review Children's Motrin Cold Suspension (NDA 21-128, Maria Lourdes Villalba, July 20, 2000)

Medical Officer Review: Children's Advil Allergy Sinus (NDA 21-587, Andrea Leonard-Segal, February 11, 2004)

Medical Officer Review: Children's Advil Cold Suspension (NDA 21-373, Linda Hu March 22, 2002)

Medical Officer Review, Advil Cold and sinus liquigels (NDA 21-374, Andrea Leonard-Segal, January 10, 2002)

Medical Officer Review, Advil Allergy Sinus (NDA 21-441, Christina Fang, December 6, 2002)



Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Neil J. Napolitano
Assistant Director, Regulatory Affairs
Tel: 973.660.5725
Fax: 973.660.8071
E-mail: napolin@wyeth.com

Wyeth

11Apr2008

RECEIVED

APR 17 2008

CDER CDR

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

N-000 C

NEW YORK

ORIGINAL

Re: New Drug Application 22-113: Information Amendment

Products: (b) (4) (ibuprofen 200mg/phenylephrine HCl
10mg/chlorpheniramine maleate) (b) (4)

Indications: Temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor body aches and pains, fever.

Sponsor: Wyeth Consumer Healthcare ("WCH")

Dear Dr. Segal:

Reference is made to NDA 22-113, submitted 25Sep2007.

In a telephone conversation between L. Quinn and E. Abraham on 18Mar2008, reference was made to the analytical method used to assay PE plasma levels for the bioequivalence studies. WCH recently became aware of a 483 that was issued to (b) (4), the testing site utilized to analyze the PK data (FDA form 483; FEI Number (b) (4)). Based on a thorough investigation, WCH maintains that the PE assay issues identified by the FDA investigator have no impact on the conclusions of the bioequivalence studies.

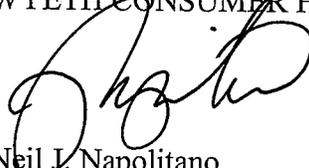
A detailed report describing the investigation, results and conclusions is included in this amendment. The following eCTD sections are affected:

- 1.1.2 Forms
 - FDA 356h Form
 - FDA 3674 Form
- 1.2 Cover letter
- 2.2 Introduction (reference to 2.5 and 2.7.1)
- 2.5 Clinical Overview
 - 2.5.2.1 Overview of Biopharmaceutics (reference to 2.7.1.1.3)
- 2.7.1 Summary of Biopharmaceutics
 - 2.7.1.1.3 Phenylephrine Assay Investigation

Please note the megabyte size, presentation (e.g. in CD-ROM form) and virus scan information is appended to this letter.

If you have any questions or comments regarding this submission, please contact the undersigned at (973) 660-5725, or Lauren Quinn, at (973) 660-6167.

Sincerely,
WYETH CONSUMER HEALTHCARE



Neil J. Napolitano
Assistant Director
Global Regulatory Affairs

cc: Robin Anderson, R.N., M.B.A., Regulatory Project Manager (NDA 22-113)

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Neil J. Napolitano
Assistant Director
Global Regulatory Affairs
973-660-5725
Fax 973-660-8761
napolin@wyeth.com

ORIGINAL

Wyeth

21 March 2008

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: New Drug Application 22-113 – 26Feb2008 Teleconference Minutes

Clarification: (b)(4) (chlorpheniramine maleate
4mg/ibuprofen 200mg/phenylephrine HCl 10mg)

Indications: Temporary relief of symptoms associated with hay fever or other
upper respiratory allergies, and the common cold.

Sponsor: Wyeth Consumer Healthcare ("WCH")

Dear Dr. Leonard-Segal:

Reference is made to the subject application dated 25Sep2007, and FDA's minutes of the
26Feb2008 teleconference (dated 15Mar2008). The minutes detail a discussion between
WCH and FDA regarding the toxicological qualification of (b)(4)

WCH would like to offer the following clarification with respect to pg 2, paragraph 3, of
the aforementioned minutes:

The HPLC peak is split because the structure contains two chiral centers.
Phenylephrine (PE) contains one chiral center, and one additional chiral center is
formed in the reaction. This results in two diastereomers, with the same
configuration at one chiral center (that from PE) but different at the other. These
diastereomers were not resolved in the original published report, but they are
resolved in our analytical method.

The analytical method for (b)(4) and most of the validation utilized PE as a surrogate
for the degradant. A more limited study using authentic (b)(4) will be detailed in a

supplemental report including a linearity study, a solution stability study, and a confirmation of the relative response factor.

With respect to the analytical method and validation report used to test (b) (4) reference is made to the minor CMC amendment dated 18Dec2007. In this amendment, analytical method A7309 was provided in section 3.2.P.5.2, and the validation report (MVR00549) for analytical method A7309 was provided in section 3.2.R.2.P.

WCH will provide a summary of the analytical development for method A7309, as well as the aforementioned supplemental report, in the April 2008 amendment.

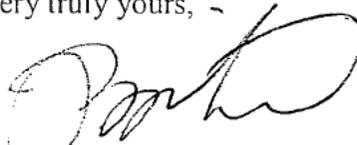
The following sections in Module 1 are affected by this submission:

- 1.2 Cover Letter
- 1.1.2
 - FDA 356h Form
 - FDA 3674 Form
- 1.6.3 FDA minutes of 26Feb2008 teleconference, dated 15Mar2008

Please note that this submission is being provided in electronic format (e-CTD). The megabyte size, presentation (e.g. in CD-ROM form) and virus scan information is appended to this letter.

If you have any questions or comments regarding this submission, please contact the undersigned at (973) 660-5725, or Lauren Quinn, at (973) 660-6167.

Very truly yours, -



Neil J. Napolitano
Assistant Director
Global Regulatory Affairs

Attachment: Technical Information

cc: Robin Anderson, R.N., M.B.A., Regulatory Project Manager



NDA 22-113

Wyeth Consumer Healthcare
Attention: Neil Napolitano
Assistant Director, Global Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Mr. Napolitano:

Please refer to your new drug application (NDA) dated September 25, 2007, received September 25, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for [REDACTED] ^{(b) (4)} (ibuprofen 200 mg/ phenylephrine HCl 10 mg/ chlorpheniramine maleate 4 mg) tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 26, 2008. The purpose of the meeting was to discuss FDA concerns regarding degradants, stability and toxicology studies for this NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Robin Anderson, Regulatory Project Manager, at (301) 796-0534.

Sincerely,

{See appended electronic signature page}

Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECON

DATE: February 26, 2008

APPLICATION NUMBER: NDA 22-113 (b) (4)

BETWEEN:

Name: Global Regulatory Affairs:
Neil Napolitano (Assistant Director)
Lauren Quinn, JD (Sr. Director)
Henry Weidmuller, R.Ph. (Sr. Director CMC)
Vonnie Lewis (Manager CMC Global Regulatory Affairs)

R&D (Chemists):
David Giamalva, PhD (Research Fellow)
Mike Eckstein (Assistant Director)

Toxicology:
Jay Goldring, PhD (Director)

Representing: Wyeth

AND

Name: **Division of Nonprescription Clinical Evaluation (DNCE):**
Robin Anderson, Project Manager
Andrea Leonard Segal, Division Director
Joel Schiffenbauer, Deputy Division Director
Bindi Nikhar, Medical Team Leader
Steve Osborne, Medical Officer
Linda Hu, Medical Officer
Paul Brown, Pharmacology/Toxicology Team Leader
Wafa Harrouk, Pharmacology/Toxicology Reviewer

Office of New Drug Quality Assessment:
Shulin Ding, Chemistry PAL
Bogdan Kurtyka, Chemist

SUBJECT: FDA concerns regarding degradants, stability and toxicology studies for NDA 22-113

Background:

NDA 22-113 is currently under review by DNCE, with a PDUFA goal date of July 25, 2008. On December 19, 2007 an amendment with updated stability data for the optimized formulation was submitted to this NDA. During the evaluation of the 6-month accelerated data for the optimized formulation Wyeth observed an additional degradant of (b) (4), referred

to by Wyeth as (b) (4). Wyeth stated that it had validated an analytical method for testing this degradant in (b) (4). Wyeth also stated that given the observation of the new degradant, the facilities specified for the manufacturing, packaging and control operations for (b) (4) would not be ready for inspection until April 21, 2008. Originally Wyeth had stated that the facilities would be ready for inspection on January 24, 2008. The FDA review chemists and toxicologists were concerned about this new degradant, the method used to validate testing for this new degradant, and the timing for the facilities inspection. The FDA toxicologists also questioned why Wyeth chose a 14-day duration for the toxicology studies since the duration range for a general toxicology study for qualifying a new degradant per ICH-Q3B is between 14-90 days, corresponding to the expected duration of use. The duration being tested by Wyeth might be too short since repeated use of this product is expected based on the sought indication (b) (4) which is likely to lead to chronic exposure for this OTC product. FDA requested a teleconference between Wyeth and FDA to discuss these issues.

Summary of Telephone Conversation:

FDA asked Wyeth to discuss the structure and levels determined for the new degradant. Wyeth referred to an article provided in the December 19, 2007 amendment. (b) (4)

The level after 9 months at room temperature was close to (b) (4) of the label claim, which is above the ICH qualification level. Wyeth stated that they had started the qualification study on the new degradant using the synthesized and isolated material.

FDA asked Wyeth (b) (4). Wyeth explained (b) (4). A complete validation of the new analytical method will be included in the April 2008 amendment. The validation will be based on the synthesized degradant, not by surrogation as was submitted in the 6 months stability update. FDA asked if Wyeth had stability data for 12 months for the caplet in the blister pack. Wyeth stated that they do have that data, and they will be submitted in the April update.

FDA asked why Wyeth chose a 14-day duration for the toxicology studies given that repeated use would be expected for this OTC product, and the duration range for this study per ICH Q3B would be 14-90 days. FDA also asked when stability testing of the material used in the toxicology studies was conducted. Wyeth replied that the stability was checked at times 0, 36 hours, 5 days, 7 days, and 14 days. Wyeth stated that 14 days of toxicology studies was acceptable and within the guidelines since the drug is labeled for 10 days of use. In response to the stability testing question, Wyeth replied that the stability testing was done concurrently with the toxicology study. Wyeth stated that a draft of the study report should be available by March 14, 2008. FDA asked if there was precedence for 14 days of study duration for other similar products, and Wyeth confirmed that there was precedence with at least one other cough and cold

product. Wyeth agreed to forward information concerning the other product to the FDA Project Manager following the teleconference. FDA stated they will review Wyeth's 14-day toxicology study data.

FDA stated that this type of product is for an indication that will engender repeated use that may add up to chronic exposure to the drug. Therefore, it is not clear that a 14-day study will be sufficient to support the safety of the drug. FDA also clarified that this combination product should be labeled for 7 days, not 10 days as Wyeth had indicated, since it includes phenylephrine which is an ingredient supported in the OTC monograph for up to 7 days of use.

FDA stated that the approval of this NDA will be dependent on the qualification of the (b) (4) degradant. Wyeth asked FDA if draft study reports should be submitted earlier than the planned April 21, 2008 amendment, but FDA stated that it prefers the study report to be complete and final so that a complete assessment and evaluation can be conducted. Wyeth should submit the full package together so that a decision can be made regarding the toxicology qualification program and the stability data.

Post Meeting Addendum:

On February 28, 2008 Wyeth sent FDA the information concerning precedence for the 14 day toxicology study for a similar product. This is NDA 21-374 (Advil Cold & Sinus Liquid-Gels). The link to the redacted SBA pharmacology section (pg. 8): http://www.fda.gov/cder/foi/nda/2002/21-374_Ibuprofen_pharmr.pdf.

Robin Anderson, Project Manager

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

/s/

Andrea Segal
3/15/2008 12:54:35 PM

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

ORIGINAL

Vonnie D. Lewis
Manager, Global Regulatory Affairs,
CMC
Tel: 804.257.2430
Fax: 973.660.7187
E-mail: lewisv@wyeth.com

ORIGINAL AMENDMENT

CDER/CDR

March 05, 2008

NDA 22-113

N-000-BC

MAR 05 2008

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(b) (4)
(ibuprofen 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate 4 mg)

**Minor Amendment to NDA 22-113 submitted in eCTD Format: Information Request
Letter dated February 22, 2008
Chemistry, Manufacturing and Controls**

Andrea Leonard-Segal, M.D., Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Leonard-Segal,

Reference is made to New Drug Application 22-113 (b) (4)
(ibuprofen 200 mg, phenylephrine HCl 10 mg, chlorpheniramine maleate 4mg), submitted to
the Agency on September 25, 2007 and a subsequent amendment dated December 18, 2007.
Further reference is made to FDA Information Request Letter dated February 22, 2008 that
is included in section 1.11.1. Wyeth hereby submits an amendment to NDA 22-113 to
provide responses to the FDA information request.

Wyeth is also including a table that summarizes Wyeth's responses to the FDA information
request letter dated February 22, 2008.

Electronic Submission Information

This amendment to NDA 22-113 is arranged according to the Common Technical Document
format and includes only sections that are impacted by the responses to the FDA information
request. Additionally, this amendment is provided entirely in electronic Common Technical
Document (eCTD) format prepared according to the FDA *Draft Guidance for Industry:
Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product*

Wyeth Consumer Healthcare
CMC Amendment:
March 05, 2008

Ibuprofen 200 mg, Phenylephrine 10 mg, Chlorpheniramine 4mg (b) (4)

NDA 22-113

2 of 4

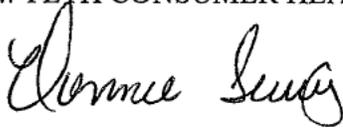
Wyeth

Applications and Related Submissions, issued in October, 2005. The archival copy is a fully electronic dossier with the exception of administrative documents requiring an original signature, which are provided in paper.

If you have any questions regarding this submission, please do not hesitate to contact me at (804) 257-2430 or Henry Weidmuller at (973) 660-5068.

Sincerely,

WYETH CONSUMER HEALTHCARE



Vonnice Lewis

Manager, Global Regulatory Affairs, CMC

cc: Robin Anderson
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Office of New Drugs
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-113

Wyeth Consumer Healthcare
Attention: Neil Napolitano
Assistant Director, Global Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Mr. Napolitano:

Please refer to your new drug application (NDA) dated September 25, 2007, received September 25, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (ibuprofen 200 mg/ phenylephrine HCl 10 mg/ chlorpheniramine maleate 4 mg) tablets.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Revise the drug product specification table for Chlorpheniramine Maleate (Table 1.0-1 on Page 1, Section 3.2.S.4) to clearly state that the identification test will be performed by Wyeth.
2. The HPLC retention time alone is not specific enough for the identity test. You must add a second identity test (such as UV spectrum by photodiode detector) for all three active ingredients to the drug product specification.
3. Provide stability data for (b) (4) to support the proposed limit of NMT (b) (4). Clarify the footnote to Table 1.0-2 on Page 4, Section 3.2.P.5.1 concerning Ibuprofen-Phenylephrine Amide.
4. Submit a Certificate of Analysis for the ibuprofen reference standard.
5. Submit a Certificate of Analysis for (b) (4) used in the manufacturing of (b) (4).
6. Your specification for (b) (4) (Hypromellose) is based on an outdated USP monograph and should be rectified.

If you have any questions, call Robin Anderson, Regulatory Project Manager, at (301) 796-0534.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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

/s/

Neel Patel
2/22/2008 01:59:32 PM
on behalf of Leah Christl

Wyeth

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Neil J. Napolitano
Assistant Director, Regulatory Affairs
Tel: 973.660.5725
Fax: 973.660.8071
E-mail: napolin@wyeth.com

31 January 2008

RECEIVED

JAN 31 2008

CDER CDR

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

N-000-EL

Re: New Drug Application 22-113: Labeling Amendment – Additional Warnings for Asthma, and Children under 12

Products: (b) (4), (chlorpheniramine maleate 4mg, ibuprofen 200mg/phenylephrine HCl 10mg) (b) (4)

Indications: Temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold

Sponsor: Wyeth Consumer Healthcare (“WCH”)

Dear Dr. Segal:

Reference is made to NDA 22-113, submitted 25 September 2007.

As part of Wyeth Consumer Healthcare’s (WCH) continuing efforts to ensure that Advil labeling reflects the currently available information regarding safety and efficacy of ibuprofen, we are proposing to amend all Advil labeling to include a Warning that recommends asking a doctor before use if you have asthma.

Advil labeling currently contains an Allergy Alert warning, which states that ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin and that symptoms may include asthma (wheezing), among others. The Allergy Alert warning, however, does not caution the use of ibuprofen in consumers with underlying asthma. WCH is proposing to update the labeling to address this population as severe asthmatics are at a greater risk for NSAID-induced asthma and as many asthmatics may be unaware that they are sensitive to

Wyeth Pharmaceuticals
Wyeth Consumer Healthcare
Fort Dodge Animal Health

NSAIDs. A summary of the available supporting information and literature references are provided in this submission.

A side-by-side comparison of the labeling sections affected by this change is as follows:



In addition, statements under the Warnings and Directions sections of Drug Facts have been changed to emphasize that this product should not be used in children under 12. We are including these statements to provide additional assurance to prevent misuse in the pediatric population and promote safe and responsible use of this product. A side-by-side comparison of the current and proposed Warnings and Directions sections of labeling, pertaining to children under 12 years of age, are as follows:



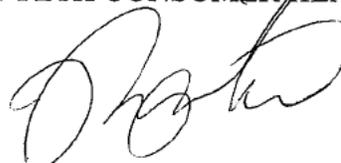
Accordingly, this electronic submission (e-CTD) contains the following updated sections in Module 1:

- 1.1.2 FDA 356h Form
- 1.14.1.1 Draft Labeling
 - AAS blister-back-RS1611
 - AAS carton-10s-UK250351
 - AAS carton-20s-UK250361
 - AAS label-ML39771
- 1.14.1.2 Annotated Labeling
- 1.14.1.3 Draft Labeling Text
- 1.14.1.5 Labeling History

Please note the megabyte size, presentation (e.g. in CD-ROM form) and virus scan information is appended to this letter.

If you have any questions or comments regarding this submission, please contact the undersigned at (973) 660-5725, or Lauren Quinn, at (973) 660-6167.

Sincerely,
WYETH CONSUMER HEALTHCARE



Neil J. Napolitano
Assistant Director
Global Regulatory Affairs

ORIGINAL

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Neil J. Napolitano
Assistant Director
Global Regulatory Affairs
973-660-5725
Fax 973-660-7187
napolin@wyeth.com

30 January 2008

RECEIVED

JAN 31 2008

CDER CDR

ORIGINAL AMENDMENT

N(BP)

N 100-BP

Wyeth

Joel Schiffenbauer, MD, Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: New Drug Application 22-113 – Response to FDA Information Request Letter (dated 16 January 2008; received 17 January 2008)

(chlorpheniramine maleate 4mg/ibuprofen 200mg/phenylephrine HCl 10mg) (b)(4)

Indications: Temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold.

Sponsor: Wyeth Consumer Healthcare (“WCH”)

Dear Dr. Schiffenbauer:

Reference is made to:

- NDA 22-113
- Your information request letter (e-signed 16 January 2008)
- Email from E. Abraham dated 24 January 2008.

In your letter you cited issues with a 14 day toxicology study qualifying the degradant, (b)(4) and requested a new study be performed, or justification why one is not needed. As discussed with Ms. Abraham:

- WCH intends to commercialize the formulation with propyl gallate (PG), in which (b)(4) degradant levels are below the ICH limit
- The formulation without PG (non-PG), for which the 14 day toxicology study was performed, will not be commercialized and was provided only to support the filing of the application.

In Ms. Abraham's email, the pharmacology/toxicology reviewer requested that WCH confirm the formulation we intend to market. Please consider this letter confirmation that we intend to commercialize the PG formulation (1232-0006), in which we do not anticipate levels of (b) (4) will exceed the ICH limit within the expiry period.

The reviewer also mentioned an (b) (4) degradant, which was not included in the original information request, and was not the subject of the 14 day toxicology study in question. Please note that unlike (b) (4), the addition of PG is not expected to affect the formation of the (b) (4) of ibuprofen (IBU) and phenylephrine (PE). Therefore the non-PG formulation (1232-0001) is expected to be predictive of (b) (4) levels in the PG formulation, and we anticipate that (b) (4) levels will exceed the ICH limit ((b) (4) relative to PE) within the expiry period for both formulations. Consequently, we request that you continue your review of the qualification program for the (b) (4) degradant.

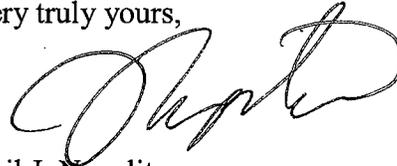
For your convenience, the following summarizes the areas of the original submission, in which information on the IBU-PE (b) (4) may be found:

- Specification in Section 3.2.P.5.5 (classified as a specified degradant).
- Drug Product release and stability specifications in Section 3.2.P.5.1 (NMT (b) (4) mole/mole relative to PE).
- Specification in QA Post Approval Stability Protocols in Section 3.2.P.8.2.
- 2-Week Oral Gavage Toxicity Study in Section 4.2.3.7.7 (report aq0711-final).

We trust that this response is sufficient to close out your information request letter. If you have any questions or comments regarding this submission, please contact the undersigned at (973) 660-5725, or Lauren Quinn, at (973) 660-6167.

Please note that this submission is being provided in electronic format (e-CTD). The megabyte size, presentation (e.g. in CD-ROM form) and virus scan information is appended to this letter.

Very truly yours,



Neil J. Napolitano
Assistant Director
Global Regulatory Affairs

cc: Elaine Abraham, R. Ph.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Office of New Drugs
Center for Drug Evaluation and Research

Wyeth

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Neil J. Napolitano
Assistant Director
Global Regulatory Affairs
973-660-5725
napolin@wyeth.com

ORIGINAL

25 January 2008

RECEIVED

JAN 25 2008

CDER CDR

ORIGINAL AMENDMENT

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

N-000-Su

N(Su)

Re: New Drug Application 22-113 – 4 month

(chlorpheniramine maleate 4mg/ibuprofen 200mg/phenylephrine HCl
10mg) (b) (4)

Indications: Temporary relief of symptoms associated with hay fever or
other upper respiratory allergies, and the common cold.

Sponsor: Wyeth Consumer Healthcare ("WCH")

Dear Dr. Leonard-Segal:

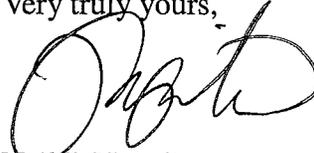
Reference is made to NDA 22-113 for the subject product.

Attached are the 4 month safety update (5.3.6.3), 4 month literature review
(5.3.6.4) and literature references (5.4). A 356h form (1.1.2) has also been
provided.

Please note that this submission is being provided in electronic format (e-CTD).
The megabyte size, presentation (e.g. in CD-ROM form) and virus scan
information is appended to this letter.

If you have any questions or comments regarding this submission, please contact
the undersigned at (973) 660-5725, or Lauren Quinn, at (973) 660-6167.

Very truly yours,



Neil J. Napolitano
Assistant Director
Global Regulatory Affairs

Attachment: Technical Information

cc: Elaine Abraham, R. Ph.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Office of New Drugs
Center for Drug Evaluation and Research

Abraham, Elaine G

From: Abraham, Elaine G
Sent: Thursday, January 24, 2008 12:44 PM
To: 'Neil Napolitano'
Cc: 'Darcy Gilson'; 'Lauren Quinn'
Subject: NDA (b) (4) 22-113

Neil-

This is in response to your voice message of January 17, 2008 which was responding to our letters dated January 16, 2008 regarding a pharmacology/toxicology information request for (b) (4) and 22-113 (b) (4)

We have the following comment and request a prompt response in order to continue our review of your NDA:

If your final to-be-marketed product will not contain degradants that exceed the allowed limit after the addition of the propyl gallate (PG) ingredient, we find it unnecessary to continue reviewing the qualification program that was submitted (b) (4), and for the 2 degradants, (b) (4) under NDA 22-113. In the event that you will be marketing the formulation without the PG ingredient, you will need to repeat the general toxicity study (for a minimum duration of 14 days) in the qualification program for degradants that exceed the allowable limits using solutions with acceptable stability profiles. Please confirm the formulation of your to-be-marketed product.

We request that you verify that you have received this e-mail. We also request that you provide your response to this information request by e-mail or fax in addition to sending a hard copy to your NDAs.

*Elaine Abraham, R.Ph.
CAPT, USPHS
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
White Oak CDER Bldg. # 22, Room 5410
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: (301) 796-0843
Fax: (301) 796-9899
e-mail: elaine.abraham@fda.hhs.gov*

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/s/

Robin E Anderson
1/29/2008 01:38:16 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-113

Wyeth Consumer Healthcare
Attention: Neil Napolitano
Assistant Director, Global Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Mr. Napolitano:

Please refer to your new drug application (NDA) dated September 25, 2007, received September 25, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (ibuprofen 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate 4 mg) tablets.

We are reviewing the Pharmacology/Toxicology section of your submission and have the following comments and information request. We request a prompt written response in order to continue our evaluation of your NDA.

We note that in one of your qualification studies (the 14 day oral gavage for phenylephrine (PE) (b) (4) in rats), the stability profile for the degradants fell below the target levels for your specification when tested on day 8 after 8 consecutive dosing days with the same solution for the 95 mg/kg/day for PE/5 mg/kg/day (b) (4) and the 98 mg/kg/day PE/2 mg/kg/day (b) (4). The No Adverse Effects Levels (NOAEL) established for the (b) (4) degradants based on the absence of toxicological findings cannot be interpreted due to the lower-than-target levels of the degradants tested in this study. To address this issue you will either need to perform a 14-day general toxicity study to qualify the amount of degradant (b) (4) in the formulation, or provide justification as to why a study is not needed.

If you have any questions, call Robin Anderson, Regulatory Project Manager, at (301) 796-0534.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Joel Schiffenbauer
1/16/2008 01:52:22 PM

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Vonnie D. Lewis
Manager, Global Regulatory Affairs,
CMC
Tel: 804.257.2430
Fax: 973.660.8823
E-mail: lewisv@wyeth.com



Wyeth

December 18, 2007

ORIGINAL

DEC 19 2007

CDER CDR

NDA 22-113

(b) (4)

(b) (4)

(ibuprofen 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate 4 mg)

Minor Amendment to NDA 22-113 submitted in eCTD Format:
Chemistry, Manufacturing and Controls

ORIG AMENDMENT

N 000-02

Andrea Leonard-Segal, M.D., Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Control Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Leonard-Segal,

Reference is made to New Drug Application 22-113 for (b) (4) (b) (4)
(ibuprofen 200 mg, phenylephrine HCl 10 mg, chlorpheniramine maleate 4mg), submitted to
the Agency on September 25, 2007. Further reference is made to the Pre-NDA Meeting
Briefing Document dated February 23, 2007 wherein Wyeth agreed to provide FDA with
updated stability data for the (b) (4) formulations during NDA
review. Wyeth committed to submitting the original application with 3 months of
accelerated stability data for the optimized formula and 12 months real time stability data for
the original formulation. Wyeth also committed to providing 6 months of accelerated
stability data for the optimized formulation during the review of the NDA. Wyeth hereby
submits an amendment to NDA 22-113 to provide updated stability data for the optimized
formulation.

During the evaluation of the 6 month accelerated data for the optimized formulation, Wyeth
observed an additional degradant of phenylephrine and maleic acid, known as (b) (4)
(b) (4). Wyeth has validated an analytical method for testing this degradant in (b) (4)
(b) (4). In addition, Wyeth is proposing to provide a commitment to establish a
specification for this degradant in the 12 month stability report based on data generated



through 12 months. This amendment includes the additional documentation to support the testing (b) (4)

Additional reference is made to the FDA Day 74 Filing Communication, received December 04, 2007, where the Agency identified potential review issues and requested additional data. This amendment also includes the method validation protocols for the analytical methods along with experimental details for the method validations in response to the FDA filing communication.

In the original application, Wyeth stated that the facilities that are specified for the manufacturing, packaging and control operations for the proposed product would be ready for inspection January 24, 2008. Based on the additional degradant, (b) (4), observed at 6 months accelerated conditions, Wyeth is revising the PAI readiness date stated in the original application from January 24, 2008 to April 21, 2008.

The facilities that are specified for the manufacturing, packaging and control operations for the (b) (4) will be ready for inspection April 21, 2008.

Electronic Submission Information

This amendment to NDA 22-113 is arranged according to the Common Technical Document format and includes only sections that are impacted by the updated stability data, analytical methods and validation packages and responses to the FDA filing communication. Additionally, this amendment is provided entirely in electronic Common Technical Document (eCTD) format prepared according to the FDA *Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions*, issued in October, 2005. The archival copy is a fully electronic dossier with the exception of administrative documents requiring an original signature, which are provided in paper.



Refer to Attachment 1 for a detailed list of changes in this amendment and the impacted e-CTD sections. The table in attachment 1 also identifies whether the impacted sections will be replaced or appended with additional information in this amendment. The CTD Sections are organized as follows:

Module 1

1.1.2

1.1.2

1.2

1.3.2

Module 2

2.3.1

Module 3

3.2.P.5.2

3.2.P.5.3

3.2.P.5.4

3.2.P.5.5

3.2.P.8.1

3.2.P.8.2

3.2.P.8.3

Module 3

3.2.R.2.P

Regional Administrative Information

Form FDA 356h

Form FDA 356h - Establishment
Information

Cover Letter

Field Copy Certification

Quality Information

Quality Overall Summary

Quality Information

Analytical Procedures

Validation of Analytical Procedures

Batch Analysis

Characterization of Impurities

Stability Summary and Conclusion

Post-Approval Stability Protocol and
Stability

Stability Data

Quality Information

Method Validation Package

If you have any questions regarding this submission, please do not hesitate to contact me at (804) 257-2430 or Henry Weidmuller at (973) 660-5068.

Wyeth Consumer Healthcare
Minor CMC Amendment
December 18, 2007

NDA 22-113
(b) (4)
4 of 4

yeth

Sincerely,
WYETH CONSUMER HEALTHCARE



Vonnie Lewis
Manager, Global Regulatory Affairs, CMC

cc: Robin Anderson
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Office of New Drugs
Center for Drug Evaluation and Research

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM: Robin Anderson, Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products

DATE December 5, 2007	IND NO.	NDA NO. 22-113	TYPE OF DOCUMENT Original NDA (505(b)(2))	DATE OF DOCUMENT September 25, 2007
NAME OF DRUG [REDACTED] (b) (4)		PRIORITY CONSIDERATION Medium	CLASSIFICATION OF DRUG cough/cold	DESIRED COMPLETION DATE April 25, 2008

NAME OF FIRM: **Wyeth Consumer Healthcare**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Wyeth has submitted a 505(b)(2) application proposing a proprietary name of [REDACTED] (b) (4). The company already has approved NDA 21-441 with the trade name "Advil Allergy Sinus" (approved 12/20/02). The proposed product incorporates phenylephrine HCL (10 mg) as the nasal decongestant ingredient in order to provide an alternative to the pseudoephedrine product since pseudoephedrine has been moved behind the counter. This NDA is also our Division's CDTL pilot NDA, so review timelines have been planned in compliance with that initiative.

PDUFA DATE: July 25, 2008

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA 22-113

HFD-560/Division File

HFD-560/RPM

HFD-560/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER

METHOD OF DELIVERY (Check one)

Robin Anderson (301) 796-0534	<input checked="" type="checkbox"/> DFS ONLY	<input type="checkbox"/> MAIL	<input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER		

5/28/05

10 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

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/s/

Robin E Anderson
12/6/2007 01:57:13 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-113

Wyeth Consumer Healthcare
Attention: Neil Napolitano
Assistant Director, Global Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Mr. Napolitano:

Please refer to your new drug application (NDA) dated September 25, 2007, received September 25, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (ibuprofen 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate 4 mg) tablets.

We also refer to your submission dated November 19, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 25, 2008.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 10, 2008.

During our filing review of your application, we identified the following potential review issues:

1. Inadequate drug product stability data for the to-be-marketed formulation.
2. Absence of method validation protocols for Methods A7277 and A7300.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Updated drug product stability data for the to-be-marketed formulation.
2. Method validation protocols for Methods A7277 and A7300. The protocols should include experimental details for the forced degradation study and the method used to assess peak purity.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients below twelve years of age.

If you have any questions, call Robin Anderson, Regulatory Project Manager, at (301) 796-0534.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Andrea Segal
12/4/2007 11:45:37 AM

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Neil J. Napolitano
Assistant Director
Global Regulatory Affairs
973-660-5725
napolin@wyeth.com

ORIGINAL

Wyeth

19 November 2007

RECEIVED

NOV 28 2007

Robin Anderson, R.N., M.B.A., Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

CDER CDR

ORIGINAL AMENDMENT

(NILE)

N-000-1313

Re: New Drug Application 22-113 – 60 Day Review Filing Issue Response

Products: (b) (4) (chlorpheniramine maleate 4mg/ibuprofen 200mg/phenylephrine HCl 10mg) (b) (4)

Indications: Temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold.

Sponsor: Wyeth Consumer Healthcare ("WCH")

Dear Ms. Anderson:

Reference is made to the subject application and your telephone inquiry on 16 Nov 2007, which was made directly after the agency's 60-day filing review meeting.

The table below summarizes our response to the filing issue identified by the biopharmaceutics reviewer, including which sections of the eCTD have been appended.

Filing Issue	WCH Response	eCTD
Adequate data to assess the potential drug-drug interactions for the ibuprofen (IBU)/phenylephrine/chlorpheniramine (CHLOR) combination.	As agreed at the May 10, 2005 pre-IND meeting, potential interactions are supported as follows: The combination of chlorpheniramine and phenylephrine are provided for in the OTC monograph on Cold, Cough, Allergy, Bronchodilator, And Antiasthmatic Drug Products For Over-The-Counter Human Use (21 CFR 341). The drug interaction between IBU and PE has been addressed in clinical study AQ-05-03. (b) (4) (b) (4)	1.2 1.6.3.4 2.2 2.7.1

CONFIDENTIAL

1

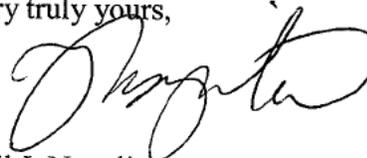
Wyeth Pharmaceuticals
Wyeth Consumer Healthcare
Fort Dodge Animal Health

As indicated in the above table, this letter provides intent to cross reference clinical study AQ-05-03, submitted in (b) (4) by WCH, and permission for FDA to do so. A 356h form has been provided under 1.1.2, and the phone conversation contact report has been added under 1.6.3.4.

Please note that this submission is being provided in electronic format (e-CTD). The megabyte size, presentation (e.g. in CD-ROM form) and virus scan information is appended to this letter.

If you have any questions or comments regarding this submission, please contact the undersigned at (973) 660-5725, or Lauren Quinn, at (973) 660-6167.

Very truly yours,



Neil J. Napolitano
Assistant Director
Global Regulatory Affairs

Attachment: Technical Information

cc: Dr. Partha Roy, Biopharm Reviewer, FDA
Dr. Wei Qiu, Team Leader, FDA



NDA 22-113

NDA ACKNOWLEDGMENT

Wyeth Consumer Healthcare
Attention: Neil Napolitano, Assistant Director
Global Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Mr. Napolitano:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: [REDACTED] ^{(b) (4)} (ibuprofen 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate 4 mg) tablets

Date of Application: September 25, 2007

Date of Receipt: September 25, 2007

Our Reference Number: NDA 22-113

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 24, 2007 in accordance with 21 CFR 314.101(a).

The NDA number provided above shown above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however,

it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Robin Anderson, Regulatory Project Manager, at (301) 796-0534.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
11/9/2007 12:28:44 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

RECEIVED

APPLICANT INFORMATION

NAME OF APPLICANT Wyeth Consumer Healthcare	DATE OF SUBMISSION 09/25/2007	SEP 25 2007
TELEPHONE NO. (Include Area Code) (973) 660-5725	FACSIMILE (FAX) Number (Include Area Code) (973) 660-7187	CDER ODR
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 5 Giralda Farms Madison, NJ 07940	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number if applicable) RECEIVED SEP 27 2007	

PRODUCT DESCRIPTION

CDER/WHITE OAK/DRI

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 22-113		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Ibuprofen, Phenylephrine HCl, Chlorpheniramine maleate	PROPRIETARY NAME (trade name) IF ANY (b) (4)	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Caplet (oval shaped tablet)	STRENGTHS: Ibuprofen 200 mg, Phenylephrine HCl 10 mg, Chlorpheniramine maleate 4 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
Pain Reliever / Fever Reducer, Nasal decongestant, Antihistamine

APPLICATION DESCRIPTION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b)(1)	<input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION		
Name of Drug	Holder of Approved Application	
TYPE OF SUBMISSION (check one)	<input checked="" type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO PENDING APPLICATION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Use of Phenylephrine HCl 10 mg as Nasal decongestant and Chlorpheniramine maleate 4 mg as Antihistamine to reestablish an OTC option for consumers.

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Manufacturing, packaging and control operations facilities specified in the attached Establishment Registration will be ready for inspection 24Jan2008.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMFs (b) (4) are referenced.

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input checked="" type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input checked="" type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input checked="" type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input checked="" type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input checked="" type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input checked="" type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input checked="" type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input checked="" type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

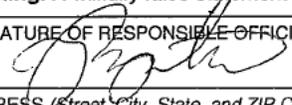
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Neil Napolitano, Assist. Dir. Global Reg. Affairs	DATE: 09/25/2007
ADDRESS (Street, City, State, and ZIP Code) 5 Giralda Farms, Madison, NJ 07940		Telephone Number (973) 660-5725

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:



Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Neil J. Napolitano
Assistant Director
Global Regulatory Affairs
973-660-5725
napolin@wyeth.com

September 25, 2007

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
ATTENTION: Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED

SEP 25 2007

RECEIVED

CDER CDR

SEP 27 2007

ORIGINAL

N-000

Re: New Drug Application 22-113

Product: (b) (4) (ibuprofen 200 mg/phenylephrine HCl
10 mg/chlorpheniramine maleate 4 mg) (b) (4)

Indications: Temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor body aches and pains, fever.

Sponsor: Wyeth Consumer Healthcare ("WCH")

Dear Dr. Leonard-Segal:

The subject application is being submitted in support of a new drug product under (b) (4). The product incorporates phenylephrine HCl (10 mg) as the nasal decongestant ingredient, in order to provide an alternative to the pseudoephedrine HCl (30 mg) product currently marketed under the trade name Advil Allergy Sinus (NDA 21-441). Although the pseudoephedrine product was approved for over-the-counter ("OTC") use, it has recently been moved behind the counter, in compliance with legislation restricting the sale of all pseudoephedrine-containing drug products (The Combat Methamphetamine Epidemic Act of 2005). The new formulation is intended to reestablish an OTC option for consumers. It is clearly differentiated from its pseudoephedrine counterpart (b) (4) in the trade name, and by unique packaging and a new caplet appearance.

The clinical development plan, protocol, and statistical analysis design was reviewed by FDA at a pre-study meeting May 10, 2005 (please reference section

1.6.3 of this submission for a detailed account of FDA interaction). The plan consisted of one bioavailability study (Clinical Study AD-05-05) which compared the combination caplet with ibuprofen 200 mg + phenylephrine HCl 10 mg + chlorpheniramine maleate 4 mg (fasted and fed) to Motrin® IB tablet (ibuprofen 200 mg/tablet), Sudafed® PE caplet (phenylephrine HCl 10 mg/caplet), and Chlor-Trimetron® Allergy tablet (chlorpheniramine maleate 4 mg/tablet) single ingredient products administered concomitantly in the fasted state. Essentially, the study showed that:

- The rate (C_{max}) and extent (AUC) of absorption of ibuprofen, phenylephrine HCl, and chlorpheniramine maleate are equivalent when the ibuprofen + phenylephrine HCl + chlorpheniramine maleate combination caplet is administered under fasting and fed conditions;
- Under fasted conditions, the ibuprofen + phenylephrine HCl + chlorpheniramine maleate caplet has an equivalent rate (C_{max}) and extent (AUC) of absorption of ibuprofen, phenylephrine HCl, and chlorpheniramine maleate relative to the single entity marketed products containing ibuprofen (Motrin IB), PE (Sudafed PE), and chlorpheniramine maleate (Chlor-Trimetron® Allergy).

Subsequent to executing the aforementioned clinical trial, WCH discovered through routine formula optimization activities that the addition of (b) (4) propyl gallate or "PG") (b) (4) The degradant, (b) (4) was not considered a toxicological concern.

On 19 March 2007, WCH and FDA held a pre-NDA teleconference to discuss bridging in vivo bioequivalence data and stability data for the original formula with the optimized formulation. According to 21 CFR 320.22(d)(4) and concurrence by FDA, WCH is also providing in-vitro dissolution data for the optimized product in support of a waiver of in vivo bioequivalence. A table summarizing results is located in section 2.7.1.4, and the full report is referenced in Module 5 under 5.3.1.3. WCH is also providing stability data for the non-PG formula to compare to the PG formulation that will be commercialized.

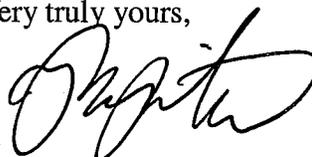
Safety data from this study (AD-05-05: A Three-Way Crossover, Food Effect/Formulation Effect, Bioavailability Study of a Caplet Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 10 mg, and Chlorpheniramine Maleate 4

mg) are described in 2.7.4. Overall, there were no serious AEs reported during the study, and there were no significant safety findings related to the study product. Based on these new data from the bioavailability study, a review of the literature, and a thorough review of adverse event databases and post-marketing surveillance no signals for concern were observed with the use of ibuprofen, phenylephrine HCl, or chlorpheniramine maleate. WCH believes the availability of the combination caplet will provide the US consumer with a safe, beneficial, OTC treatment option for the symptoms associated with hay fever or other upper respiratory allergies, and the common cold, without compromising the favorable benefit to risk profile of OTC ibuprofen.

Please note that this submission is being provided in electronic format (e-CTD), and contains: Administrative Information (Module 1), Summaries (Module 2), Quality (CMC; Module 3), Nonclinical (Module 4) and Clinical Study Reports (Module 5). The megabyte size, presentation (e.g. in CD-ROM form) and virus scan information is appended to this letter.

If you have any questions or comments regarding this submission, please contact the undersigned at (973) 660-5725, or Lauren Quinn, at (973) 660-6167.

Very truly yours,



Neil J. Napolitano
Assistant Director
Global Regulatory Affairs

Attachment: Technical Information

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	(b) (6)	
	(b) (4)	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Emanuel S. Troullos, D.M.D., M.P.H.	TITLE Director, Clinical Research
FIRM / ORGANIZATION Wyeth Consumer Healthcare	
SIGNATURE 	DATE 7/2/07

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
FOOD AND DRUG ADMINISTRATIONPRESCRIPTION DRUG USER FEE
COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

WYETH CONSUMER HEALTHCARE
Neil Napolitano
5 Giralda Farms
Madison NJ 07940
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-113

2. TELEPHONE NUMBER

973-660-5725

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

 YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

 THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

(b) (4) ibuprofen 200 mg, phenylephrine HCl 10 mg, chlorpheniramine maleate 4 mg)

6. USER FEE I.D. NUMBER

PD3007494

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

OMB Statement:

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Asst Director
Regulatory Affairs

DATE

02 Jul 2007

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$448,100.00

Form FDA 3397 (03/07)

Close [Print Cover sheet](#)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

(b) (4)

NDA 22-113

Wyeth Consumer Healthcare
Attention: Neil Napolitano
Assistant Director, Global/US Regulatory Affairs
5 Giralda Farms
Madison, NJ 07940

Dear Mr. Napolitano:

Please refer to your New Drug Application (NDA) files for (b) (4)

(b) (4) (ibuprofen 200mg/phenylephrine 10mg/chlorpheniramine 4mg)
[NDA 22-113].

We also refer to the meeting between representatives of your firm and the FDA on March 19, 2007. The purpose of the meeting was to discuss chemistry and clinical pharmacology issues related to the submission of your applications.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Elaine Abraham, Regulatory Project Manager, at (301) 796-0843.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: March 19, 2007
12:30 - 1:30 p.m.
Meeting Location: Teleconference
Application Number: NDA (b) (4) 22-113
Product Name: (b) (4)
Received Briefing Package: February 23, 2007
Sponsor Name: Wyeth Consumer Healthcare
Meeting Requestor: Neil Napolitano
Assistant Director, Global/US Regulatory Affairs
Meeting Chair: Andrea Leonard-Segal, M.D.
Meeting Recorder: Elaine Abraham, R.Ph.

Meeting (Teleconference) Attendees:

FDA Attendees

Division of Nonprescription Clinical Evaluation

Elaine Abraham, R.Ph.	Regulatory Project Manager
Leah Christl, Ph.D.	Chief, Project Management Staff
Wafa Harrouk, Ph.D.	Pharmacologist
Andrea Leonard-Segal, M.D.	Director
Lolita Lopez, M.D.	Medical Officer
Bindi Nikhar, M.D.	Medical Team Leader
Joel Schiffenbauer, M.D.	Deputy Director
Daiva Shetty, M.D.	Medical Team Leader

Office of New Drug Quality Assessment

Gene Holbert, Ph.D.	Chemistry Reviewer
---------------------	--------------------

Office of Clinical Pharmacology

Sayed Al Habet, Ph.D.
Emmanuel Fadiran, Ph.D.

Clinical Pharmacology Reviewer
Clinical Pharmacology Team Leader

Sponsor Attendees:Wyeth Consumer Healthcare

Roger Berlin, M.D.
Paul Bryers, Ph.D.
Lauren Quinn, J.D.
Neil Napolitano

President, Global Scientific Affairs
Vice President, Global Regulatory Affairs
Director, Global/US Regulatory Affairs
Assistant Director, Global/US Regulatory
Affairs

Henry Weidmuller, BS, R.Ph.
Vonnice Lewis, B.S.
Frank Nowaczyk, Ph.D.

Sr. Director, Global/US CMC
Manager, Global/US CMC
Associate Director, Research &
Development

1.0 BACKGROUND

Wyeth Consumer Healthcare (WCH) submitted a meeting request to FDA on January 29, 2007, to discuss chemistry and clinical pharmacology issues related to the submission of their NDAs. The NDAs propose new products incorporating phenylephrine as the nasal decongestant ingredient and will be offered as alternatives to the currently approved products (NDA 19-771, Advil Cold & Sinus; NDA 21-441 Advil Allergy Sinus, Advil Multi-Symptom Cold). (b) (4)

(b) (4) The proposed product under NDA 22-113 is (b) (4) (ibuprofen 200 mg/phenylephrine 10 mg/chlorpheniramine 4 mg).

2.0 DISCUSSION

On March 16, 2007, FDA sent preliminary responses to WCH to address the questions in their February 23, 2007 meeting package. The questions from WCH appear below followed by the preliminary FDA responses in italics. Wyeth submitted written responses to FDA's preliminary responses prior to the meeting and these follow the preliminary FDA responses. A summary of the discussion that occurred during the meeting follows each question.

2.1 Question 1

Does the Agency agree that the proposed stability data package will be acceptable for filing the NDA, i.e., 3 months accelerated data on PG formulations plus 6 months accelerated data on non-PG formulations?

FDA Preliminary Response:

This proposal is acceptable; however you have proposed updating the stability data two months prior to the goal date. We are concerned that there will not be sufficient time to review the data before final approval. We cannot guarantee review of information submitted so late in the review cycle.

WCH Written Response:

WCH accepts the Agency's comment, and proposes the following: WCH will be able to provide 9 month data on the PG batches in November 2007, five months prior to the proposed action date. Would the agency consider a stability package containing 9 months on the commercial PG formulations with 12 month data on the non-PG batches to be supportive of 18 month expiry dating at approval?

Discussion:

FDA accepted WCH's proposal for the submission of stability data, but reminded WCH that the decision of an 18-month expiry is still a review issue. Wyeth stated that non-PG data should be predictive of PG stability and asked if 18 months of non-PG data can be submitted to support the 18-month expiry. FDA agreed that this data can be submitted and would be considered in FDA's review.

WCH asked if 12 months of PG data submitted 2 months prior to the goal date would be acceptable, and if not, how early stability data should be submitted. FDA responded that it would prefer receiving the data at least 3 months prior to the goal date.

2.2 Question 2

Does the Agency agree that the proposed stability data package provided during Agency review, will be acceptable to support 18-month expiry dating on the PG formulations, i.e., 6 months accelerated data on the PG formulations and 12 real time data for all formulations?

FDA Preliminary Response:

Yes, if no significant changes are noted at the accelerated condition and provided that FDA receives and reviews the 12 month stability update.

WCH Written Response:**WCH accepts the Agency's comment.****Discussion:**

There was no discussion on this issue.

2.3 Question 3**Does the Agency agree that a request for a waiver of bioequivalence studies demonstrating equivalence between the formulas will be acceptable for NDA filing, assuming:**

- a) Dissolution data are adequate to satisfy the requirement for in vitro testing under this waiver request, and**
- b) Results of the in vivo bioavailability/bioequivalence studies on the non-PG formulations are found to be acceptable?**

FDA Preliminary Response:

- *This is acceptable provided that the in vitro dissolution profiles using multiple dissolution media are identical between PG and Non-PG products. In addition, the f2 test should provide evidence of sameness (≥ 50). You are advised to use SUPAC-IR guidance (SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation - <http://www.fda.gov/cder/guidance/cmc5.pdf>) for selection of multiple dissolution media (Case C) for the in vitro dissolution profile comparison between PG and non-PG formulations.*
- *The data from the bioavailability and bioequivalence for the non-PG product appear to be acceptable. However, adequacy of the results remains a review issue at this time.*
- *We noted that in study # AQ-05-03 you addressed the PK interaction for phenylephrine only for (b) (4) but not for ibuprofen. However, you are planning to use the historical data for ibuprofen. The historical data for ibuprofen (Motrin IB) will be a review issue.*

WCH Written Response:

WCH accepts the first two bulleted items in the Agency's response, but seeks clarification on the third.

The use of historical data for ibuprofen was confirmed at a pre-IND meeting in May 2005 (minutes attached). While we understand that the evaluation of the data with respect to bioequivalence will be a review issue, please confirm that the use of historical ibuprofen data as the comparator in these studies is of itself not a review issue.

Discussion:

WCH asked FDA to elaborate on bullet 3. FDA stated that the approach that WCH proposes is acceptable, but that the data submitted will still require review.

2.4 Question 4

Does the Agency concur that the agreements reached on the three previous questions apply equally to both applications: (b) (4) NDA 22-113 (see Attachment II for Data for NDA 22-113)?

FDA Preliminary Response:

- Yes, FDA's responses for Questions 1 and 2 related to chemistry apply to both NDAs.
- From the clinical pharmacology perspective, the response to question 3 applies to both NDAs. However, you should note that the comment on the dissolution profile comparison between the PG and non-PG formulations applies to NDA 22-113.
- It is not clear from the summary information in the submission if the PK interaction between phenylephrine and ibuprofen/chlorpheniramine has been addressed for NDA 22-113. Therefore, you need to provide this information in your NDA submission.

WCH Written Response:

WCH accepts the two bulleted items in the Agency's response, but seeks clarification on the third.

The clinical program for the proposed drug product with chlorpheniramine, ibuprofen, and phenylephrine was executed as agreed with FDA at a pre-NDA

meeting conducted on May 10, 2005. At that time it was agreed that the potential drug interactions between ibuprofen and chlorpheniramine would be addressed through cross-reference to a PK study submitted in NDA 21-441 (AD-99-01) which demonstrated that there are no drug interactions between ibuprofen and chlorpheniramine. Other possible drug interactions were also discussed. FDA noted that the monograph allows for the combination of chlorpheniramine and phenylephrine. FDA also noted that the interaction between ibuprofen and phenylephrine could be addressed with the PK study from the double combination product, AQ-05-03 (b) (4)

Please confirm that the Agency is still in agreement with this approach.

Discussion:

WCH asked FDA to elaborate on bullet 3. FDA stated that the approach that WCH proposes is acceptable, but that the data submitted will still require review.

2.5 Additional Comments

FDA Preliminary Comment:

1. *Final study reports for all genotoxicity assays conducted as discussed in your toxicology summary (Attachment 1) will need to be submitted for the Division's review and evaluation at the time of the NDA submission.*

WCH Written Response:

WCH accepts the Agency's comments and will provide the study reports in the application.

Discussion:

There was no discussion on this issue.

FDA Preliminary Comment:

2. *The currently approved Advil Allergy Sinus/Advil Multi-Symptom tablets contain ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2mg. Your proposed reformulated product contains 4 mg of chlorpheniramine. If you reformulate with chlorpheniramine 4 mg, you cannot rely on the clinical data that supported approval of Advil Allergy Sinus/Advil Multi-Symptom (NDA 21-441). In addition, your proposed dosing directions and "Uses" section for the (b) (4) (b) (4) are different from that of Advil Cold & Sinus (NDA 21-374).*

Depending on the ultimate labeling of your new products, you will need to justify all deviations from those approved under NDA 21-441 and NDA 21-374.

WCH Written Response:

WCH seeks clarification on two points:

- **The formulation for the (b) (4) (IBU 200mg/PE 10mg/CHLOR 4mg) was agreed upon with the Agency in the May 2005 pre-IND meeting. The regulatory pathway proposed by WCH was to file the application as a 505(b)(2), referring to the cough/cold monograph for the safety and efficacy data on chlorpheniramine and phenylephrine and cross-referring to WCH NDAs for the safety and efficacy of ibuprofen.**

The rationale for the 4mg chlorpheniramine provided by the Agency was that when a company cross-references to the monograph for the safety and efficacy of an ingredient, the monograph dosages must be used. Therefore, regardless of the NDA approved dosing for the (b) (4) product, WCH would be required to use 4mg chlorpheniramine in the formulation for the new product

Given the prior discussion between WCH and the Agency, please confirm that the Agency is still in agreement with the original proposal.

- **Please confirm the specific ‘differences’ that will need justification in the NDA so that we may be sure to capture them in our application.**

On our review, we find the only differences to be in the Directions section, to reflect the different dosing instructions due to the change in formulation:

(b) (4)

Discussion:

FDA noted that WCH’s NDA (Advil Allergy Sinus/Advil Multi-Symptom) data showed that the lower dose of chlorpheniramine 2 mg was as effective as 4 mg. The use of a 2 mg dose of chlorpheniramine also had a lower incidence of adverse events compared to the 4 mg dose. WCH agreed that 2 mg of chlorpheniramine is less sedating than 4 mg but noted that 4 mg is generally recognized as a safe and effective OTC antihistamine. FDA agreed with this statement.

FDA explained that the labeling statement (b) (4) does not follow the monograph dosing for phenylephrine. FDA stated that WCH should follow the

phenylephrine monograph dosing interval of “every 4 hours”. Otherwise, WCH should justify the dosing interval (b) (4). This comment applies to the two ingredient and three ingredient combination products. WCH explained that (b) (4) is taken from the current approved product with pseudoephedrine.

FDA stated that the labeling for the proposed products should be consistent with the monograph dosing for each active ingredient. FDA further explained that the labeling of the WCH products cannot exceed the maximum accepted OTC daily dose for each active ingredient (1200 mg for ibuprofen, 60 mg for phenylephrine, and 24 mg for chlorpheniramine).

2.6 Pediatric Research Equity Act

Regarding PREA, WCH noted that they would be requesting a waiver for children under the age of 12 years because there are other alternative therapies and the dosage form (tablet) of the PE product and dosage amount is not appropriate for children under 12.

FDA stated that WCH should submit their waiver request and justification with the submission of their NDAs and that FDA would review the material.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Neither WCH nor FDA identified any issues that were not addressed during the meeting that would require further discussion.

4.0 ACTION ITEMS

There were no action items.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts at this meeting.

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

/s/

Andrea Segal

4/12/2007 11:24:20 AM

RECORD OF TELECONFERENCE

Date: March 28, 2006
Project Manager: Elaine Abraham
Subject: Discuss safety reporting issues
Sponsor: Wyeth Consumer Healthcare
Product Name: [REDACTED] (b) (4)
Phone No: (973) 660-6167

FDA participants: Andrea Leonard-Segal, M.D., Director, DNCE
Daiva Shetty, M.D., Team Leader
Linda Hu, M.D., Medical Reviewer
Elaine Abraham, R.Ph., Project Manager

Wyeth participants: Lauren Quinn, J.D., Regulatory Affairs
Paul Desjardins, Ph.D., Global Clinical and Medical Affairs

Background: Wyeth is planning to submit NDAs reformulating their Advil Cold and Sinus products to replace pseudoephedrine with phenylephrine. Last year, Wyeth asked FDA what should be included in the safety data. FDA's original response is included as attachment 1. Wyeth requested this Tcon to propose an alternate way of looking at the data (attachment 2) and obtain FDA agreement.

Discussion: FDA initially asked Wyeth to provide cardiovascular and cerebrovascular adverse events associated with ibuprofen use from the published literature, AERS, and any in-house data, but did not specify a time interval. FDA clarified that for the AERS data, Wyeth should go back one year.

Wyeth had proposed that when examining AERS and Wyeth databases describing the co-ingestion of both ibuprofen and phenylephrine where both ingredients were assigned as suspect, interacting, or concomitant, data from "mixed role code assignments", e.g., ibuprofen interacting and phenylephrine suspect, would not be provided. FDA asked Wyeth to explain this proposal. Wyeth responded that since phenylephrine has such a long history of use, they did not see the "mixed role code assignments" as providing new data. FDA asked if Wyeth planned on conducting noninterference biopharmaceutical studies and Wyeth replied that they would conduct such studies. FDA agreed if noninterference is shown in the biopharmaceutical studies then mixed role code assignment data would not be necessary.

Wyeth had proposed analyzing the ibuprofen and phenylephrine co-ingestion data from 1997 to the 2nd quarter of 2005. FDA stated that Wyeth need only go back 5 years for

this information, but that in addition to case forms, narrative and discussion would be helpful.

For cardiovascular adverse events from the literature, Wyeth was planning on updating their Advil NDA and asked if FDA was interested in cardiovascular or general safety. FDA said to provide general safety and separate out the CV events.

For updating chlorpheniramine in the triple combination product, Wyeth asked if it is acceptable to provide an update to the last annual report for NDA 21-441 which has pseudoephedrine. The update would be specific for chlorpheniramine. FDA stated that literature should be provided for ibuprofen (IBU) plus chlorpheniramine (CPM), IBU plus CPM plus phenylephrine (PE), and IBU plus PE.

Wyeth had proposed not submitting (but having available on request) the Appendix tables and actual Medwatch forms for serious adverse events. Wyeth stated that they can send the line listing and if FDA has a concern, we can request the Medwatch forms from Wyeth. FDA asked if this would be a quick turnaround, and Wyeth replied it would be quick. Wyeth plans to order Medwatch forms and have them in-house. Wyeth noted that it is an onerous task to put the Medwatch forms into electronic submissions, but they would have the forms available to send to FDA. FDA agreed to this proposal.

Attachments

Attachment 1: FDA's initial request for safety reporting for phenylephrine

As part of your NDA submission integrated summary of safety review for the ibuprofen/phenylephrine product, we request that you review, summarize, and analyze the cardiovascular and cerebrovascular adverse events associated with ibuprofen use from the published literature, AERS, and any in-house data you may have. In addition, please include the following items in electronic form:

- alphabetized listing (by author) of abstracts
- tabular summary of individual adverse events by article
- copies of the articles
- alphabetized table of contents for articles

A template for the adverse event table is attached. Please group article listings by study type. For example: clinical trials, meta-analyses, case-control, cohort, and case reports. Within each study group listing, list articles in alphabetical order by first author.

The following adverse events must be included: cardiovascular death, myocardial infarction, stroke, hospitalization for congestive heart failure.

As a second part of the NDA safety review, we request a review of serious AEs from AERS and worldwide databases from marketing of oral phenylephrine, including concurrent oral phenylephrine and ibuprofen use. Also review, summarize, and analyze serious AEs from oral phenylephrine use in the literature. Discuss whether phenylephrine has ever been pulled from the market for safety reasons in any country.

The above information should be included as part of the Integrated Summary of Safety for the proposed Ibuprofen/Phenylephrine product. For the triple combination product, you should also provide a safety update on chlorpheniramine that covers the time period from when NDA 21-441 (Ibuprofen 200 mg/ Pseudoephedrine 30 mg/Chlorpheniramine 2 mg) was approved to the present time.

Attachment 2: Wyeth's alternate proposal for safety reporting for phenylephrine, sent by email on February 23, 2006.

Product(s): [REDACTED] (b) (4)
Topic: T-Con on Safety Data

...[You asked us to] provide the following safety information for the [REDACTED] (b) (4) reformulated products:

1. IBU - Review of CV events in AERS and Literature (no specified time interval)
2. Review of SAES for oral PE, single ingredient and in combination with IBU (no specified time interval)
3. Review of SAEs for oral PE from literature (no specified time interval)
4. An update of single ingredient chlorpheniramine for the 3x submission from the approval of 21-441 to present.

Our Safety Group proposes that from our experience there is an alternate way to look at the data that will be more likely to reveal safety-related concerns for the proposed combination, and we are looking for the Medical Reviewer to agree:

Using the ICH PSUR format, we would analyze data from AERS and Wyeth databases from 1997 to 2Q05 (from the inception of AERS to the latest available update), and examine in detail cases that describe the co-ingestion of both ibuprofen and phenylephrine where both ingredients were assigned as being:

- Suspect (either primary or secondary)
- Interacting
- Concomitant

"Mixed role code assignments", e.g., ibuprofen interacting - phenylephrine suspect would not be discussed, nor would we prepare tables of events for these cases.

This same approach would be taken with the IBU/PE/CHLOR product.

With respect to the literature search, can you confirm whether the ibuprofen CV review is in addition to what we normally do for the safety literature, (i.e. summarize the safety literature for all the other organs systems and special populations, etc.)?

And last, we would like your agreement that it is acceptable for us to not submit (but have available upon request) the Appendix tables and the actual MedWatch forms for the SAEs?

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/s/

Elaine Abraham
10/24/2006 08:37:39 AM
CSO

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/s/

Elaine Abraham
9/19/2007 02:16:30 PM
CSO

NDA (b) (4) /22-113 Pre-NDA Meeting

1. *Does the Agency agree that the proposed stability data package will be acceptable for filing the NDA, i.e., 3 months accelerated data on PG formulations plus 6 months accelerated data on non-PG formulations?*

This proposal is acceptable, but the applicant has proposed updating the stability data two months prior to the goal date; however we are concerned that there will not be sufficient time to review the data before final approval. We cannot guarantee review of information submitted so late in the review cycle.

2. *Does the Agency agree that the proposed stability data package provided during Agency review, will be acceptable to support 18-month expiry dating on the PG formulations, i.e., 6 months accelerated data on the PG formulations and 12 real time data for all formulations?*

Yes, if no significant changes are noted at the accelerated condition and provided that FDA receives and reviews the 12 month stability update.

3. *Does the Agency agree that a request for a waiver of bioequivalence studies demonstrating equivalence between the formulas will be acceptable for NDA filing, assuming:*
 - a) *Dissolution data are adequate to satisfy the requirement for in vitro testing under this waiver request, and*
 - b) *Results of the in vivo bioavailability/bioequivalence studies on the non-PG formulations are found to be acceptable?*
4. *Does the Agency concur that the agreements reached on the three previous questions apply equally to (b) (4) applications: (b) (4) and NDA 22-1 13 (see Attachment II for Data for NDA 22-113)*

Yes to 1 and 2.

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/s/

Gene Holbert
3/20/2007 10:38:42 AM
CHEMIST

Shulin Ding
3/20/2007 12:24:10 PM
CHEMIST